Volume 14 Issue 6

JCS
Journal for Clinical Studies

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mRNA Vaccine Applications in Global Health
Promise and Challenges

Taking a Long-Term Approach to
Improving Vaccine Trial Recruitment

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PUBLISHED BY
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Email: info@senglobalcoms.com

www.journalforclinicalstudies.com

Journal by Clinical Studies – ISSN 1758-5678 is published bi-monthly by Senglobal Ltd.

SENGLOBAL

Volume 14 Issue 6 December 2022
Senglobal Ltd.

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Foreword

The festive season is drawing ever closer and here at JCS, we are thrilled to bring you our sixth and final issue of the year!

In the past few years, there has been increasing focus on the use of messenger RNA (mRNA) as a new therapeutic modality. Current clinical efforts encompassing mRNA-based drugs are directed toward infectious disease vaccines, cancer immunotherapies, therapeutic protein replacement therapies, and treatment of genetic diseases.

The global COVID-19 pandemic has focused intense attention on the potential benefits and continuing challenges of vaccine development. In the twentieth century, a large number of important vaccines were developed empirically, without clear understanding of molecular immunology. Mass vaccination with these products successfully eliminated the scourge of smallpox, and greatly reduced and contained the global burden of other diseases such as measles, pertussis, chicken pox, and polio. **Daniel Kavanagh at WCG** outlines the promises and the challenges of mRNA vaccine applications in global health.

Quality healthcare outcomes depend upon patients' adherence to recommended treatment regimens. Patient nonadherence can be a pervasive threat to health and wellbeing and carry an appreciable economic burden as well. In some disease conditions, more than 40% of patients sustain significant risks by misunderstanding, forgetting, or ignoring healthcare advice. While no single intervention strategy can improve the adherence of all patients, decades of research studies agree that successful attempts to improve patient adherence depend upon a set of key factors.

These include realistic assessment of patients' knowledge and understanding of the regimen, clear and effective communication between health professionals and their patients, and the nurturance of trust in the therapeutic relationship. Poor adherence to the investigational product can bring even the most carefully planned clinical trial to its knees. It is time to accept that traditional approaches such a pill count do not work. **Bernard Vrijens at AARDEX Group** shows the need to upset the status quo by embracing the potential of modern medication adherence management.

In this journal, we will also explore more about the Impact of Electronic Signature towards Clinical Trial Agreements. The use of electronic signature is desirable for companies nowadays as technology has growingly become an integral part of our life. Not only that, implementing it can reduce the turnaround time and ensure business efficiency. Electronic signature is defined as a set of symbols or other data in digital form attached to an electronically transmitted document as verification of the sender's intent to sign the document. **Heidi Nai Soraya Roslan, Siti Nuralis binti Abd Muis and Nurul Atiqah Binti Abd Rahman at Clinical Research Malaysia** show the impact of Electronic Signature towards Clinical Trial Agreements.

I hope you all enjoy your festive season and I look forward to welcoming you back in the new year, with more enthralling articles to be included in JCS.

Beatriz Romao, Editorial Manager
Journal for Clinical Studies

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Recent FDA Advancements in Rare Diseases – Funding, Partnerships, and Programs

Paucity of therapeutic choices is a reality often acknowledged by the US Food and Drug Administration (FDA) as it reviews applications for new medical products or expansions to approved indications. This is especially true in the case of rare diseases, the majority of which lack any approved treatments. The FDA continues to emphasize the importance of promoting medical product development for rare diseases, including actions taken within the past few months.

"One of the greatest obstacles facing individuals who suffer from rare diseases is the limited treatment options currently available," said FDA Commissioner Robert M. Califf, MD, in a statement issued in October 2022.[1] The agency announced that it had awarded 19 new grants and two new contracts totaling more than $38 million in funding over the next four years to support clinical trials, natural history studies, and regulatory science tools related to rare diseases.

These grants and contracts were funded by the FDA's Orphan Products Grants Program.[2] The agency received 33 clinical trial grant applications, of which 11 were chosen to receive funding (more than $25 million) over the four-year period. Seven of the awards fund studies of rare cancers, largely targeting cancers of the brain and peripheral nerves:[3]

- Phase 2 study of multi-tumor–associated antigen-specific T-cell therapy (MT-401) for the treatment of relapsed/refractory acute myeloid leukemia (AML) patients following allogeneic stem cell transplant.
- Phase 1/2 study of ^{177}Lu-DOTATATE for the treatment of recurrent/progressive high-grade central nervous system (CNS) tumors and meningiomas that express somatostatin type 2A receptors.
- Phase 2 study of ASTX727 (combination of decitabine and cedazuridine) for the treatment of malignant peripheral nerve sheath tumour.
- Phase 2 study of palbociclib (CDK4/6i) plus INCMGA0012 (PD-1 blockade) for the treatment of well-differentiated or dedifferentiated liposarcoma.
- Phase 2 study of SONALA-001 sonodynamic therapy for the treatment of diffuse intrinsic pontine glioma.
- Phase 2 study of neoantigen-specific adoptive T-cell therapy for the treatment of glioblastoma.
- Phase 1 study of RNA-lipid particle vaccines for the treatment of newly diagnosed glioblastoma.

Among the 43 natural history grant applications received by the FDA, eight were chosen to receive more than $11 million over the next four years.[3] Three of the selected natural history studies are related to rare neurodegenerative diseases: 1) a retrospective and prospective study in amyotrophic lateral sclerosis (ALS) of clinic-based multicenter data collection, 2) a prospective study in ataxia-telangiectasia, and 3) a prospective study in myotonic dystrophy type 1 to establish biomarkers and clinical endpoints. These studies serve to meet a requirement under Public Law 117-79, the Accelerating Access to Critical Therapies for ALS Act (ACT for ALS),[4] signed into law in December 2021, for the FDA to award grants or contracts to public and private entities to cover costs of research on and development of interventions intended to prevent, diagnose, mitigate, treat, or cure ALS and other rare neurodegenerative diseases in adults and children.

The two contracts that received funding are also related to rare neurodegenerative diseases. One contract, co-funded by the US National Institutes of Health (NIH) and the FDA, will study whether a physical assessment of ALS patients, usually performed in a healthcare professional's office, can be done remotely at home to minimize patient burden. The second contract is a landscape analysis of patient-preference information studies focused on brain-computer interface (BCI) devices. For this analysis, the FDA is interested in BCI devices that communicate with the brain and provide patients who are no longer able to speak or move with the ability to interact with their families and healthcare professionals.

Research in the area of rare neurodegenerative diseases was bolstered earlier this year when the FDA unveiled its Action Plan for Rare Neurodegenerative Diseases including Amyotrophic Lateral Sclerosis (ALS)[5] in June. Developed in accordance with provisions of the ACT for ALS, the five-year strategy aims to improve and extend the lives of people living with rare neurodegenerative diseases by advancing the development of safe and effective medical products and facilitating patient access to novel treatments. An element of the plan is the ALS Science Strategy, which provides a "forward leaning framework" for FDA activities to evaluate key regulatory science priorities. The focus areas of the ALS Science Strategy relate to characterisation of disease pathogenesis and natural history; patient access to treatments and participation in clinical trials; and clinical trial enhancements (e.g., optimisation of trial design, reduction of development costs).

