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Decentralized Clinical Trials (DCTs) and the Expansion of mRNA Technology beyond COVID-19: Innovations, Challenges, and Future Directions

Huda Abdalla

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ABSTRACT
The COVID-19 pandemic triggered an unprecedented change in the medical research paradigm and fueled the expansion of decentralized clinical trials (DCTs) and the promotion of the possibility of messenger RNA (mRNA) technology. Though the two innovations have been key in combating the health crisis globally, they have currently taken paths that are way beyond COVID-19. The paper at hand dwells upon the intersection of DCTs and mRNA-based therapeutics and discusses how recent changes are transforming drug development, trial logistics, and patient engagement.
The technology, including telemedicine, remote monitoring, and electronic consent, has allowed DCTs to show potential to improve the clinical trial implementations, diversify the participating patients, and diminish the geographic and logistical challenges. At the same time, mRNA platforms, distinguished by flexibility, development speed, and capability to customize any therapy, are branching out into therapeutic diseases oncology, infectious diseases, and autoimmune disease areas.
This paper outlines synergies between decentralized trial models and mRNA technology through a thorough examination of the most significant post-pandemic innovations, such as an increased speed of enrollment, enhanced patient monitoring, and affordable data collection. Nevertheless, it also speaks about the obstacles that are continuing, such as law fragmentation, data safety issues, and the technical restrictions of remote environment.
Based on the latest case studies, the trial registries, and industry reports, the investigation provides a prospective insight into the role of DCTs integration with mRNA technology in making high-tech treatments more affordable and speeding up the global development of precision medicine. All of these findings demonstrate the necessity of coherent regulations, the further development of technological innovation, and the design of trial inclusiveness to make all the potential of this convergence possible.

I. INTRODUCTION

This paper investigates how recent advancements in clinical research have changed with the use of the Decentralized Clinical Trials (DCTs) and mRNA technology. DCTs present new strategies of recruiting and engaging patients, which contribute to modifying the conventional designs of trials greatly. Meanwhile, the new mRNA technology has become a radically different way of developing vaccines and therapies with huge scalability and adaptability.

This study aims at examining how well DCTs are effective in strengthening trial outcomes and exploring the more global practice of mRNA technology in other spheres of therapy. Through scrutinizing the two transformative aspects, the study will present information that can be used to determine best practices and regulatory standards in clinical research. The results will help to determine the relationship between the cause and effect of such innovations to the improvement of patient experiences and outcomes in the dynamic healthcare environment.

Overview and Background

The COVID-19 pandemic has significantly upset the traditional paradigms in biomedical research, specifically, on the basis of conducting clinical trials and developing vaccines. There are two prominent examples of innovations at the center of this disruption, which include decentralized clinical trials (DCTs) and messenger RNA (mRNA) vaccines platforms. Both solved serious problems of the whole world both quickly and flexibly. Under the impulse of digital technologies and remote patient management

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solutions, DCTs became the means to continue research even during the periods of lockdowns and social distancing policies. At the same time, the new type of vaccines based on mRNA, like the ones produced by Moderna and Pfizer-BioNTech, became a historical step in the modern science of immunization and provided effective response to SARS-CoV-2 in a few months.

The innovations have not just maintained after the pandemic but they are developing at a high pace. DCTs are redefined as the long-term solutions to the better accessibility, efficiency, and inclusivity of clinical trials. Similarly, mRNA solutions are leaving COVID-19 behind and are being extended to oncology, rare genetic disease, and other endemic infectious diseases like influenza, RSV, and HIV. The nexus between these trends has presented a singular opportunity that holds the promise of transforming the future of drug development through the ability to utilize the decentralized infrastructures to develop next-generation and fast-moving therapies.

Research Objectives and Research Questions

The two-fold advent of decentralized clinical trials (DCTs) and mRNA therapy marks a paradigm-changing transition in the scope of biomedical research and therapeutic innovation. as the two markets mature in the post-COVID-19 era, however, it is essential to comprehend the contours of their natural evolution, the areas of convergence and the impact they will have on further development processes of clinical studies.

Research Questions

The following were the main questions that will guide this paper:

1) What has changed on decentralized clinical trials (DCTs) since the COVID-19 pandemic and which technological and regulatory frameworks favor their continued deployment?
2) Which are the existing and future applications of mRNA technology outside of COVID-19, especially in oncology, infectious diseases, and rare diseases?
3) How do the two methodologies of DCTs and mRNA clinical trials complement one another, and how might these two approaches be combined to drive more rapid development of a new therapeutic and patient access therapeutic?
4) What are some of the major challenges, scientific, regulatory, ethical, and logistical to the implementation of DCTs in relation to mRNA-based clinical research?
5) Which innovations, policy changes and digital technologies are needed to make the most of the synergy between DCTs and mRNA platforms in the short and long term?

Research Objectives

In the light of these questions, the paper will answer the following specific objectives:

- To the structural and operational aspects of DCTs such as telemedicine, remote monitoring, eConsent and digital data capturing technologies.
- Among the growing pipeline of mRNA-based therapies, determining disease areas, companies, and research partnerships that go outside the COVID-19 picture.
- To case studies and trial data in which DCT methodologies have been utilized during mRNA trials to determine their capability in enhancing the trial efficiency, diversity and patient retention.
- To keeping obstacles and hazards that accompany the establishment of decentralized models in high-tech, high-accuracy sectors such as mRNA therapeutics.
- To future opportunities in the alignment of regulatory policies, development of enabling technologies, and engagement in international research cooperation on facilitating scalable, inclusive and efficient conduct of translational mRNA trials with the DCT models.

Introduction of Methodology

The study is of a qualitative and analytical nature, utilising various sources and means of research to thoroughly look into the overlap of the concept of decentralized clinical trials (DCTs) and mRNA technologies. Its methodology is built based on three main components:

1. Literature Review

- A composition of a literature review was done to ascertain the theoretical as well as practical basis of DCTs, and mRNA technology. Sources included:
- Scientific journals (e.g. The Lancet, Nature Reviews Drug Discovery, NEJM)
- Regulatory guidelines and white papers of organizations, e.g. FDA, EMA and WHO
- Biotechnology industry reports by biotechnology companies and clinical research organisations
- Clinical trial databases (e.g., ClinicalTrials.gov, WHO ICTRP)

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This review allowed suggesting the trends, technological enablers, regulatory frameworks, and disease areas, where DCTs and mRNA technologies are already used or are suggested to be implemented.

2. Case Studies

Case studies of some of the selected clinical trials that utilize decentralized models on mRNA-based drugs have been analyzed. Selection of these case studies was carried out on the following basis:

- Therapeutic area - Diversity (e.g. oncology, infectious disease)
- Remote / digital tools (e.g. eConsent, remote diagnostics)
- Type of a trial sponsor (biotech companies, academic institutions)

To assess the real-world implementation, operational efficiencies, patient outcomes, and the impediments during the decentralized of mRNA trials, case studies have been deployed.

3. Comparative Analysis

A comparative model was utilized to determine the variations between the conventional and the decentralized strategies in mRNA clinical research. Major parameters that were analyzed:

- The rate of enrollment and initiation of trials
- Demographic coverage and geographic coverage
- Expense and resources consumption
- Data quality and retention of patients
- Regulations and ethics

This relative comparison gave us insight into the strengths and weakness of each model, and the way in which DCTs can be perfected to serve mRNA research in the future.

DEFINITION DECENTRALIZED CLINICAL TRIALS (DCTS)

Decentralized Clinical Trials (DCTs) are the new clinical research type that applies the digital health technologies and remote methods to achieve some or all of a clinical trial beyond the usual research locations. In terms of patient-centered interests, DCTs shift the center of interest away from conventional sites-based trials as they allow patients to have the ability to participate in trials either at home or in a local healthcare environment. Such a model will ease the load on the patient, speed timelines, and increase enrollment diversity through the use of technologies like telehealth, eConsent, wearable sensors, and direct-to-patient logistics.

New government guidelines, such as those provided by the U.S. Food and Drug Administration (FDA), have also been embracing use of DCTs, and in response, the European Medicines Agency (EMA) has more recently acknowledged accessibility as a reason to support DCT methodologies.

Principal C's of DCTs

1. Electronic informed consent (eConsent)

eConsent is used to enable participants to review and understand informed consent document, and sign the consent electronically remotely. The component plays a crucial role as far as ethical compliance and transparency are concerned and that it will be more convenient to the participants who might not afford travelling to the research sites. Fully featured eConsent systems are likely to contain multimedia descriptions, knowledge monitoring, and multilingual support, to increase knowledge of participants and participation in the trial.

2. Telemedicine and VV

Telemedicine makes possible clinical contact with the investigation participants and a clinician in the form of a safe video or phone consult. Virtual visits lessen face-to-face visits and, as a result, minimize geographic obstacles and enhance retention. With telehealth services, there is also the ability to real-time monitor adverse events, symptom changes, and compliance with the treatment, particularly significant in a longitudinal trial or during a pandemic and other public health emergencies.