An additional development relating to rare neurodegenerative diseases occurred in September 2022, when the FDA and the NIH announced the launch of the Critical Path for Rare Neurodegenerative Diseases (CP-RND).[6] A public-private partnership, CP-RND is aimed at advancing the understanding of neurodegenerative diseases and encouraging the development of treatments for ALS and other rare neurodegenerative diseases. Said the FDA's Chief Medical Officer, Hilary Marston, MD, MPH, in the announcement, "There is a crucial need to develop new treatments that can improve and extend the lives of people diagnosed with rare neurodegenerative diseases, including ALS. Collaboration across public and private sectors can accelerate the progress to address this urgent need."

Endpoints for Rare Diseases

In October 2022, a notice published in the *Federal Register* announced that the FDA is establishing a Rare Disease Endpoint Advancement (RDEA) Pilot Program to support novel endpoint efficacy development for drugs that treat rare diseases.[7] The RDEA Pilot Program fulfills a commitment under the seventh iteration of the Prescription Drug User Fee Amendments (PDUFA VII), which required the FDA to establish a pilot program for the development of novel efficacy endpoints in rare disease drug development programs for sponsors with an active investigational new drug application (IND) or pre-IND for the rare disease or sponsors who do not yet have an active development program but have, or are initiating, a natural history study where the proposed endpoint is intended to be studied.

Via the pilot program, which will run through September 30, 2027, selected sponsors will have the opportunity for increased engagement with FDA experts from the Center for Drug Evaluation and Research (CDER) and/or the Center for Biologics Evaluation and Research (CBER) to discuss novel efficacy endpoints intended to establish substantial evidence of effectiveness for a rare disease treatment. The program includes a series of focused meetings between sponsors and the FDA.

Although the FDA stated that it "welcomes RDEA proposals related to any eligible novel endpoint for a rare disease," it will give preference to proposals that 1) have the potential to impact drug development more broadly (e.g., use a novel approach to develop an efficacy endpoint or an endpoint that could potentially be relevant to other diseases); 2) reflect/impact a range of different types of endpoints; and 3) for surrogate endpoints, those that use novel approaches for collecting additional clinical data in the pre-market stage to advance the validation of these endpoints. The FDA will begin accepting proposals on a quarterly basis for admission into the RDEA Pilot Program on July 1, 2023.

In his prepared remarks for delivery at the Rare Diseases and Orphan Products Breakthrough Summit, hosted by the National Organization for Rare Disorders (NORD) on October 17–18, 2022, Califf emphasized the importance of engagement and collective work in the field of rare diseases, including collaboration among patients and their advocates, representatives of industry, government, researchers, academia, and many other stakeholders. "Only through these collaborations can we develop efficient and respectful approaches to the necessary clinical trials to sort through treatments and quickly identify those that turn out to be effective while getting rid of ineffective or dangerous treatments,"[8] he stated.

Regarding the rare disease space, Califf noted that the FDA is working "to embrace greater regulatory flexibility to help meet unmet medical needs." Rare diseases require "a unique balance between regulatory flexibility and the scientific evidence necessary to ensure that a product is safe and effective," he said. An example of regulatory flexibility in the context of a rare disease is to accept clinical trials that have lower sample sizes. Califf stressed that any such an approach would not compromise the integrity of the results. Rather, these approaches "are designed and intended to help generate more high quality evidence that could support a drug approval." Any decisions "will be based on the best available science," he said.

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Impact of Electronic Signature Towards Clinical Trial Agreements

The use of electronic signature is desirable for companies nowadays as technology has growingly become an integral part of our life. Not only that, implementing it can reduce the turnaround time and ensure business efficiency. Electronic signature is defined as a set of symbols or other data in digital form attached to an electronically transmitted document as verification of the sender's intent to sign the document.[1] It is a form of technology which allows you to sign a document via online. The legal definition of it is governed under Section 5 of the Electronic Commerce Act 2006, Malaysia (ECA 2006) where it states that 'Electronic Signature' is defined as any letter, character, number, sound or other symbol or combination thereof created in electronic form adopted by a person as a signature. And pursuant to Section 7 of the ECA 2006 a contract formed in accordance with the Contracts Act 1950, Malaysia through electronic communication is valid, binding, and enforceable by and on the contracting parties. In practice, most documents can be signed by form of electronic signatures however this is usually based on the discretion of the contractual parties.

Clinical Trial Agreements can be Signed Remotely

Traditionally, Clinical Trial Agreements (CTAs) were signed by way of wet ink as this is the most common method used to execute agreements. However, the COVID-19 pandemic has taken a toll towards how normal processes are usually managed. The impact of advanced technology in the world of signatures which is known as 'E-signatures' has paved a way for CTAs to be signed in a much convenient way as implementing electronic signatures can eliminate the need for the contractual parties to physically post the documents to sites which in effect will make the whole execution process more cost-saving. Not only that, but the signing parties can also sign the CTAs anywhere and they are able to use any type of electronic devices which the electronic signature software is compatible with.

Expedite the Number of Days to Execute CTAs

Previously, it took more time for sites to sign a CTA, sometimes it could take several weeks for it to be executed. There are many possible factors which could affect the delay however the primary factor of it could be that the contractual parties are in different locations, so it takes a long time to complete the execution process as the CTAs must be posted to different places. However, with the implementation of electronic signature, the agreement can be signed promptly, and this could also avoid the risk of the agreements being lost during delivery as lost paper documents necessitate starting the signing process over again and this may increase the chance of legal liability.[2] In results, this could improve the start-up timeline of the CTAs which could be a driving factor for sponsors to do more clinical trials.

Minimise the Risk of Unauthorised Signing and Error in CTAs Execution Process

Utilising electronic signature in CTAs would help to minimise the risk of unauthorised execution of CTAs, especially when an electronic signature platform or software are used. This is because, most of electronic signature platform offers multiple options to verify the signatory's identity before they can sign the agreement, for example the signatory would have to enter a one-time passcode sent via text message or insert one time passcode provided by sender.

Besides that, this electronic signature platform provides certificate of completion of signatory, and they have an encryption software that able to verify the signatory's identity and provides an audit trail which is a digital log that archives when and where a document was viewed, signed and by whom it was signed[3] with real date and time stamp captured including the IP address of the signatory. This helps to verify the signature made in the CTAs where we could trace it back to the signatory and further this audit trail capability provides secure verification to fight against fraud as it is much harder to forge the signature since it can easily track the user IP address. Thus, this increased the evidential weight to the electronic signature process.

Further, through this electronic signature's platform, which can automatically detect even a minor altering,[4] we could easily identify and detect if there are any changes made by any of the parties prior to the signing as there is a record for any changes made to the agreement during or after signing.

Besides that, through the electronic signature platform, it helps us to identify any error made in signing of the agreement for example, it can detect when the signatory did not sign on the required intended part, inadvertently missed any required signature or even when it comes to the duplication of signature.[5] From this setting, we would be able to avoid any negligence or human error in the signing process and this will prevent the parties from having to send or post the CTAs again for re execution due to such error. This proved that using electronic signature will help to lessen and reduce the dispute arise concerning the authenticity and error in the execution process.