3. Remote patient monitoring (RPM)

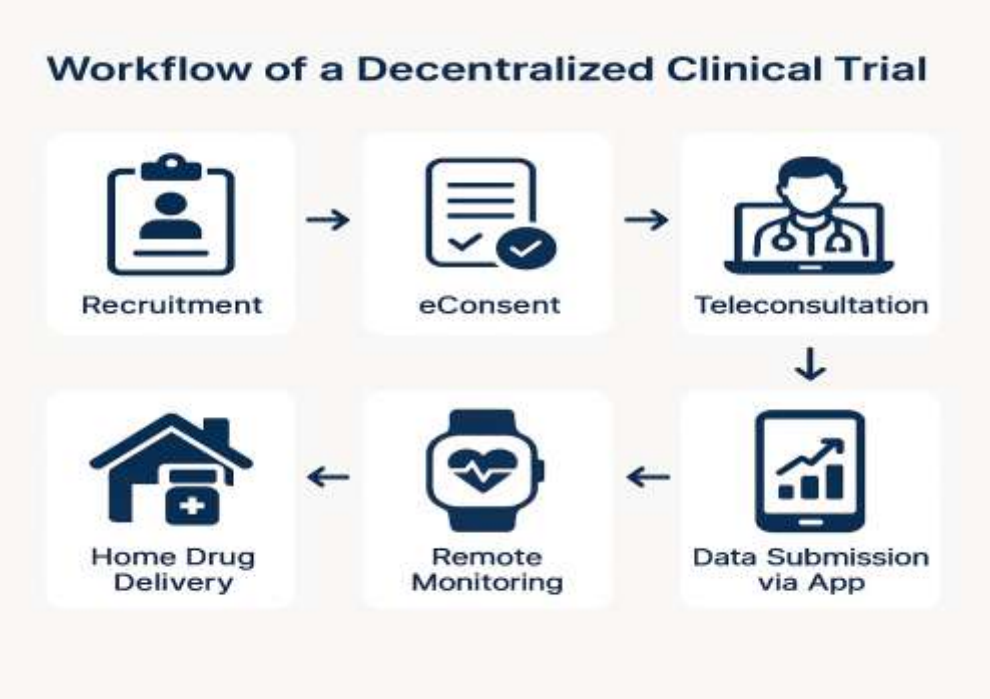
A new type of remote monitoring makes use of digital technologies (e.g., m-Apps, wearable-biosensors as well as interconnected medical devices) to capture real-time physiological and behavioral data. All those metrics are measured by means of such tools as heart rate, sleep patterns, temperature, the level of activity, and medication adherence, and no physical presence in the sites is necessary as the data can be constantly collected. RPM makes performance of more detailed and quicker checkups of treatment efficacy and safety.

4. Direct-to-Patient (DTP) Drug Delivery A Direct-to-Patient (DTP) Drug Delivery is a new system of drug delivery.

The DTP delivery systems allow shipping of investigational medicinal products (IMPs) to the

International Journal of Advances in Engineering and Management (IJAEM)
Volume 7, Issue 10 Oct. 2025, pp: 195-217 www.ijaem.net ISSN: 2395-5252

homes of the individuals participating in the study eliminating the necessity of visiting the test sites and increasing the convenience. It means that this logistics, temperature-sensitive shipping (this applies to mRNA-based biologics particularly), and real-time tracking of supplies are needed to comply with the regulations and to maintain drug integrity. DTP systems facilitate a high rate of adherence and enhances scalability of trials coupled with virtual supervision.



History of development

The history of decentralized clinical trials (DCTs) development is the result of a somewhat confluence of technological advancements and functional requirements coupled with global health epidemics. Although the idea of decentralization in clinical trials had been around long before COVID-19, the pandemic served as the significant inflection point that impetuously fast-tracked both the uptake and the regulatory approval process.

Pre-COVID Early adopters

Before the COVID-19 pandemic Decentralized clinical trials were to a large extent experimental and carried out on a small scale, frequently in hybrid models, which featured site-based activities alongside remote aspects. One of the first adopters were:

- Digital health startups and small biotechnology companies, which aimed at increasing the engagement of patients and efficiency of trials with the help of innovative platforms.
- Disease-specific parties, especially those with rare and chronic disease (e.g. multiple sclerosis, epilepsy) where gets remotely monitored and visited home in order to meet patients at their locations in geographically disparate sites.
- Wearable device trials and mobile health (mHealth) which was the first to report on the gathering of real-world patient data not undertaken within a clinical setting.

These attempts notwithstanding, extensive use remained fettered by the absence of regulatory instructions, interoperability of data and ingrained industry timidity. The use of DCTs was frequently considered as supplementary and not as a replacement of the traditional trial models.

Speeding Up in the Pandemic

The COVID-19 pandemic became a driver towards the fast implementation of the DCT strategies into the pharmaceutical and clinical research markets. Broad quarantines, overburdened medical systems and the virus spread-hindering needs mandated the urgent introduction of a replacement system to physical visits.

Important modifications of the period were:

International Journal of Advances in Engineering and Management (IJAEM)
Volume 7, Issue 10 Oct. 2025, pp: 195-217 www.ijaem.net ISSN: 2395-5252

Mass adaption of telemedicine to study visits and follow-ups

- Accelerated application of eConsent platforms in order to reduce the wait time of the onboarding of the patients
- Off-site data recording and surveillance of mobile applications, bio sensors, and cloud-based systems
- Direct to patients models of drug deliveries to allow treatment follow up and compliance monitoring

Large trial sponsors, e.g., Pfizer, Novartis and Johnson & Johnson have started using DCT tools in COVID-19 related and non COVID-related trials. Contract Research Organizations (CROs) and digital trial infrastructure technology vendors further supported these changes (under the labels of DCO, CRCO, or DCO/CRCO).

Regulatory Changes in support of DCTs

To address the pandemic, international regulatory agencies made pro-active measures to support decentralized research. Improvisational emergency protocols were handed out, several of which became subsequent, permanent structures:

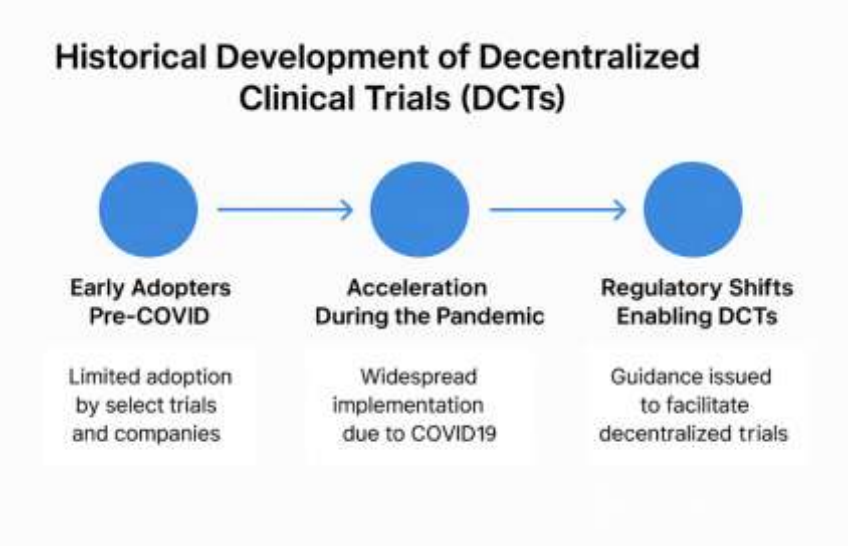
March 2020 - U.S. FDA released Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency Which encouraged the performance of virtual visits and electronic records, as well as the need to use alternative methods that allow the delivery of investigational products.

- EMA Guidance: The European Medicines Agency made the same recommendations, with particular regard to trial flexibility and participant right and data protection.
- Involvement of MHRA, PMDA and WHO: Other agencies did the same and in a globally harmonised effort the trend was for decentralised approaches.

Moreover, the DCT as a model of trial was institutionalised as the FDA from its Decentralized Clinical Trials Program released draft guidance Decentralized Clinical Trials for Drugs, Biological Products and Devices, (2023)

Important Players and Technological Enablers

Decentralized clinical trials (DCTs) are dependent on a wide ecosystem of participants, all of which bring specialized abilities, infrastructure, or regulatory control. At the same time, technological facilitators such as tactile gadgets, portable well-being apps, and artificial intelligence are critical to completing the decentralized protocols in an adept and safe manner.



Key Stakeholders

1. Clinical research organizations (CROs)

CROs are no longer acting in their customary roles they played as they have moved to become the key conductors of the DCT activities. They offer virtual platforms, workflows of virtual trials, and guarantee data integrity in a decentralized world. Numerous CROs have started to provide hybrid and fully remote trial models, which are backed by the collaborations with tech vendors and the services of remote nurses.

2. Sponsors (Pharmaceutical and Bio pharmaceutique Co.)

In trial design and strategy, key decision-makers are sponsors. They combine efforts with

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technology suppliers and CROs to install patient-centric tools and logistics systems in the DCT model. Pfizer, Novartis, and Moderna are major sponsors that are returning to the decentralized models at an increasingly high pace as an attempt to shorten the time limit of the the trials and better diversity recruitment.

3. Technology Companies

DCT infrastructure is now dependent on new health tech firms and already existing digital companies. They provide:

- Virtual visit solutions (e.g. Teladoc, Zoom healthcare)
- eConsent& patient engagement (e.g., e.stromediadata, Los angelesveeva)
- Cloud-Based Remote Monitoring and Data capture Tools (e.g. Apple Health Kit, Fitbit)

4. Regulatory Agencies

The most important regulators leading to legitimization of DCT models include the FDA, EMA, MHRA, and the PMDA. Their developing advice has facilitated the processes of adherence to distance consents, virtual site visits, data privacy, and cross-border care of patients. They are vital in confirmation of the trust in DCT results.

Technological Enablers

1. Wearable sensor devices

Biosensors, implantable, and smartwatches allow a real-time monitoring of the physiology of patients. Such devices monitor vital signs (i.e., heart rate, oxygen saturation, activity levels) and send the data to centralized databases in order to analyze them in the real time, which increases the safety and limits site visits.

2. mHealth Mobile Health Applications

mHealth applications are a way of allowing patients to submit symptoms reporting, provision of reminders, virtual visit scheduling, and trial-associated data. These apps make the process of real-time interaction, self-reporting, and education reinforcement much easier and greatly enhance compliance and retention.

3. Machine learning and Artificial Intelligence (AI)

AI algorithms are also finding use in optimal patient recruitment, anomaly detection of real-time monitoring data, and predicting risk of dropout, as well as in personalization of interventions. Another way AI-driven platforms assist in clinical trials is by allowing the analysis of reposted data sets on decentralized trials and provide a new perspective into the treatment or the actions of a patient.

4. Cloud, Data Infrastructure integration

The real-time data aggregation, interoperability and analytics at many digital endpoints are possible, with the help of secure cloud platforms. They help to gain regulatory compliance and are able to perform encryption, audit trait, and role-based access to ensure that multi-country, multi-device DCTs are coordinated to scale.

PLATFORM ADVANTAGES AND MECHANISM OF ACTION

Mechanism of Action: Molecule synthesis and Delivery of mRNA

The Technology Messenger RNA (mRNA) technology is revolutionary in that the

International Journal of Advances in Engineering and Management (IJAEM)
Volume 7, Issue 10 Oct. 2025, pp: 195-217 www.ijaem.net ISSN: 2395-5252

technology is used to develop drugs using man-made pieces of genetic code that are administered to direct cells to generate therapeutic or immune-generating proteins. mRNA therapeutics have a transient and non-integrative biological mechanism of action in contrast to traditional vaccines or biologics that administer pre-formed antigens or that use viral vectors.

Mechanism of action entails the following steps:

1. **Design and production of mRNA**

- Scientists design a nucleotide amino acid chain that encodes a target antigen (e.g. spike protein of some virus, or tumor asociated antigen).

Alterations on nucleosides are usually done to improve stability and limit innate immune responses.

2. **Lipid Nanoparticle (LNP) encapsulation**

The mRNA molecules are fragile and protecting them against enzyme degradation and promoting cellular delivery require lipid nanoparticle encapsulation.

- LNPs perform a carrying role and facilitate the delivery of mRNA to the host cells especially antigen-presenting cells.

3. **Protein Translation and Up take into the Cells**

- In the case where the mRNA enters the cytoplasm in the host cell, cellular ribosomes use the mRNA to create a protein coded in it.

The expressed protein is subsequently prepared, and brought to the cell surface to stimulate the adaptive immune system (in vaccines) or other cellular effects (in therapeutic situations).

4. **Activation of the immune system or therapeutic effect**

- Compared to vaccines, the experienced antigen triggers the B and T cell responses that cause the long-term immunity.
- In the therapeutic context, the protein can heal damaged tissue, control immune regulation or attack the malignant cells.

It is neither-integrating, transient mechanism, which prevents risks associated with genome manipulation and allows prototyping across indications in relatively short time.

Platform benefits: Plasticity, Quickness, and Extendibility

The mRNA technology is associated with the following innate benefits that differentiate it with utilization of traditional therapeutic platforms:

1. Flexibility

Design Flexibility: mRNA can be designed to be matched to any protein of interest, viral antigens, tumor antigens, etc.

- Multivalent Formulations: a single construct of mRNA may contain numerous antigens allowing combination therapies and increasing the multi-valency of the vaccine.

2. Speed

Once a target antigen is identified, mRNA constructs can be made in weeks, Fast Development Timelines. It allowed creating vaccines against COVID-19 within short periods of time.

- Efficient Manufacturing The common core production infrastructure can be re-utilized on other mRNA therapeutics, decreasing production lead time and cost.

3. Scalability

- Modular Manufacturing Platforms: The modular platforms are cell-free producing (e.g., in vitro transcription) that uniformly produces at scale with Good Manufacturing Practice (GMP) environment.
- Potential for Global Distribution: mRNA products are currently feasible in global distribution with the improvement in the methods of cold-chain logistics and lyophilization processes.

The benefits stated above predestine mRNA to not only solve pandemics but also they have a universal application in the fields of oncology, infectious diseases, autoimmune disorders, and genetic disorders.

Expansion Therapeutic

The triumph of COVID-19 mRNA-based vaccines has justified the potential of the platform and catalyzed the expansion of its implication towards a wide range of diseases. The sonic fluidity mRNA technology is now maturing at dizzying pace as pharmaceutical companies and research centers work to extend this technology to diverse treatment fields such as oncology, infectious diseases, autoimmune diseases, and rare genetic diseases. Its modularity and flexibility as well as the achievements on the basis of the delivery platforms, immunogenic optimization, and scalable production make the mRNA platform disruptive in modern medicine.

International Journal of Advances in Engineering and Management (IJAEM)
Volume 7, Issue 10 Oct. 2025, pp: 195-217 www.ijaem.net ISSN: 2395-5252

1. Oncology: Disease-Individualized Cancer Vaccines

The immunotherapy of cancer, and especially the design of individualized cancer vaccines, is one of the most promising fields of mRNA technology. These treatments embrace tumor-specific neoantigens, or proteins that grow due to mutations of an individual patient, and trigger personal response.

Key Initiatives:

- Moderna & Merck: Their Personalized Cancer Vaccine mRNA-4157/V940 In combination with Immune Checkpoint Inhibitor drugs, Keytruda, has demonstrated promising outcomes electric melanoma patients, creating decreased chances of reoccurrence and mortality.
- BioNTech: BioNTech is in collaboration with Genentech and the consortium, working on a collection of personalized suites of neoantigen-based mRNA vaccines against solid malignancies, including colorectal, pancreatic, and lung cancer.

The benefit of mRNA cancer vaccines is that they can be synthesized in a matter of a few weeks once a genomic sequence of a tumor is known, and that is paired with a magnified level of precision compared to any other type of platform in traditional use of vaccines.

2. Infectious Diseases: Expanding the Scope of Immunization

In addition to COVID-19, mRNA vaccines are in development against numerous infectious diseases where more traditional methods have not been timely, effective, or highly versatile.

Vaccine candidates, Targeted diseases:

- Influenza: mRNA-1010 by Moderna and flu mRNA by Pfizer are both advanced development candidates geared to increase matching with strains and shorten production schedules in comparison with traditional influenza vaccines.
- Respiratory Syncytial Virus (RSV): Meanwhile, Respiratory Syncytial Virus (RSV) is also the subject of current mRNA vaccines being developed by Moderna and Pfizer, with various contenders in Phase III testing against older and infant individuals through maternal immunization.
- Zika Virus: Candidates of mRNA-based Zika vaccine, including Moderna mRNA-1893, are now in Phase II clinical trials to treat the lack of protection against congenital Zika syndrome.
- HIV: HIV experimental mRNA vaccines are in development, which may have the ability to provide sequential immunogens and generate broadly neutralizing antibodies- another challenge in preventing HIV.

The combination of mRNA encoding of complex antigen structure and potential to mutate with a viral infection means mRNA is suited to deal with emerging infectious diseases.

3. Rare and Autoimmune Diseases

mRNA therapeutics are also under development in the field of autoimmune disorder and rare monogenic diseases, in which specific protein expression or immune modulation is first needed.

App dev:

- Autoimmune Diseases: BioNTech is also working on mRNA-based autoimmune disease development that can lead to immune tolerance in diseases like multiple sclerosis (MS) and type 1 diabetes to reprogram the immune system without generalized immunosuppression.
- Rare Genetic Disorders: mRNA therapies to replace missing or erroneous proteins are under development by companies such as Translate Bio (purchased by Sanofi) and Moderna, to cure such disorders as cystic fibrosis, methylmalonic acidemia (MMA), and propionic acidemia.

These applications include therapeutic, not only prophylactic, use of mRNA and increases its opportunity beyond vaccines to a new category of injectable biologics and gene expression modulators.

Large Players and R and D Pipe-lines

The fast pace of mRNA vaccine development and distribution because of the COVID-19 outbreak placed a series of biotechnology companies in the position of international leaders of mRNA technology. These companies now over those years (and others coming into the field as well as academic consortia) have increased their research and development (R&D) pipeline to span a broad disease continuum. Strategic collaborations, licensing, and investment in both the public and the private sectors have also contributed to the growing

International Journal of Advances in Engineering and Management (IJAEM)
Volume 7, Issue 10 Oct. 2025, pp: 195-217 www.ijaem.net ISSN: 2395-5252

energy toward research and commercial development of mRNA across the globe.

1. Moderna, Inc. (USA)

Moderna is an mRNA innovation giant that has a broad pipeline not limited to COVID vaccines. The proprietary platform of the company is based on the lipid nanoparticle (LNP) technology and internal manufacturing capabilities, making it possible to scale up and enter clinical use very quickly.