Maintain the Confidentiality of CTAs

Utilising electronic signature in the execution of CTAs is safe and secure as it provides a stringent level of security in order to maintain the confidentiality of data. Most electronic signatures platform use world-class security software and hardware to protect the physical integrity of electronic signature, all associated computer systems and networks that process customer data.[6]

This electronic signature platform comes with built in security protocols implemented in order for the parties to securely send, receive, store the electronic agreements and safeguards the data that are stored in their systems.[7] This built-in security protocol able to maintain the confidentiality of information in the CTAs. Moreover, most of the electronic signature software for example DocuSign is in compliance with applicable industry standards, laws, and regulations that governs the digital transaction and electronic signatures which

includes ISO 27001:2013, an internationally recognised specification for an Information Security Management System.[8]

Better Recordkeeping of CTAs

By practising electronic signature, a better record management can be achieved. First of all, we are all aware that not every business has adequate storage space, and because working from home has become the norm, not everyone may have access to physical copies of the executed CTAs. Hospitals are also dealing with the same storage problem, particularly in government hospitals where patients take up a lot of space. Additionally, it is quite common in today's business world, particularly in large multinational pharmaceutical companies, for the contract manager or legal counsel to be located overseas; therefore, by using an electronic signature, the contract manager or the legal counsel would have quick access to the document in question. As such, with having electronic signature for the CTAs the same can be stored in common folder or shared drive where people who have the right to access can do so anytime and anywhere, they wish to. However, it should be highlighted that the record of the electronically signed CTAs should be made at the moment of the transaction or incident to which it pertains, or shortly thereafter, by people with first-hand knowledge of the facts, or using tools that are typically used by the company or organization to accomplish the transaction.

Secondly, because electronic storage is more durable, it can assure that the CTAs' signatures remain visible and traceable for many years to come. This is due to the fact that storing physical copies may cause the wet ink signature to fade over time, preventing parties from exercising their rights when the time comes. Some clinical trials can last for several years, and some claims can be filed by a claimant even after the clinical experiment has physically ceased. Physical wet ink copies may potentially be lost in the event of a fire, flood, earthquake, or other uncontrollable force majeure event.

Thirdly, electronic storage of the electronically signed CTAs can aid in document verification. The electronically signed document will include a signature certificate that identifies the signatory, verifies the legitimacy of the digitised signature, and specifies the exact date and time the signatories signed the agreement.[9] With this, the integrity of the record is being complete and consistent provided always that the electronic storage via shared folder, OneDrive or any company's platform are made timely as mentioned above.

Conclusion

It is crystal clear that electronic signature practices will certainly benefit CTA parties. Accelerated timelines for completing CTAs execution will allow parties to start clinical trials as soon as possible, wherever they wish, without undue delay. Electronic signatures reduce the risk of losing physical documents or error in signing, and the confidentiality of contracts is protected by the practice of electronic signatures. In terms of recordkeeping, since the CTA is a very important legal document in clinical trials, an electronic record of the CTA with an electronic signature is a better choice.

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Taking a Long-Term Approach to Improving Vaccine Trial Recruitment

The groundbreaking mRNA technology used in the COVID-19 vaccine has potential applications in preventing a number of other infectious diseases and is ushering in a wave of new vaccine development. At the time of writing, there are over 1,700 active vaccine trials found on clinicaltrials.gov. In our own practice at Accellacare, we've experienced a sharp increase in the number of vaccine trials we're supporting; we estimate that we're recruiting for 30 percent more trials today than in the pre-COVID era. Covid-19 also highlighted the need to increase diversity in clinical trials for equity and also to ensure that the vaccines have been tested in appropriate subgroups. This has heightened the need for finely tuned recruitment strategies.

At the same time, the public's experience with COVID-19 vaccines has led to a degree of "vaccine fatigue and hesitancy" that makes recruitment for vaccine trials challenging, over and above the growing competition for participants. There are, however, a number of strategies and tactics that have proven successful in reaching potential participants, educating them on the value of vaccine research, and motivating them to take part.

Numerous Factors at Play

Enrolling participants into clinical trials for vaccines is challenging for several reasons.

First, there's simply a greater demand for the eligible pool of participants, and enrolment periods are typically short. Not only are there more studies, but studies are also larger; it is not uncommon to seek 20,000 to 25,000 participants per trial. Plus, participants should represent the target population in all of its diversity. The US Food and Drug Administration (FDA) encourages drug sponsors to ensure that "people of different ages, races, ethnic groups, and genders are included in clinical trials."[1]

Second, factions of the public have questions about the new technology used in the COVID-19 vaccines and the apparent speed with which they were developed. The political climate – coupled with misinformation and disinformation about the virus, treatments, and the vaccines – has fuelled vaccine hesitancy and polarised people. And a pre-existing mistrust of the medical community in some demographic groups has made matters worse.

Third, the public has been exposed to a glut of vaccine-related news for nearly three years. A Google search for "vaccines" netted 3.5 trillion results. Yet, ironically, it seems that the public is largely unaware of the risks posed by the many other non-COVID diseases (such as respiratory syncytial virus (RSV)) on which vaccine research is being conducted.

Multi-level Solutions

The traditional methods of recruiting participants – connecting with investigators and employing digital media to reach potentially interested/eligible people – are no longer sufficient. These pre-pandemic tactics must be augmented with initiatives at the community, site and individual participant level.

Build Relationships within the Community

If we are to overcome vaccine hesitancy, the public must come to trust the research community and to understand the research process. Long before the start of any study, sites and site networks need to be engaged within their communities to develop relationships and demonstrate being trusted partners who will be around for the long haul. Sites can, for example, offer value to the community by holding general health screenings, mental state exams, blood pressure or diabetes screenings, and increasing access to healthcare. Sponsoring community organisations and events at the senior centre, children's sporting events, and church activities are all ways of connecting to potential participants.

Accellacare has pursued this approach with success. To mark the grand opening of a treatment centre on a busy urban street, we sponsored a food truck over the lunch hour and gave tours of the clinic. Over 200 people attended, with 140 opting into a database of interest in clinical trials. The cost of acquisition per name was calculated at just $40 – far less than the cost associated with digital advertising campaigns and enabling us to have a more targeted approach to recruitment.

Educate the Public

Sustained information campaigns at various levels can help to counter disinformation and misinformation by providing factual material on diseases, and the risks/benefits of trial participation as part of this.

Public service announcements (PSAs) explaining the value of vaccines and the indications they prevent would be valuable in raising the public's awareness of, and appreciation for, vaccine research. Year-round advertising and community outreach sponsored by the pharmaceutical industry and clinical sites could supplement these PSAs. The messaging and imagery, however, needs thoughtful consideration with regards to each community's specific concerns and be sensitive to cultural differences.