Attractions of Pipeline:

- Oncology: mRNA-4157/V940 (pneumalysin-based nanolipid delivery system,Phase II/III)
- Infectious Diseases: mRNA-1010, (influenza), mRNA-1345 (RSV), and mRNA-1283 (next-gen COVID-19)
- mRNA-3705 (rare methylmalonic acidemia) mRNA-3927 (rare propionic acidema)
- Public Health: Continued work with the NIH, CEPI and Gavi to create mRNA vaccines addressing global health priorities including HIV and Nipah virus.

Moderna retains over 40 preclinical and clinical programs on mRNA making it one of the most developed mRNA companies in the world.

2. BioNTech SE (Germnay)

In collaboration with Pfizer, BioNTech became well-known using the BNT162b2 vaccine against the coronavirus disease (COVID-19). The company uses mRNA know-how and strong immuno-oncology and precision medicine skills.

Highlights Pipeline:

- Oncology: several personalized cancer vaccine candidates (iNeST, FixVac, CARVac) including BNT122 and BNT111 against melanoma, colorectal, and prostate cancer
- Infectious Diseases: Tuberculosis, malaria and influenza vaccine under-development (in conjunction with the Bill & Melinda Gates Foundation and WHO)
- Autoimmune Disorders: Investigative Work of Preclinical Tolerogenic mRNA Therapeutics

BioNTech has also placed mRNA manufacturing and development hubs in Africa (e.g. Rwanda) which indicate its intentions of mRNA equity any where in the globe.

3. CureVac N.V. (Germany)

CureVac is an old, and one of the first mRNA biotech companies, that is known to work on thermostable mRNA and cost-effective delivery platforms. Although it experienced COVID-19 vaccine trials failures earlier, the company has lately realigned itself to second-generation mRNA technologies with GSK on board.

Key Programs:

- Infectious Diseases: seasonal influenza, COVID-19 and RSV
- Oncology: immuno-oncology mRNA immunotherapies with Genmab and Myeloid Therapeutics

Platform Innovation: mRNA next-gen design, better translation and immune modulation

The completed strategic agreement between CureVac and GSK promises to drive up to five mRNA-based vaccines with over 1 billion euros added to financing a combined effort.

4. Arcturus Therapeutics (USA)

Arcturus is a pre-clinical/clinical-stage biotech company with self-amplifying mRNA (saRNA) platforms, needing a few doses, and having prolonged protein expression.

Pipeline Overview:

Health care • COVID-19: ARCT-154 is a self-amplifying mRNA vaccine co-developed by ARCT and the Vietnamese company Vinbiocare that has achieved regulatory approval in some markets
Influenza and RSV: Preclinical and early development
Rare Diseases: ARCT-810 ornithine transcarbamylase(OTC) deficiency a Phase I/II trial
Arcturus still advancing the additional use of sa-RNA in a preventive and therapeutic setting.

5. Global Trends Trends in Funding and Partnerships

Since 2020, mRNA has become an exponentially growing field in funding and partnerships because of research demands in the context of public health and investor confidence:

- Venture Capital and IPOs In the case of pipeline expansion, companies such as GreenLight Biosciences, Nutcracker Therapeutics, and eTheRNA have received multi-million rounds of venturing capital.
- Public-Private Partnerships: Many organizations are funding mRNA platforms against priority pathogens. The Coalition for Epidemic Preparedness Innovations (CEPI), Gavi, and BARDA are all actively financing mRNA platforms of selected pathogens, and

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Volume 7, Issue 10 Oct. 2025, pp: 195-217 www.ijaem.net ISSN: 2395-5252

the WHO is currently also discussing the financing of mRNA platforms.

- Pharma Partnerships: Big pharma groups (various examples include Pfizer, Sanofi, GSK, Roche) have struck collaborations with mRNA startups in terms of co-development and licensing.
- Geopolitical Investment National governments are also investing into national mRNA-manufacturing capabilities, so as to secure vaccine sovereignty (e.g. Japan, India, South Africa, Australia).

TRIALS WITH MRNA AS TROJAN HORSE TO DECENTRALIZED CLINICAL TRIALS (DCTS)

The mRNA technology has enabled and enhanced the adoption of Decentralized Clinical Trials (DCTs) in modern biomedical studies and research. One of the interesting attributes of mRNA clinical trial is that they perfectly fit the principles and operational advantages of DCT models. The trials are of hurried nature, geographically dispersed, and sometimes demand site-specific strategies, rendering them to be primed particularly to decentralization.

1. Rapid Development Life-Cycles

Among the most distinctive features of the mRNA technology, one must distinguish its excessive speed of development. As compared to typical vaccine or therapeutic candidates, mRNA-based candidates take only weeks to design and produce after target antigen identification as opposed to years through typical pipelines. The fast time scale requires nimble trial hardware as well.

- DCTs assist in parallel trials, including remote patient onboarding, telemedicine visits and digital processes of consent, which is consistent with the mRNA R&D speed requirements.

As an example, in the case of Moderna, the COVID-19 vaccine trials combined electronic consent and mobile monitoring systems to enroll tens of thousands of participants within several weeks.

DCTs eliminate geographic and logistical challenges, so mRNA innovators stay on the pace necessary to facilitate a rapid clinical verification and regulatory submission.

2. The Requirements of Patient Recruitment in the Global environment

The mRNA trials are frequently intended to enrol patient groups representing different continents, sometimes with the view outwards to regulatory demands and sometimes with the view inwards, to overall generalisation of the findings. This specially pertains to:

- Vaccines against infectious diseases, which are required to be tested in the disease-endemic areas (Zika, HIV, malaria, etc.).
- Personalized cancer vaccines, in which a large variety of tumor subtypes as well as genetic alterations should be represented within trial populations.

Summary

Feature	mRNA Trial Requirement	DCT Enablement
Speed	Fast protocol execution	eConsent, remote monitoring, real-time data capture
Global Reach	Diverse, multi-national participants	Telemedicine, mobile recruitment, digital platforms
Personalization	Adaptive dosing, biomarker-based response	Wearables, at-home diagnostics, AI-driven analytics

INTEGRATED MRNA DCT MODEL CASE STUDIES

It is starting to come into form in the real world when it comes to decentralized clinical trials (DCTs) in mRNA research, with a possible answer to the question of how this synergy between the two innovations can become a driving force of the fast-tracking of therapeutic development, enhanced patient involvement, and globalization. In this segment, three examples of illustrative case studies, industry-driven, and academic-driven, will be presented in evidence of the operationalization of DCT frameworks in clinical research of mRNA.

1. The Decentralized Influenza Vaccine Trials of Moderna

Background:

Moderna is currently conducting one of the largest mRNA clinical programs with its quadrivalent mRNA-1010 investigational influenza

International Journal of Advances in Engineering and Management (IJAEM)
Volume 7, Issue 10 Oct. 2025, pp: 195-217 www.ijaem.net ISSN: 2395-5252

vaccine planned to run part of the program on a decentralized model. Started in Phase 3 in 2022, these trials had the goal of proving efficacy, along with the feasibility of conducting a logistically complicated intervention in dispersed populations.
Highlights of use of DCT Integration:

- eConsent& Telehealth: eConsent and introductory health evaluation through telemedicine was facilitated on a secure site to enroll each participant remotely.
- At-home Data: The data were gathered at-home by recording symptoms, adverse event diaries, and temperature reports using mobile health apps and wearable devices.

Direct-to-Patient (DTP) Drug Delivery: A direct-to-patient delivery process was also tested on some trial areas where doses of the vaccine were sent directly to the patient along with the licensed professionals giving the shots in areas close to the patient at their home or at the local community centers.

Impact:

Deployment of decentralized components for recruitment (especially in rural and elderly patients), smaller burden on the sites, and live monitoring of adverse events throughout flu season made the difference.

2. Oncology Trials of BioNTech using Remote Monitoring

Background:

BioNTech has initiated several solid tumor-focused mRNA-encoded vaccine trials such as BNT122 in partnership with Genentech. These experiments are based on very personalized manufacture of the vaccine depending on the tumor mutational profile.

Some of the Highlights of the DCT Integration are:

Unobtrusive Biometric Monitoring: Patients had wearable electronics such as ECG monitor and the activity motion tracker to measure fatigue, immune symptom-related symptoms, and markers of physical function after the vaccine.

- Hybrid Site-Home Models: In such a model, the imaging and biopsies were performed on site, whereas the routine follow-ups and blood draws were performed by mobile nurses, or labs in the area.
- Data Aggregation in the Cloud: Immune profiling data, genomic reads and wearable measurements were transferred and stored in a centralized analytics environment to make adjustments to the protocol.

Impact:

This hybrid DCT model maintained the complexity of the protocol with a degree of flexibility to immunocompromised cancer patients, most of whom had mobility or travel restrictions.

3. Academic-Business Venture Low-Resource Academic-Led Trials

Background:

Trial of decentralized mRNA vaccines in low-resource settings, Decentralized vaccine or vaccine delivery platforms have been piloted at the University of Cape Town and Oxford Jenner Institute and particularly in sub-Saharan Africa and Southeast Asia. Such trials involve the testing of prospective cures such as HIV, malaria and Lassa fever vaccines.
Some of the Highlights of the DCT Integration are:

- Mobile Health (mHealth) Devices: Those involved utilizing digital layering by patient education, data collection, and adverse event monitoring, with limited access to a conventional healthcare system.