To address questions about clinical research and to dispel their fears of the investigational process, sites, sponsors and CROs could commit to sponsoring educational programs about the role of clinical research, accomplishments, and what participation entails. Again, this is a tactic that Accellacare has used successfully. We've held seminars for members of the public who meet basic study inclusion criteria to convey general information about clinical trials as well as trial-specific details. Attendees were encouraged to bring a friend, to extend the outreach and were given an opportunity to tour sites and meet clinical teams, removing fear of the unknown.

Communicate with Participants/Potential Participants

To build relationships, site staff should engage in open, interactive communication with participants, answering questions and validating their concerns. Conducting surveys with participants to better understand concerns with the goal of constantly improving relations can reveal important patient insights. Also, it's advantageous for the site to maintain connections with prospective participants. While they may not initially be interested in participating in vaccine studies, they could change their minds. What's more, they may have an interest in studies in other therapeutic areas or may be open to referring a friend.

Figure 1: Sample Diversity Strategy

Striving for Diversity

Increasing the diversity of study participants cannot not be tackled one study at a time, but rather should stem from a broad commitment that will improve diversity within all studies. Figure 1 displays the four phases of a well-developed strategy for expanding trial diversity: assessing the baseline state, gathering insights from participants/patients, taking active steps to support diversity and measuring and reporting on progress against the baseline.

In following this strategic approach, Accellacare conducted focus groups among Black and Latino communities to gain insight into their current understanding of clinical research, motivation and hesitation around participating, as well as into their sources of information. Based on the findings, we developed a patient partnership program featuring patient navigators who help build collaborative and sustainable relationships in the community. Specifically, they identify outreach opportunities for us, preview our marketing materials and represent us at community events.

Developing and Measuring the Recruitment Plan

A good participant recruitment plan is foundational to enrolment success and should encompass both resourcing needs and accountabilities.

The first step is to analyse historical data from analogous trials, examining no-show rates, not-eligible rates and not-interested rates. These should be calculated by month, weekday, and around holidays to identify patterns in the data. (See Figure 2.) Next, the logic derived from the historical data should be used to model enrolment rates for the upcoming trial. This exercise will reveal when peak enrolment and enrolment delays could be expected – insight that can be used in resource planning.

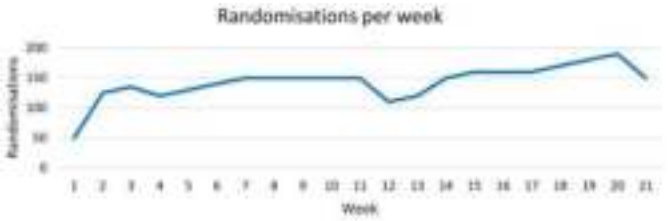

Figure 2: Historical Randomisation Trend

Once the plan is enacted, the team will be able to measure success against established key performance indicators (KPIs) such as the number of leads obtained, enrolments per site, and enrolments against diversity targets.

Conclusion

The current challenges in recruiting participants for vaccine studies can't be overcome simply by relying on traditional means of outreach and advertising. Helping people overcome their vaccine fatigue and/or hesitancy will take a concerted effort on the part of sponsors, CROs and sites. By striving to become trusted partners in the community, building and maintaining relationships and keeping the lines of communication open, researchers can expect to access a wider pool of potential participants.

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Dinah Knotts-Keeterle

Dinah has been working in the clinical research industry for more than 25 years and in her current role is leading the Accellacare Site Network for North America. She started her career working at University Park Research Centre as a study coordinator and then moved to the CRO side as a CRA and progressed in various study leadership roles. She moved to Sarah Cannon Research Institute as Director of Clinical Operations, working closely with the site network on both sponsor and investigator initiated trials. Dinah has been at ICON for more than 11 years and has held many leadership roles across multiple therapeutic areas including oncology, cardiovascular, rare disease, vaccines, dermatology, CNS and gastrointestinal. She has over 5 years' experience leading and overseeing the operational delivery of large Tier 1 partnerships with the largest having over 75 active studies and achieving over $300 million in new awards. Dinah led the operational delivery of the first Pfizer COVID vaccine study with over 48,000 subjects enrolled, receiving Emergency Use Authorisation in an unprecedented 247 days and full FDA approval in record time. Dinah holds a BA in Mathematics from Purdue University and Post Graduate Diploma in International Business Management, University College of Dublin, Michael Smurfit Graduate Business School.

Nazneen Qureshi

Nazneen Qureshi is the Director of Patient Recruitment at Accellacare, where she oversees all patient engagement and recruitment activities for the US. She is committed to developing a patient centric framework as she builds the centralised marketing and recruitment function - with focus on driving engaged, motivated participants and advocates for clinical research. Qureshi has over 10 years of experience in patient recruitment and was the recipient of the SCRS 2017 Site Patient Recruitment Innovation Achievement Award.

Improving Clinical Study Publishing Success

Academic publishing is highly competitive, and this competition is only growing as more and more research papers are being submitted to top journals – submissions to Elsevier alone were up by around 270,000 in 2020.[1] To get published in a scientific journal, researchers must not only focus on their research quality but ensure their work is presented effectively, including images, references, and writing style, and is in keeping with journal-specific requirements. To ease some of this pressure on authors, artificial intelligence (AI) is being used to enhance academic writing and get manuscripts up to the high standards expected from journal editors and peer reviewers.

Clinical study research is critical for the future of science but it is equally important to publish your work in prestigious journals. This is important to communicate your findings to the academic community and the general public, which in turn helps advance global science. However, scientists don't generally go into research careers due to a love of manuscript writing.

According to Kazuhisa Takahashi in his paper Pleasure of discovery: why we love research, "It is simply because the process itself is delightful. This is especially true in medicine, as research can lead to the well-being of the people. At the same time, the experience of research also enriches the life of the physician".[2]

Scientists are passionate about and are typically enthralled by their research, whether it's designing experiments, observing results or testing hypotheses. Collecting data and seeing the results of an experiment right in front of you is arguably one of the most exciting aspects of research.

Overall, most people tend to prefer performing the research rather than writing about why and how they did it. Despite the desire to showcase their results, many researchers actually find writing about their research findings a 'necessary evil' – a tedious task that often involves trying to avoid the dreaded writer's block and spending many hours in writing multiple drafts.

Barriers to Publishing

It doesn't help that getting published in an industry leading publication is no easy feat. In her paper Rejection Blues: Why Do Research Papers Get Rejected?, Suvarna Satish Khadilkar points to how many high-tier academic journals have rejection rates of around 80%.[3] The paper also highlights the main reasons for rejection, such as weak research hypothesis, incomplete or inconsistent data, references that don't match the journal style, and poor language with spelling and grammatical mistakes.

This goes to show that despite being an expert researcher with extensive knowledge in a particular field, it does not guarantee your ability to deliver a well-produced manuscript. Technical and academic writing is an art that must be learnt and perfected. The problem is that most academic training does not focus on this critical aspect of being a researcher. Instead, courses often focus on developing specific research practices like quality data collection, methodology, and analysis. While these are valuable skills that address many of the common reasons for rejection listed in Khadilkar's paper, academics can be left without the necessary writing skills required to produce a compelling manuscript.

This means that one of the main barriers to publishing a scientific manuscript for many researchers is the quality of the language in their papers. Developing writing skills and optimising the language before journal submission can reduce the likelihood that a researcher's paper will be desk rejected by the editorial team, which also increases its likelihood of progressing to peer review and eventual publication. It's possible that many of the errors resulting in rejection could have been identified in the early stages of writing if researchers had used a sophisticated AI English editing tool.

AI in Clinical Science

According to Deloitte's life sciences digital innovation survey, 76% of the respondents are currently investing in AI for clinical development.[4] When discussing AI in clinical studies, it's often regarded in terms of improving research quality and accelerating clinical trials. In reality, researchers can use AI at every step of the research process, from conducting trials to collecting data and even manuscript writing, to overcome traditional barriers to publishing.

As a result of technological innovation, emerging AI tools can now help researchers develop several areas of the manuscript writing and journal submission processes. For example, Clarivate Analytics recognised the problems faced by academic journal editors and integrated AI into the editorial workflow. The AI software helps publishers connect with researchers to make sure content is peer-reviewed, published, marketed, and cited by the right audiences. The software allows publishers to access their journal's performance, manage workflows, and find reviewers.

Proofig is another AI software designed to help researchers by automatically scanning all images included in a research paper. The software checks each image against itself and other images in the paper, looking for any anomalies that might be caused by duplications. Researchers and publishers can use the final report to resolve any issues before it is seen elsewhere. This prevents journals from being forced to make retractions due to small mistakes that could likely be missed by the human eye.

"Computers work harder, faster, and more accurately without tiring, making it much easier to detect image issues like size, location, orientation, overlap, partial duplication or any combinations of these," explained Dr. Dror Kolodkin-Gal, Founder of Proofig Ltd.

AI in Manuscript Writing

AI-powered language and English editing tools can improve both the overall manuscript preparation experience and researchers' confidence in their work. Emerging technology can support researchers by helping them overcome basic spelling, grammar, and language issues, thus enhancing the chances of your paper being accepted by a journal's editor. English editing and writing tools like Paperpal are based on robust AI algorithms that refer to millions of

scientific research papers to determine patterns and assist with tasks such as language editing and technical checks.

Many software tools on the market use deep learning models to detect mistakes in citations, stylistic issues, and science-related language problems. Some AI applications even offer quality scores before and after manual editing to evaluate the proficiency of copyeditors.

While AI writing tools have been around for a while, and are relatively easy to find with a quick Google search, many of them cannot be tailored to a specific expert's industry or subject. Academics using these universally known tools may not find it as effective as they do not receive corrections or recommendations based on their specific discipline or subject area. While these tools can identify minor grammatical errors, they're unlikely to offer researchers more complex editing improvements. Without highlighting these areas of development, it's difficult to instill confidence in a researcher's writing skills and increase their chances of getting accepted by top journals.

Real-time AI assistive writing tools can reduce such issues by assisting authors and giving them the opportunity to develop their writing skills for future papers. To help researchers improve their chances of catching language errors early on, Paperpal analysed 2,674 pre-edited research papers to find the most common mistakes in manuscripts.

In the research papers analysed, the tool identified 134,105 errors, with an average of 50 mistakes per manuscript. Grammar accounted for 43% of the flagged errors, with article usage, preposition usage, and verb form being the top three grammar issues. This is primarily due to the fact that many researchers haven't been offered a refresher on grammar since compulsory education, which makes identifying grammatical mistakes rather difficult. Identifying grammatical mistakes is particularly difficult for non-native English speakers, or individuals with dyslexia, where the writing and editing stages can be even more challenging.

In the Paperpal analysis, 28% of the errors found were issues with readability. Common issues related to readability include redundancies, comma splicing, conciseness and rephrasing suggestions.

Another 19% of identified errors related to mechanics and style. Punctuation emerged as the most common problem area, accounting for 43% of the mechanics and style corrections. Other mechanics and style errors included corrections in capitalisation, conventions, hyphenation, and spacing. A careful proofread and reading the paper out loud can help authors eliminate such avoidable mechanics and

style issues. It can also prove helpful with typos such as 'its' and 'it's', 'there' and 'their', and so on.

While most academics are well-versed in the correct language to be used in their research fields, it was still among the top types of errors. For example, Paperpal flagged 13,598 vocabulary recommendations, which amounted to around 10% of identified errors, so this is one aspect that is important to double check before submission.

Using an AI tool can be beneficial in finding such errors, identifying areas for improvement so researchers can go over the basics of writing and refresh the standard grammatical rules. If researchers find themselves making the same mistakes in multiple pieces, this AI assistant can make it easier to look out for and fix such errors.

How do AI Tools Perform?

Dora Alexopoulou, Principal Research Associate at The University of Cambridge, recently released a report titled Comparison of Automated English Editing Tools. She compared seven different writing tools – Paperpal, InstaText, Grammarly, AJE, Trinka, Writefull and QuillBot – and evaluated their performance with regards to enhancing academic content. Each of the seven language tools was tested on three 500-word sample texts from separate humanities, life sciences, and physics papers. They were then evaluated on the number and type of language edits suggested, with corrections being classified into spelling, punctuation, grammar, and word choice suggestions. When assessing each tool's performance, the report also factored in the rate of acceptance and the extent to which these corrections coincided with edits done by professional human editors.

The report found that "different tools target different types of corrections and show varying performance across the different categories".[5] The differences in corrections and rate of acceptance reflected the user experience of each tool. For example, a tool that mostly focused on corrections for word choice and clarity enhances the readability, while a focus on grammar improves language quality. However, a large volume of irrelevant edits means that most of the user's time will be wasted rejecting suggestions, which could affect their perception of the tool's usefulness.

The report concluded that with 149 editing prompts, of which 38.9% were accepted, Paperpal provided a high number of alternative suggestions (words and phrases), which were in line with suggestions made by human editors, to help enhance the language and readability of the texts.

The Future of Scientific Writing

Advanced AI-powered tools are set to change the way researchers develop their papers, helping them overcome some of the challenges associated with scientific publishing. AI writing tools have been designed to help authors polish their academic writing, minimise editing time, and reduce the risk of desk rejection due to language issues. These tools can also help lessen the load for journal editors, who can focus on evaluating the merit of the research findings, rather than be distracted by errors in the writing.

Rejection is never easy and it's a verdict that can be difficult for many academics to overcome. It can damage an academic's confidence, particularly when combined with the competition in the scientific community and the immense pressure to "publish or perish". However, with the growing popularity of AI writing assistants, researchers have the tools that empower them to overcome desk rejection and ensure their paper meets all the criteria needed for successful publication.

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Beyond Pill Count: Challenging the Status Quo for Medication Adherence in Clinical Trials

Poor adherence to the investigational product can bring even the most carefully planned clinical trial to its knees. It is time to accept that traditional approaches such a pill count do not work. We need to upset the status quo by embracing the potential of modern medication adherence management.

Suboptimal medicine taking behaviour, which affects around 30% of all trial participants by day 90,[1] reduces effect size and increases variability, draining painstakingly calculated study power and resulting in non-significant findings.