Teleconsultation Hubs: The remote monitoring of physicians by the rural patient was achieved through solar powered internet kiosk in rural settings, and thus achieved their remote clinical supervision.

Community-Based Distribution: We used partnerships with local community health workers to complete trial logistics, with the help of whom informed consent, sample collection, and vaccination ensued.

Impact:

This community-based, decentralized model allowed the reduction of infrastructure limitations and labor force, drop-out rates, and inclusivity of trial participants in geographically different locations.

International Journal of Advances in Engineering and Management (IJAEM)
Volume 7, Issue 10 Oct. 2025, pp: 195-217 www.ijaem.net ISSN: 2395-5252

Summary Table: Case Studies Overview

Trial Sponsor	Therapeutic Focus	DCT Elements Used	Key Benefit
Moderna	Influenza vaccine	eConsent, telehealth, DTP drug delivery	Faster enrollment, improved retention
BioNTech	Cancer vaccines	Wearables, home nursing, remote diagnostics	Reduced burden for oncology patients
Academic Consortia	HIV, malaria, Lassa	mHealth apps, local health workers, teleconsults	Expanded access in underserved populations

Advantages of Integration

Decentralized Clinical Trials (DCTs) and mRNA technology have come as a decisive fusion in clinical research. Sponsors and stakeholders can discover many efficiencies and scientific advantages by matching the flexible, patient-centric design of DCTs with the fast, nimble character of mRNA platforms. In the case of this section, the first presentation describes the key advantages that come out of integrative work of these two paradigms.

1. Quick Data Collection and Enrollment

Conventional clinical trial designs are commonly limited by physical locations, prolonged recruitment procedures, and lousy reporting of data. Conversely, the DCT methodologies incorporated into the study of mRNA allow:

- On-the-spot registration on digital platforms to include participants that cannot be found in urban clinical centers,
- eConsent workflows, which decreases the burden of regulation and enables instant patient activation,
- Remote diagnostics and wearable devices, which enable constant recording of data and the minimization of the number of visits to sites.

These innovations saw faster recruitment periods and interim data reports in trials such as Moderna mRNA-1010, BioNTech oncology pipelines, which made the trials take a step towards the next stage much faster.

2. Improved access and diversity in patients

Illustration of such inefficiencies in traditional clinical trial system is the under-representation of the demographic groups including minority, rural, elderly, and socioeconomically disadvantaged groups. DCTs assist in the accomplishment of these obstacles by:

- Enabling recruitment that is geographically distributed with use of telehealth and mobile technologies,
- Less consumption of time and money on travelling and face-to-face meetings,
- Promoting at-home activities that make the process more inclusive to the people who have limited mobility, childcare, or work-related issues.

In the case of trials mRNA trials in infectious disease and rare disease, this access expansion will be vital to the establishment of a generalizable safety and efficacies profile-especially when the trials have a focus on global or underserved populations.

3. Economy of Costs, Economy of Time

The nature of mRNA clinical trials makes it extremely resource-intensive given that it involves creation of personalized vaccines, testing of biomarkers, and distribution by cold-chain logistics. Yet, in combination with DCT infrastructure, many operation expenses can be considerably minimized:

- The overhead costs related to sites (e.g. physical space, staff) will be reduced with a transition to virtual/hybrid modalities of trials,
- The monitoring and data collection performed remotely minimize the number of visits and the expenses of visiting a site and checking its results in the lab,

Improved reactions to data provided in real time facilitate the decision making process, allowing the go/no-go decisions at interim checkpoints faster.

An increasing amount of industry reports put the estimation of development time saved with decentralized trial models at 10-30%, and this is especially useful in the time- and competitive-sensitive environment of mRNA therapeutics.

International Journal of Advances in Engineering and Management (IJAEM)
Volume 7, Issue 10 Oct. 2025, pp: 195-217 www.ijaem.net ISSN: 2395-5252

Summary Table: Integration Benefits

Benefit Area	Specific Impact	Example
Enrollment Speed	Rapid participant onboarding via digital tools	Moderna flu vaccine trial enrolled in weeks
Patient Diversity	Inclusion of rural, elderly, and minority populations	Academic trials in Sub-Saharan Africa
Operational Efficiency	Reduced site visits and staff burden through virtual processes	BioNTech oncology trial with home-based care
Data Collection Timeliness	Real-time monitoring using wearables and mobile apps	Remote AE reporting in mRNA cancer studies

CHALLENGES AND LIMITATIONS: LEGAL AND MORAL RESTRICTION:

Just as the combination of Decentralized Clinical Trials (DCTs) and mRNA technology holds the power of tremendous transformation, it does not come without significant challenges, especially on the regulatory and ethical front. Internationalization of the mRNA research, along with the new model of decentralized operation, brings along complicated challenges of regulation of legal compliance, rights of participants, and data management. These challenges should be overcome at both the scientific and popular level.

1. Fragments of Worldwide Regulatory Systems

Among the strongest impediments to DCT implementation may be the absence of a harmonized set of regulatory requirements or guidance on a cross-jurisdictional basis. Whereas in certain jurisdictions, e.g., the United States and the European Union, guidelines have been issued to facilitate DCT elements, in other countries no specific policy or still stringent clinical trial regulations are in place.

- In the U.S., methods of DCT are supported by FDA guidance such as Digital Health Technologies for Remote Data Acquisition in Clinical Investigations, although application to specific trials is left to the discretion of trial sponsors.
- In Europe, the EMA position on decentralized trial evolves, with pilot projects, however, national regulations continue to vary especially in relation to telemedicine and drug delivery remotely.
- Regulation infrastructure is also poor or old in most of the low-income and middle-income countries, which becomes an obstacle to trials approval and the utilization of data across national boundaries.

This discrepancy causes fragmented trial structures, more compliance expenses, and jurisdiction-specific adjustment, all of which has the potential of slowing down multinational mRNA-DCT research.

2. Informed Consent in the cyber-world

One of the key components of DCTs, eConsent, has opportunities and ethical issues. Though capable of enhancing accessibility and understanding with the help of multimedia formats, it poses a question of:

- Sincerity of consent: The need to make sure sure, in cases where the research process is remote and self-paced that the participants really know what they signed up to be part of,
- Digital literacy: Different individuals can have difficulties with complicated digital interface: elderly people or individuals with low education level can become burdened with digital interface vandalism

Legal status: Not every jurisdiction acknowledges electronic signatures of a clinical consent on legal basis.

Such issues are particularly pronounced in mRNA oncology trials when the patients are quite susceptible and need to accept personalized, genomics-based therapies. Ethical protections, including interactive educational modules and telehealth-aided consent and independent consent monitors are becoming a mitigative technique, although inconsistently implemented in trials.

3. Information Security and International Governance

- DCTs are strongly dependent on online sites, wearables, cloud and remote data, which produce wide health data streams. Securing, anonymizing and legally utilizing this data is ethically necessary and legally confusing:
- The European General Data Protection Regulation (udpr) places stringent rules on trans-border data transfer and individual rights over information (e.g. right to be forgotten).

International Journal of Advances in Engineering and Management (IJAEM)
Volume 7, Issue 10 Oct. 2025, pp: 195-217 www.ijaem.net ISSN: 2395-5252

- In the U.S., the U.S. compliance with HIPAA should be reconciled with collecting real-time data across a variety of devices and platforms.
- The less developed countries might not have sound cybersecurity measures, and thus the risks associated with exposing patient data become higher when DCTs take place in low-resource locations.

The situation is further complicated by the usage of artificial intelligence (AI) to explain clinical data, causing concerns regarding transparency of algorithms and autonomy patients should enjoy regarding choices.

Summary Table: Key Regulatory and Ethical Challenges

Challenge Area	Specific Issue	Impact on mRNA-DCT Integration
Regulatory Disparities	National variation in DCT laws and permissions	Delays in multinational trial approval
Informed Consent	Ensuring comprehension and digital accessibility	Ethical risks, possible invalid consent
Data Privacy	Cross-border data transfer and cybersecurity	Legal noncompliance, patient trust erosion
AI Interpretation	Use of opaque algorithms in decision support	Ethical transparency and accountability issues

TECHNICAL AND LOGISTIC PROBLEMS

Although there are numerous potential benefits to integrating Decentralized Clinical Trials (DCTs) with mRNA-based therapeutics, this process also brings with it a collection of technical and logistical difficulties that hamper trial continuity, data integrity, fair participation. Such limitations may compromise scalability-especially in multi-site or international/global studies- and they must be resolved systematically in order to optimize the full potential of integrated mRNA-DCT models.

1. RMI Blind Spots

One of the most valued pillars of DCTs is the approach of digital health devices, i.e., wearable devices, biosensors, mobile applications, and telemedicine services, that help assess patient safety and capture efficacy data even when they are not in the clinic. Nevertheless, infrastructure mismatch might also have considerable impacts on the performance of trials:

- Digital Divide: Lack of quality broadband communications, use of smart phones, or digital literacy training is experienced by numerous participants, particularly in the rural or low-income locations.
- Device Compatibility and Maintenance: Not only is it logistically difficult and resource-intensive to make sure that the participants have appropriate devices, but also make sure that they are properly calibrated, updated, and, lastly, use them.
- Real-Time Data Reliability: Device failures, power failure, or software bugs in continuous monitoring may cause data loss or cause delayed safety plans, etc.