A 2012 review of six HIV pre-exposure prophylaxis (PrEP) product trials demonstrated this perfectly, by showing a direct correlation between medicine taking behaviour and recorded drug efficacy. An oral FTC/TDC for women (FEM-PrEP) with an adherence rate of less than 30% reported an efficacy of just 6%, whereas another, of Truvada, achieved an adherence rate of 96% and an efficacy rate of 100%. This was despite the products being similar in mode of action.[2]

Growing Awareness

Sponsors who neglect to manage this important source of variation leave themselves open to wholly avoidable study failure. When we consider the expense of modern clinical trials, and that just 13.8% of products entering industry-sponsored Phase I trials ever go on to obtain FDA approval,[3] it is clear why pharma is starting to acknowledge the impact of poor medication adherence in clinical trials. They need to give their candidates every chance of success.

Last month, drug giant Pfizer said study participants not adhering to their investigational product regimen was "corrosive to the integrity of the trial itself". It increases the number of patients required to complete a study, prolongs study length, and drives up costs, as well as masks important safety signals and greatly complicates trial execution, said the organization's chief medical officer, Dr. Freda Lewis-Hall.[4]

It is a similar story at Novartis, which has highlighted the role of poor medication adherence in the fight against the current cardiovascular disease (CVD) epidemic. Speaking as part of a company-sponsored video series, Dr. Steven Nissen, researcher, patient advocate, and chairman of cardiovascular medicine at the Cleveland Clinic, explained that CVDs are the leading cause of mortality the world over, accounting for 32% of all deaths.[5] This is despite the emergence of highly effective, evidence-backed drugs for primary and secondary prevention, such as statins and angiotensin-converting enzyme (ACE) inhibitors, he said, adding: "We have powerful drugs, but they don't work if you don't take them…the problem is adherence."[6]

Regulators are also placing an additional emphasis on adherence rates. The FDA's 2019 Enrichment Strategies for Clinical Trials to Support Determination of Effectiveness of Human Drugs and Biological Products, for instance, said that reliable patient adherence data "provided valuable safety and efficacy information". As such, more attention should be paid to this information during regulatory review, it went on.[7]

Traditional approaches

Tackling a problem like medication adherence requires the right tools for the job but, until relatively recently, they have been in short supply.

Pill count has been a mainstay of dose tracking for decades. Its accuracy, however, has been in question for more than 30 years. Back in 1989, researchers compared adherence as recorded by pill count to that as measured by plasma phenobarbital concentration in 216 patients from three separate studies. They found that 161 appeared to have between 90% to 109% compliance by return tablet count, yet, of these, 51 (32%) had plasma phenobarbital concentrations less than 90% of the lowest value previously found in normal volunteers. The authors concluded that return tablet count "grossly overestimates compliance", and this finding has been reproduced multiple times in the intervening years.[8]

Self-report, which relies on the study participant's memory making it vulnerable to recall bias, is equally problematic. The trial included in the HIV PrEP review that returned a statistically insignificant efficacy rate of just 6%, for example, recorded self-reported adherence at 83%, but this figure stood at 30% when measured by blood concentrations.[2]

Measuring drug and drug metabolites in blood, urine, or hair, however, is far from an ideal approach. Aside from their invasive nature making them burdensome for patients and sites alike, it is also subject to the 'white-coat adherence' adherence effect.[9] This short-term escalation in adherence during the few days prior to a scheduled clinic visit means results can only provide a snapshot of medicine taking behavior at the stipulated timepoint.

Crucially, traditional approaches cannot provide the holistic, granular data needed to not only monitor, but to manage medication adherence during clinical trials.

Connected solutions

Enrichment Strategies for Clinical Trials to Support Determination of Effectiveness of Human Drugs and Biological Products outlined two approaches that could help in the quest to improve adherence in modern clinical trials.

The first was identifying and selecting patients with good adherence patterns, via a run-in phase ahead of trial initiation,

though this is rarely used in the industry. The second was to encourage medication adherence throughout the study with adherence prompts and alert systems, and tools such as smart pill bottles, or medication adherence packaging.[7]

Combining medication adherence packaging with powerful data analytics takes this approach one step further by giving teams all the information they need to spot red flags and take meaningful action – long before poor adherence has a chance to affect study results.

Microcircuitry in the packaging, whether it be a connected inhaler, capsule bottle, or pre-filled syringe, records dose administration and other essential information, and automatically transmits it to the study team. Our cloud-based platform, MEMS AS®, then uses sophisticated algorithms to analyse medication-taking behaviour, and flag any erratic dosing patterns, such as overdosing, missed doses, or medication holidays.

This information, which includes participant risk stratification & prevention, is presented to the study team as data visualizations, allowing them to plan and deliver individualised corrective interventions.

Importantly, it is evidence based. Studies have shown that it is 97% accurate, compared to 60% for pill count, 50% for healthcare professional rating, and just 27% for self-report.[10]

In practice: Data-driven feedback

That which can be measured can be improved – and more 30 papers have shown that utilizing electronic monitoring data to inform adherence feedback works.

Study investigators and patients discuss the data during the scheduled appointments, with a view to understanding the reasons behind the patterns. This enables the design and delivery of individualized interventions – whether they be reminder messages for the forgetful or education for the concerned. It is an approach that can be further enhanced by training the investigators in methods such as motivational interviewing.

One review and meta-analysis of 79 randomized clinical trials (RCTs) that electronically compiled drug dosing histories found the sharing of dosing patterns to be the most important adherence-influencing factor. In fact, interventional studies that included focused patient/ study team discussions around medicine taking behavior were 8.8% more effective than those that did not include feedback. This resulted in an average 20% overall improvement in adherence, and in some patients, this figure was as high as 50%.[11]

Sponsors are increasingly looking at digital adherence solutions to optimize their drug development and provide regulators with solid information on drug exposure. The granular, holistic data generated during electronic monitoring meets this need perfectly.

Digital future

Poor adherence to the investigational product is a long-standing, stubborn challenge in clinical trial execution. While the industry has long been well aware of the frequency and consequences of patients deviating from the protocol, however, a lack of workable solutions has meant the problem has been largely ignored.

Advanced, digital approaches that utilise the power of medication adherence packaging and powerful data analytics are now starting to challenge the status quo for medication adherence. This evidence-based model enables study teams to not only measure, but manage, adherence in real time throughout the trial and beyond.

It holds huge potential for sponsors wanting to truly understand and demonstrate the efficacy and safety of their products, and give their expensive, investigational candidates every chance of success.

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Bernard Vrijens

Dr. Vrijens, CEO, Scientific Lead, AARDEX Group, Invited Professor of Biostatistics, Liège University, Belgium, holds a PhD from the Department of Applied Mathematics and Informatics at Ghent University, Belgium. He currently leads a research program investigating (a) the most common errors in dosing using a simple but robust taxonomy, (b) particular dosing errors that can jeopardize the efficacy of a drug, and (c) the optimal measurement-guided medication management program that can enhance adherence to medications and maintain long-term persistence. Dr. Vrijens is also the co-author of seven book chapters, over 100 peer-reviewed scientific papers, and named as inventor on 6 patents. He is a founding member of the International Society for Medication Adherence (ESPACOMP), and an active member of several EU- and US-funded collaborative projects around the theme of adherence to medications.