Such constraints hold particular influence in the trial of mRNA vaccines in remote or low-resource areas and the power and internet systems might not be able to facilitate the long-term monitoring of patients with real-time data.

2. Standardization of Data and Interoperability

Data-intensive mRNA trials will have features, including non-traditional outcomes, high-throughput genomic sequencing, immunological markers, adverse event reporting, and patient-reported outcomes. DCT models create this information using a wide array of data sources wearable devices, mobile health applications, remote laboratories, and EHRs, making data fragmented.

- Inconsistency with Unifying Industry Standards: Remote trial data does not have a uniform standard that all industries use, there is no easy way to combine and analyze that data across platforms.
- Interoperability Problems: Data in third-party wearables and other telehealth equipment, clinical lab software, and other sources can be difficult to interface with centralized trial management systems.
- Regulatory Misalignment: The formats that are acceptable in one country could be unacceptable to the needs of regulators in

International Journal of Advances in Engineering and Management (IJAEM)
Volume 7, Issue 10 Oct. 2025, pp: 195-217 www.ijaem.net ISSN: 2395-5252

another one, especially when artificial intelligence is involved in the analysis.

These difficulties impair real-timeable data synthesis and cross-trial comparison, essential both to adaptive trial design and assuring similar outcomes in different study arms and sites.

3. Cold Chain and Supply Chain Restraint

Most of the mRNA therapeutics, particularly vaccines, may need to be shipped via a cold chain (e.g., requires freezing to temperature ranges of -20- -80 C), which is in itself incompatible with the home- or community-based delivery models of DCTs.

- Cold Storage Logistics: High level of cold storage equipment, skilled workers, and time-sensitive conveyance facilities are needed to deliver mRNA products to patients in their home and to remote clinics.
- Distribution Reliability: A breakdown in the cold chain provides ineffective product efficacy and patient safety, increase the complexity in trial operation in geographically spread locations.

This is why the best aspect of DCTs and a very promising aspect of direct-to-patient drug delivery is still underutilized when it comes to temperature-sensitive products when studying mRNA.

Summary Table: Logistical and technical Challenges

Challenge	Impact	Category
Remote Monitoring	Lack of digital connectivity, hardware malfunction	Unfull analysis, low patient adherence
Data Interoperability	Broken data format across platform	Reduced speed of analysis with possible protocol deviations
Cold Chain Logistics	Failure to deliver temperature-sensitive therapy	Constrains DTP models, particularly, vaccine trials

COMPLEXITIES SCIENTIFIC AND CLINICAL

The mRNA technologies, however, bring new clinical and biological issues to the area of scientific integration that cannot be simply solved by providing efficient operations, which entails the framework of decentralized clinical trials (DCTs). Contrary to small-molecule medicines, the mRNA-based treatments, including vaccines and cancer immunotherapies, represent inherent scientific barriers, including their unpredictable immunogenic reactions and long-term patient follow-up. These complexities are further compounded when such efforts are carried in the decentralized forms.

1. Variability and Immunogenicity in mRNA testing

One of the fundamental characteristics of mRNA-based therapeutic agent is that they can produce specific immune responses. Nevertheless, the inter-patient variability in immunogenicity is a major concern to those who develop and regulate this process. High volatility may be the result of such factors as:

- Epigenetic and genetic diversity, that influences the way patients process and react towards mRNA constructs;
- Comorbidities, or immunocompromised conditions (e.g. cancer, HIV, autoimmune disorders) that will obfuscate or flatten vaccine responses;
- Variations in the composition, carrier (e.g. lipid nanoparticles) and dosage schedule.

In scenario when these trials are performed under a DCT model, scientists are forced to guarantee superior-quality, real-time biospecimen collection and immunoactivity assessments, the arrangement of which may be logistically challenging when performed remotely. Moreover, correct and consistent shipment of blood and tissue samples based on the cold-chain option is also necessary to maintain the biological integrity at the remotely located sites.

2. Long Term Follow up in Decentralized Contexts

This is the case contrasting with the short periods during which acute conditions are studied, but the case is true in mRNA clinical trials, particularly oncology and prevention of infectious disease, where longitudinal follow-up times extend to 12 months and 5+ years. In the decentralized environments, this raises a number of clinical and operation issues:

- Patient retention: It is hard to maintain long-term engagement when the patients are not physically tied to a trial location. There will be

International Journal of Advances in Engineering and Management (IJAEM)
Volume 7, Issue 10 Oct. 2025, pp: 195-217 www.ijaem.net ISSN: 2395-5252

a tendency of higher dropout rates in virtual models.
- Observing Adverse Events (AEs): the delayed-onset / chronic adverse events (such as myocarditis, autoimmune flares, immune evasion of tumors) need prolonged and complex surveillance tools, which are difficult to build through solely mobile applications and teleconsultation.
- Adherence to Protocol: It goes without saying that it is not very easy to make sure patients adhere to prescribed protocols (e.g., booster dosing schedules, visits to the lab, submission of biosamples), and this is done off-site.

As a way of reducing the above, a few trials have also gone hybrid by incorporating remote monitoring with periodic in-person visits at the satellite sites or local laboratories. Such designs, however, are more expensive and cumbersome and in part can be offsetting the benefits of complete decentralization.

Summary Table: Scientific and Clinical Complexities in mRNA-DCT Trials

Complexity	Description	Implications for DCT Integration
Immunogenicity Variability	Unpredictable immune responses across diverse patient populations	Requires frequent, high-quality biosampling
Long-Term Follow-Up	Need for multi-year outcome tracking and AE monitoring	Challenges patient retention and remote data completeness
Protocol Compliance	Adherence to complex dosing/lab schedules in remote settings	Increased risk of data gaps and protocol deviations

COMPARATIVE OUTCOMES TRADITIONAL VS. DCT MRNA TRIAL PERFORMANCE

The application of Decentralized Clinical Trials (DCTs) in mRNA studies has produced quantifiable trial differences with the tried and tested site-based approach to trials. This section describes four of the important performance metrics: trial speed, cost efficiency, participant retention, and safety reporting through comparative analysis of available research, regulatory reports, and examples of other case studies (e.g., Moderna influenza trials and BioNTech oncology pipelines).

1. Speed and Enrollment Time Trials

The faster rate of recruitment and shorter startup time of mRNA trial has always proved faster and shorter with the use of DCTs as compared to conventional models. This is mostly as a result of:
- Geographic flexibility: Patients no longer have to be physically located in the premises of the physical trials.
- Online recruitment tools: eRecruitment through social media, online health communities and mobile apps can be highly scalable.
- Easier onboarding: eConsent, remote-based screening, and checking the eligibility increase the speed of enrolling procedures.

Example: A trial of a flu vaccine using DCT developed by Moderna was found to have an enrollment 40 percent faster than in a site-based comparator, based on the internal sponsor data published in 2023.

2. Cost Efficiency

DCTs involve an initial outlay of investment in digital instruments and infrastructure (e.g. remote monitoring devices, telemedicine platforms and safe data storage), yet often provide a cost benefit throughout the entire trial life cycle:
- Reduction in the cost of site management (e.g. no leasing of facility, staff reduced)
- Less reimbursement is needed to travel, lodge and time on the part of patient
- Automated data capture that reduces the across manual data entry and cleansing

Reported Trend: A Deloitte review as of 2022 showed that the use of DCT Vaccine trials resulted in a 10-15 percent reduction in operational expenses, and reductions could be even higher on the smaller multi-regional trials.

3. Diversity and patient retention

Diversity and retention can be enhanced in DCT models, especially when doing underserved or remote populations trials.
- Enhanced retention: Patient retention and continuation of the trial can be enhanced because of the fewer travel burdens, open schedule of visitations as well as support at home.
- Expanded demographic: Trials can access demographically diverse populations,

International Journal of Advances in Engineering and Management (IJAEM)
Volume 7, Issue 10 Oct. 2025, pp: 195-217 www.ijaem.net ISSN: 2395-5252

including ethnic, geographic, and socioeconomically diverse populations-required in gaining generalizable efficacy of mRNA.

- BioNTech Case: The oncology pilot study in 2022 by BioNTech, reported a 93 per cent participant retention compared to 80 per cent in similar site-based oncology studies.