Learning From The Past

How Sharing Clinical Science Research During the Pandemic has better Prepared Us for The Future

"The scientific community working together can do some pretty amazing things." That was the conclusion of John Cooke, M.D., a hospital director from Houston, when reflecting on the pandemic. Previously, vaccine development has taken up to 20 years, but researchers were able to accelerate the process to produce a coronavirus vaccine in only eleven months, changing the future of drug development. Here Charlie Rapple, co-founder of science showcase Kudos, explores other ways the pandemic has been a catalyst for research discoveries.

People want to believe that science deals in absolute truths – that scientific 'facts', once established, don't change, but they do. Science is a process of constantly expanding knowledge, and new research can contradict what was previously understood to be true. The pandemic threw this reality into stark relief – both in terms of the public's expectations of scientific infallibility and the pace that scientists' own beliefs were challenged. In a 2022 Guardian interview, several scientists acknowledged they had changed their minds as the pandemic progressed, on topics ranging from vaccines to the use of masks. Professor Peter Openshaw of Imperial College London, for example, had not expected COVID vaccines to work, explaining "there had been no example of a vaccine for a human coronavirus, yet they were more effective than I'd hoped."

Innovation

There was a lot of innovation during the pandemic, from increased telemedicine devices to experimental treatments. As the pandemic identified one area for improvement, scientists and healthcare practitioners strove to solve it.

One of the biggest challenges faced during the pandemic was the ability to stay ahead of the virus. Hospitals and other care facilities became overwhelmed at the high infection rate before they could find a solution, needing to process high volumes of data to identify patterns in symptoms, infection rates and virus longevity.

However, this helped fast-track automated processes. For example, developments in artificial intelligence that can identify patterns in symptoms and other 'red flags' to healthcare professionals. These can help provide early diagnosis of infections, quicken drug discovery and identify warning signs for diseases so that healthcare workers can better manage cases early on. AI and machine learning can then build platforms for automatic monitoring and predicting the spread of the virus, including identifying virus 'hot spots' to make it easier to find those who had come into contact, like the NHS Track and Trace app.

According to research by De Gruyter, the World Economic Forum used its ML expertise to help researchers and practitioners analyse large volumes of data to forecast the spread of COVID. The tools acts as an early warning system for future pandemics while also identifying vulnerable populations and predicting what treatment will be the most effective.

While this study showed the benefits of using digital technologies in healthcare, it also explored its limitations. Currently, AI technologies are not as advanced as they need to be, hindering accuracy when making predictions. AI can also amplify inequalities and bias in training data.

This research highlighted both AI's advancements and limitations, giving scientists a deeper understanding of how reliable AI can be and the steps needed to improve this in the future. The improvements outlined in the research can help contain future virus outbreaks to avoid the challenges faced over the last few years.

Treatment

During the pandemic, scientists used research conducted during previous research into other illnesses to streamline treatment options. For example, there was already research conducted on the Coronavirus family – SARS and MERS by The University of Oxford. This research offered scientists a head start on COVID-19.

As of early 2022, very few drugs have been approved by the World Health Organization to treat critical COVID cases. During the pandemic Hoang Linh Nguyen et al found that remdesivir, which can block the activity of RNA-dependent RNA polymerase (RdRp) in old SARS-CoV and MERS-CoV viruses, had been used to treat symptoms of COVID in many countries.

The drug was originally developed to treat hepatitis C and respiratory syncytial virus, but was later used as one of the medications during the Ebola outbreak. Studies in cells and animals suggested that remdesivir was effective against viruses in the Coronavirus family, by preventing the virus from multiplying. After testing 1,062 hospitalised patients with either remdesivir or a placebo, they found that it could help speed the recovery of covid.

Using drugs like remdesivir for more than one condition not only speeds up the treatment process for the patient, but also avoids time and money spent during clinical trials for drug safety. Repurposed drugs are a gold mine in pharmaceutical research, particularly during times where drug discovery is declining or when treatment options are needed at an accelerated rate. In 2016 Professor Jan Baumbach from the University of Denmark and his team found thirty thousand "repurposable" drug candidates using pharmaceutical data. Eleven thousand had been mentioned in scientific literature, and about 1,400 were described as concrete "repurposing" options. This left roughly 19,000 highly confident drug-disease combinations yet to be investigated.

Research conducted to identify potential drugs suitable for repurposing will offer significant benefits for future pandemics to avoid the high mortality rates faced globally over the past two years. This may also allow us to continue to create vaccines and treatment options at a much quicker rate than before.

Welfare

Another factor that wasn't initially considered during the early stages of the pandemic was the amount of patients experiencing symptoms after the two week isolation period. While originally thought to only last during those few weeks, around a third of

people diagnosed with covid experienced long-term effects and symptoms.

Patients experiencing 'Long Covid', as it has now been described, often continue having symptoms for months. There was also no correlation between how critical the patient was and the length of symptoms to identify why some experienced this. In many cases it was young and healthy patients that suffered from Long Covid.

This identified a gap in research and patient care, particularly as non-critical patients weren't offered many treatments for their symptoms when healthcare workers initially identified Long Covid as an illness. This is primarily due to how overwhelmed the healthcare system was at the time due to rapid COVID infection rates, which meant doctors focused primarily on providing resources to patients in a critical condition.

However post-COVID, some scientists and healthcare practitioners believe that the gap between researchers and patients should close. For example, research published by the International Association for the Study of Pain suggested that more researchers should partner with patients and create patient-led research to gain better insight and design effective solutions.

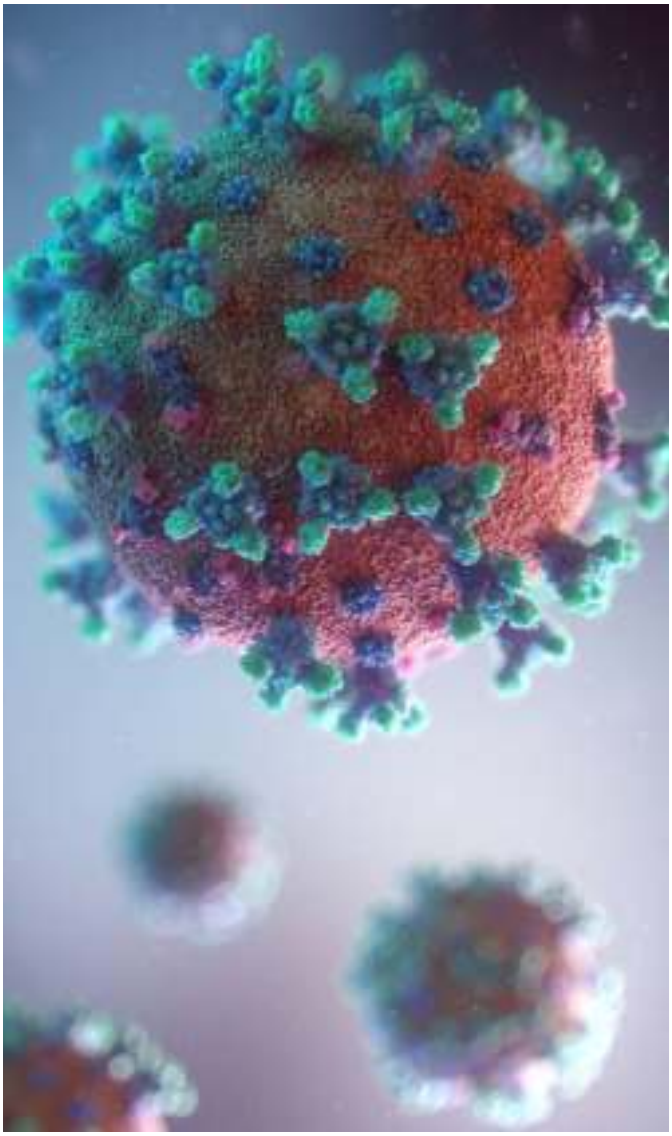
Power of the People

While critics suggest that the public do not have enough knowledge to be involved, having access to resources and clinical research will not only help researchers understand what patients are experiencing more clearly, but also give them the knowledge to advise doctors on how to treat specific symptoms more effectively.