4. Monitoring Safety and Adverse Events Reporting

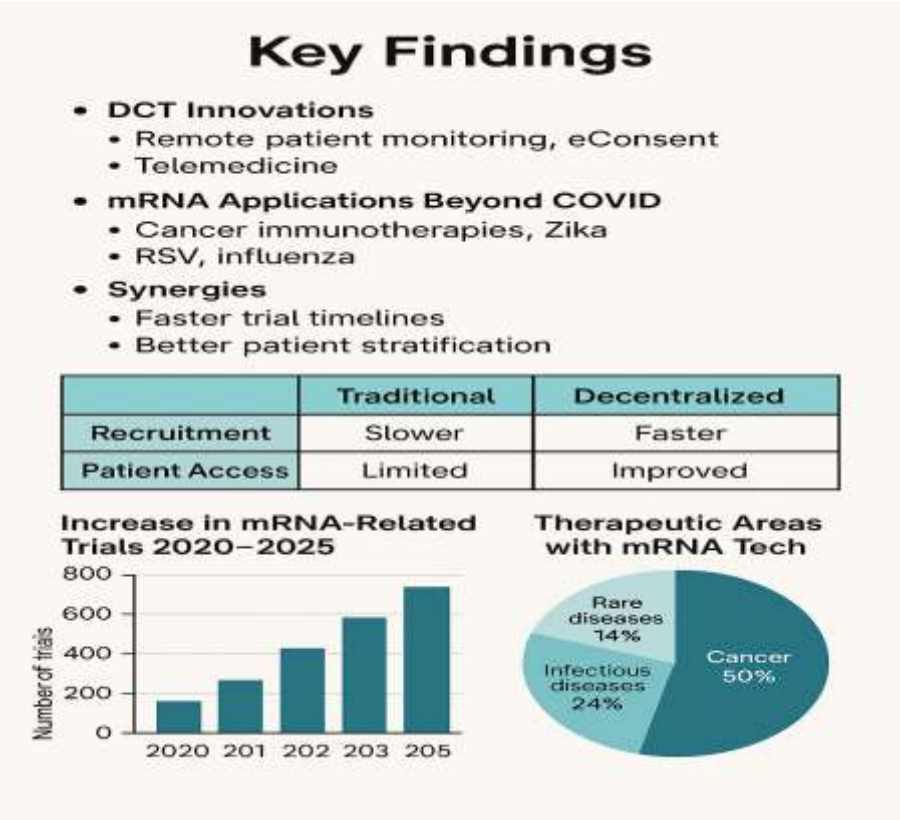
Although DCTs support the reporting of AEs in real time via the use of apps and wearables, they can also have limitations in identifying any minor or late emerging safety issues.

- Advantages: By integration into a wearable, the vitals monitoring (e.g. heart rate, temperature) can be monitored near real-time as well as the assessment of the vaccine response can be assessed early.
- Limitations: infrequent or subjective AEs (e.g. neurological) are unlikely to be reported unless noticed by the clinician.

To handle this, periodic in-person check-ins tend to be introduced in hybrid DCT models so that the findings can be validated and supplemented.

Table: Comparative Performance Metrics of Traditional vs. DCT mRNA Trials

Metric	Traditional Trials	DCT-Based Trials
Enrollment Speed	Slower (site-dependent, 6–12 months)	Faster (digital onboarding, ~30–50% faster)
Operational Cost	High (site leasing, staff-intensive)	10–15% lower (automation, remote ops)
Patient Retention	Moderate (~75–85%)	Higher (up to 93%)
Participant Diversity	Often urban-biased	More geographically and demographically diverse
Safety Signal Detection	Strong for in-person symptoms	Strong for vitals; weaker for subjective AEs



International Journal of Advances in Engineering and Management (IJAEM)
Volume 7, Issue 10 Oct. 2025, pp: 195-217 www.ijaem.net ISSN: 2395-5252

STAKEHOLDER VIEWPOINTS: BARRIERS AND PREDICTED OPPORTUNITIES

The interplay between Decentralized Clinical Trials (DCTs) and mRNA-based therapies is a complex issue, that cannot be viewed through the prism of technology and the operation. These trade-offs and workability of these models can be understood by putting the views of key stakeholders like clinical investigators, trial sponsors, regulators, and the patients. Based on the available published survey data, syntheses of interviews, and industry roundtables (e.g., TransCelerate, CISCRP, reports of industry consultation rounds with the EMA and FDA), this section describes the perceived barriers and opportunities of each group of stakeholders.

1. Pharmaceutical Companies and Sponsors

Perceived Opportunities:

- Operation Efficiency: Site infrastructure costs are minimized with DCTs, and they enable faster go-to-market plans, which is even more capitalized in competitive mRNA environments (e.g. influenza, RSV).
- Real-World Data (RWD): Decentralized tools can sustain patient flow of information and can supplement real-world evidence (RWE) initiatives and post-marketing monitoring efforts.

Perceived Barriers:

- Regulatory Uncertainty: The major factor so cited by sponsors is regulatory dispersion in different regions as a deterrent to the global harmonization of trials.
- Data Integrity Issues: In spite of the many perceived benefits of the digital, sponsors are concerned with data reliability, discrepancies, and protocol violations, and other lack of controls regarding remote data collection.

EMA Roundtable: 2024:

We also like the scalability of DCTs, but mRNA needs close supervision that is also a drawback of its use as close pharmacovigilance cannot be done so the on-site oversight has become an issue. --Senior Clinical Operations director, Pharma Europe

2. CROs and Clinical Investigators

Perceived Opportunities:

- Increased Enrollment: Investigators indicate that DCTs have an increased enrollment, particularly among the rural and minority groups.

Adaptive Trial Designs: Remote models are flexible to adaptive mRNA trials that can be modified, as results are discovered, through interim measurements of immunogenicity or biomarkers.

Perceived Barriers:

- High Complexity: Investigators need to regulate on several digital platforms, organize a remote biosampling and comply with different local laws.
- Decreased Patient-Physician Interaction: Certain clinicians feel that they will lose physical examination data as well, particularly when dealing with subtle safety measures such as oncology or autoimmune mRNA trials.

3. Patients and Participants

Perceived Opportunities:

- Convenience and Access: The majority of patients value the benefit of breaking the travel burden, particularly those with mobility problems or someone who needs to tend to them.
- Increased Autonomy: eConsent, mobile reminders and other tools give patients more power to take an active part in care and decision-making.

Perceived Barriers:

- Tech Literacy and Trust: Elders and low-income respondents say they have had problems with the use of digital tools and are worried about data security.
- Weak Human Contact: Patients who are a part of DCTs occasionally feel that they are isolated digitally and lack the comfort associated with in-person communication.

According to the 2023 CISCRP survey result:

Two-thirds of the participants (71%) requested hybrid or fully decentralized trials but non-trivial proportions of the patients (58%) were concerned with the management of technology on their own.

4. Regulators Policy Makers

Perceived Opportunities:

- Wider Inclusion: Regulators welcome the fact that DCTs may increase trial diversity, which is becoming a requirement of the FDA and the EMA.
- Policy Innovation: New trial designs (e.g., decentralized adaptive platforms) are becoming more acceptable at agencies, especially with pandemic preparedness and rare diseases.

International Journal of Advances in Engineering and Management (IJAEM)
Volume 7, Issue 10 Oct. 2025, pp: 195-217 www.ijaem.net ISSN: 2395-5252

Perceived Barriers:

- Harmonization lags: Global unification on the best practice of DCTs is yet to emerge and this is a principal issue, particularly regarding remote monitoring and information privacy.
- Strengths in the control: The regulators point out challenges in auditing DCT, particularly, when third-party tech providers carry out data transfer and security.

Summary Table: Stakeholder Perspectives on DCT-mRNA Integration

Stakeholder	Opportunities	Barriers
Sponsors	Faster trials, RWD, scalability	Regulatory fragmentation, data fidelity
Investigators/CROs	Faster recruitment, flexible design	Operational complexity, reduced clinical oversight
Patients	Convenience, autonomy	Tech literacy gaps, reduced emotional support
Regulators	Inclusivity, trial innovation	Auditability, lack of global standards

HARMONIZATION OF POLICY AND DESCRIPTION OF REGULATION

With the convergence of decentralized clinical trials (DCTs) and mRNA technologies, the necessity of the international harmonizations of the regulatory frameworks is ever more significant. The present regulatory state is dispersed and there is a massive disparity between the countries and regions with regard to the interpretation and the enforcement of remote component factors, including eConsent, telemedicine, data security and drug shipment. Such asymmetry in regulations poses an insurmountable obstacle to the international scaling of mRNA-DCT models, particularly those with multinational trials in the infectious disease and cancer immunotherapies.

Global Agencies and Variants Standards

Guidance documents of a larger regulatory authority like the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) on decentralized approaches have also been issued, especially post-COVID-19. Nevertheless, they are only non-binding and unaligned, in particular, in the areas of:

- Long-distance patient identification Authorization
- Multijurisdiction Telehealth licensing
- Regulatory submissions acceptance of electronic data sources

Chain-of-custody specifications of an investigational product (IP) delivery

In its turn, the World Health Organization (WHO) has requested the emergence of more inclusive systems to allow the implementation of DCT in low- and middle-income countries (LMICs), with the notion placed on equity of access to new mRNA treatments. However, there has been uneven implementation in Africa, Latin America, and the Southeast Asia regions because of inherent local governing weakness and infrastructure deficits in the regions.

Major Priorities of Harmonization

To liberate mRNA-DCT combinaison potential all over the globe, it will require global troubleshooting in many areas:

1. Digital Identity and eConsent Standards

All borders would allow a more secure and compliant eConsent through a harmonized digital way of identifying patients (e.g., biometric verification, government-issued eIDs). At present the entire world has no common standard that would allow minimization of the dimension of trial activation and consent disputes.

2. Remote Surveillance and Testing

Remote data monitoring and regulatory auditing requires clear international direction. Although real-time clinical data can be provided by decentralized data platforms and wearables, sponsors and regulators should come to a compromise with regard to:

What can be considered as audit-ready remote data;
How is it possible to document the adherence to the protocol without the on-site inspection;

- Admissibility of metadata trails and of records held in the cloud.

There is currently international cooperation between the FDA, EMA, Japan PMDA, and Australia by the TGA, although global convergence remains in its infancy.

3. Telepharmacy Regulations and IP Delivery Regulations

Major requirements of DCTs related to mRNA therapeutics (particularly vaccines or

International Journal of Advances in Engineering and Management (IJAEM)
Volume 7, Issue 10 Oct. 2025, pp: 195-217 www.ijaem.net ISSN: 2395-5252

individualized cancers) include tight serialization and cold-chain management and direct product shipment of the investigational products to patients. The limits given by national governments toward drug deliverance and telepharma cylicensing are extremely different. The harmonized model would necessitate a demand:

- Telepharmacy laws across nationwide borders;
- Normalisation of transport assurance of temperature-sensitive mRNA formulations;
- Effective protocols of emergency management and reporting of adverse events when being administered at home.

Issue On Global Environmental Planning

To correct such inequalities, a few proposals may be utilized, or scaled up:

- ICH GCP E6(R3) updates: The future amendments to the Good Clinical Practice standards are likely to support the idea of remote data collection and decentralized activities.
- International Coalition of Medicines Regulatory Authorities (ICMRA): Has the potential to act as a negotiating platform and an opportunity to coordinate policies.
- Pilot programs in the use of harmonized standards in cross-border trials may be facilitated through the public-private partnership (e.g., TransCelerate, IMI Trials@Home).

The full benefits of decentralized mRNA research cannot be achieved without strong and organized modernization of regulation. However, any future policy work should go beyond the local asseveration of trial ability, bowing toward global harmonization, interoperability, and compliance, as well as patient safety guarantee.

Technology breakthroughs

Regulatory harmonization is not the only aspect that will determine the future of decentralized mRNA trials; it is the technology as well. The best practices include the use of new tools and technologies, artificial intelligence (AI), blockchain, and sophisticated biosensors, that can further improve decentralized clinical operations, the quality of data, and specific interventions on a personalized basis using mRNA. Such innovations have the potential to transform the design, monitoring, and measurement of the mRNA trials in a new era of precision, security, and scalability.

1. AI-powered Trial Design and Digital Twinst

Artificial intelligence (AI) is a trend in making clinical trials easier and better in design and execution. In the scenario of using AI to integrate mRNA and DCT the following major functionalities are possible:

- Patient selection using predictive analytics: by using AI models, electronic health records (EHR), genetic information, and biomarkers, it could quickly be possible to pick the best patient to test mRNA vaccine or immunotherapy in.
- Real-time adaptive protocols: Machine learning allows dynamic trial designs, modifiable with each outcome terminated, which allows the adaptation of the dose or cohort size, even without formal amendments.
- Digital twins: They are digital images of trial subjects that are developed through modeling of in-time physiologic, genomics data. Digital twins will enable safety risks to be mitigated and personalization to be enhanced in mRNA oncology trials by simulating the immune (adverse) response and forecasting dose-limiting toxicity.

Example: Moderna applied AI-based modeling to simulate immune kinetic, dosing response, in influenza and RSV vaccine clinical trials that shortened time-to-development.

2. Blockchain of Secure Data Transfer and Consent

Blockchain technology, characterized by tamper-proof and decentralized infrastructure is increasingly becoming popular in clinical research as a means of:

- Unalterable data files: Ensuring that the information of patients, namely the wearables, labs away and genomic testing, is recorded in materials with evident and time-stamped audit mixed ups.
- Consent management: Smart contracts on the blockchain are able to document, update and validate eConsent interactions in real time, allowing patients to take greater control over the use of their data.
- Cross-platform compatibility: enables safe, de-identified information sharing between sponsor, CROs and regulators, even when trials have a multi-site or multi-nation design.

Asset: Blockchain alleviates the issue of data manipulation and unauthorized access, which is especially critical to trials where sensitive genomic data on mRNA is concerned.

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3. The next-generation wearable bioselectors

Remote monitoring is all about integrating the most sophisticated biosensors with DCT platforms, especially among the high-risk groups in the mRNA trials, like oncology patients and autoimmune patients.

Future capabilities of next-gen wearable are:

Multi-parameters tracking: Not only heart rate and temperature, new devices are capable of measuring blood pressure and oxygen saturation, ECG, and inflammatory markers and analyze interstitial glucose levels.

- Constant data transfer: Combined with 5G or low-power wide-area networks (LPWAN), biosensors are able to transmit live data so safety warnings or clinical judgement can be made in time.
- Miniaturization and biocompatibility: The technology that creates devices tends to be of a discrete nature (i.e., smart patches or Yogi Bear sensors, ingested sensors) that enhance patient comfort and adherence.

Case Example: BioNTech has an oncology study underway, which employs wearable ECG devices and smart rings to monitor immune-associated adverse events in people which go directly to digital dashboards that the physician can observe.

Summary Table: Key Emerging Technologies in mRNA-DCT Trials

Technology	Function	Potential Benefit
AI & Digital Twins	Trial design, patient modeling	Personalized protocols, faster dose optimization
Blockchain	Data security and consent tracking	Transparent, immutable, patient-controlled data records
Wearable Biosensors	Continuous remote health monitoring	Improved safety, real-time intervention, better retention

ACHIEVING MORE ACCESS AND EQUITY

The need to ensure equity and inclusivity is always an urgent necessity in the advent of mRNA technology and decentralized clinical trials (DCTs). Underserved groups are historical excluders in clinical research, such as racial and ethnic minorities, rural populations, and people living in low- and middle-income countries (LMICs). With a growing trend toward digitization and individualization of healthcare, the inability to overcome these disparities threatens to expand health disparity around the world and narrow the reproducibility of the trial outcomes.

DCTs- as long as they are not thoughtlessly put into place- possess the potential to democratize contribution to leading-edge mRNA research within the aspects of geographic, logistical, and financial obstruction. This part talks about the increasing access, the persisting difficulty and the implementation tactical that is conceivable to put up global trial capacity.

1. Incare of Underserved Populations

The main problem of traditional clinical trials has always been diverse and limited inclusion of participants because of the urban locations of trials, the physical presence of people and local infrastructure. Decentralized designs provide a number of means to turn around this tendency:

- The remote enrollment and the eConsent enables a wider participation of the populations that are rural and homebound.
- Telemedicine and multilingual digital interface can help to lower linguistic, and cultural barriers.
- Sample collection kits that can be used at home and local laboratories cut down the travel expense, particularly in chronically ill or disabled patients.

Impact Example: Influenza Vaccine Trials (Moderna): The trial of the decentralized model of influenza vaccine conducted by Moderna was associated with a 30 percent rise in the involvement of racial and ethnic minorities in the United States over the previous site-based models.

2. LMICs and mRNA Trials/DCTs

Most trial activity in mRNA to date has focused on high-income geographies but there is developing pressure to expand both mRNA trial infrastructure and mRNA therapeutic pipeline into LMICs. This is informed by need of science (e.g. burden of endemic diseases) as well as global demands of equity.

Opportunities:

- The application of decentralized tools (e.g., mobile health apps, solar-powered biosensors)

allows performing trials in distant places or infrastructurally poor regions.
- Collaboration with local educational institutions and non-governmental organizations can integrate trials into a health system of care delivery.

Areas of disease targets of importance to mRNA expansion include Zika, malaria and HIV that disproportionately affect LMICs.

Barriers:
- Low internet access and smartphone/internet mind infiltration
- Lack of regulation or regulation/alignment with international regulations
- Poor digital health literacy among certain groups of people

Case Example: In South Africa and Kenya, academic consortia have conducted pilot studies on decentralized mRNA vaccine research employing community health workers to collect data using digital platforms in the field, which proved to be possible and cost-effective.

II. CONCLUSION

The combination of the decentralized clinical trials (DCTs) and mRNA technology is a breakthrough in the future of biomedical research. Fuelled by the exigency of the COVID-19 pandemic, both paradigms have morphed to being both experimental and even vital. The paper has addressed the fast innovation, how the operation has been restructured, and international collaboration that has characterized the new research frontier.

DCTs are the new face of clinical trials since they provide more flexibility, inclusivity, and patient-pronomen, which is made possible by technology, including telemedicine, eConsent, remote monitoring, and AI-aided trial design. Simultaneously, mRNA platforms, initially concentrated on COVID-19 vaccines, are diversifying into oncology, infectious diseases, autoimmune diseases and rare diseases, at unprecedented speed and scale.

This mingle has already indicated potential results in the form of accelerated recruitment, increased inclusiveness of the underserved communities and decreased trial costs, with no safety or data quality trade-offs. The enormous advantages of the combination of these two innovations can be seen through the example of two case studies airing Moderna and BioNTech and academic-led experiments. In parallel, there are still major issues to address, such as splintered regulatory policies, technical constraints, and ethical challenges, especially the privacy and fair access to data.

In the future, the future of decentralized mRNA research will rely on some few key factors:
- International regulatory harmonization of policies (e.g. FDA, EMA or WHO)
- Investing on the new promising technologies like AI, blockchain, and next-gen biosensors
- Development and capacity building of low- and middle-income countries infrastructures
- Pledge to equity and inclusion during trial creation, access and data control

After all, not only could the combination of DCTs and mRNA platforms allow scientists to work much faster, but it would also have the potential to revolutionize the way--and to whom--medicine is being made. It provides a roadmap to developing a more mobile, available, and cross-domain integrated clinical research ecosystem that is 21 st century appropriate.

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