This is because researchers sometimes have a different sense of what is important compared with patients, such as common symptoms versus less common symptoms that cause more discomfort. This can then reduce the immediate benefit to the patient. It's important to understand the patients' experiences to address the most relevant issues and tackle them efficiently. Having a more patient-centred focus also adds more value, as patients will feel listened to.

Providing access to research summaries on the latest research about infectious diseases can offer non-academics an insight into their own health. Research is often hosted in paid-for, individual academic journals, making it difficult for the general public to access credible information. Academic research is also complex, with technical language that makes it harder for people to digest. Platforms like Kudos offer access to academic content that has been summarised into short, easy-to-understand language by expert writers.

Users can also find all content surrounding a given topic by searching for themed keywords. Collating information in one place allows users to find specific content from different publishers and universities at once, making it easier to absorb, understand and act on findings.



As the number of patients experiencing the impact of COVID and Long Covid increases, focus on patient-specific symptom management will offer significant advantages. Monitoring its prevalence and developing effective management strategies based on patient experience can help minimise its impact on both their mental and physical health.

Prevention

Clinical research has not only offered insight into how to improve treatment options for patients with COVID, but also how to predict future pandemics using improved data collection.

Data collection is beneficial for every industry but can drastically improve challenges faced during virus outbreaks and better prepare healthcare practitioners for what's to come. COVID spread to over 180 countries, threatening both public health and social stability, something that many didn't see coming.

It also highlighted limitations in the current ways data is being recorded, leading to inaccurate estimations that left both the public and hospitals unprepared for the surge in cases. Enhanced data collection can help countries better protect themselves against the virus and future pandemics by predicting its spread.

Documenting data during COVID was difficult, as countries documented their data in different ways. Numerical models were the common method to document COVID cases as they estimate how the disease spreads, infection rates and the number of infections. Yet it proved challenging as predictions made needed a deep knowledge of how the disease spread, something that was hard to do, especially early on in the pandemic. This led to inconsistencies and data needing to be redone, causing delays and preventing institutions from effectively predicting future cases.

Instead, researchers at the American Institute of Physics have offered improved ways to collect data using numerical models and the main factors affecting prediction accuracy. While numerical models are useful, they are only as effective as the data used. An important takeaway from the pandemic is that the initial data from the early stages is critical, as well as taking regional variables into account.

Further outbreaks of this kind are likely to occur in the future, so having the ability to predict them accurately is crucial. It will also provide the public with accurate stats on infection and mortality rates to avoid any miscommunication.

COVID 2.0

Unfortunately, many experts believe that another pandemic is inevitable. According to Dr. Larry Brilliant, an epidemiologist and CEO of Pandefense Advisory, we "live in an age of pandemics," with the last pandemic occurring only ten years prior with the H1H1 virus swine flu.

More than six out of every ten infectious diseases have originated in animals and jumped to humans. This risk has "been increasing for the last 20 years," explained Brilliant. "Every year, the risk increases more." Other factors such as population growth, climate change, staff shortages in healthcare and urbanisation all effect the likelihood of additional pandemics.

As future pandemics loom over us, it's more important than ever to enhance research and its accessibility, so that both healthcare practitioners and the general public have a deeper understanding of infectious diseases and the current technology and medicine available to help prevent future scenarios like COVID.

The research conducted during the pandemic helped healthcare practitioners and researchers improve data collection, patient welfare, predicting infection rate and developing treatment. However, it also identified the need to share such research with the public, and make it more accessible for everyone, not just other scientists. Better sharing of research will prevent fear mongering, reduce the spread of fake news and help individuals feel more knowledgeable about current and future events.

Charlie Rapple

Charlie Rapple set up Kudos because she believes that every paper deserves to have a platform where it can be found and understood by both academia and the public, removing any barriers to publishing research. Charlie strives curate content that is easy to access and digest, by creating summaries of each piece of content into short and easy-to-understand language, so the public can easily find and read credible research. Her marketing background helps her understand the importance of clear communication and promoting important topics of discussion to the public.

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The Future of Clinical Research in Ukraine

Ukraine is currently experiencing difficult times due to an unprovoked act of aggression from a neighbor. As a country with its 40 million+ inhabitants, it has a tremendous potential for international clinical research. The clinical research infrastructure, well-educated and clinically experienced investigators as well as firm regulatory policies together with young and IT committed generations should constitute a solid base to build upon for the International Clinical Research Society.

General

Ukraine is an economically developing country. The potential of Ukraine as a location for clinical trials has not yet been fully explored. The location in Eastern Europe, population, and political and economic development of Ukraine could provide a volume of clinical trials in the country comparable to Poland. In the period 2010-2020, this was facilitated by such factors as:

- doctor's and scientist's interest in the field of clinical research
- support by Government line ministries and local executives
- integration development with EU
- positive experience by patients participating in clinical trials
- an emerging positive image of clinical trials in the general population

Patients were recruited quickly, study protocol procedures were adhered to, and deviation rates were minimal due to the investigators' high qualifications and interest in the research work.

Therefore, the impact of clinical trials in Ukraine has been significant and is rising.

Patients

Patients suffered the most when the conflict began. Those who remained in the territory involved in the conflict lost the opportunity to continue treatment or receive it by participating in new studies. Those patients who were forced to change their place of residence often lost the opportunity to participate in studies because they did not have access to physicians with similar experience and expertise in clinical trials as their previous treating physicians. In addition, a radical change of residence most often involves a deterioration in quality of life, which affects overall health and the ability to receive treatment. Expensive treatment for many therapeutic indications has become practically inaccessible to people, since with the outbreak of war, the financial situation of Ukraine citizens has deteriorated significantly. For many patients, participation in a clinical trial is a chance for a cure, as well as free ongoing health monitoring. This is the reason for the high number of recruitment of patients and their desire to participate in the study. Both men and women of different ages are willing to participate in the research, depending on the nosology of the study.

Investigators

Since the military conflict in 2014 stabilised quickly and territorially affected only a small part of the country, there was an internal migration of the population. Many Investigators changed their place of residence when the conflict at Crimea started in 2014 and moved to regions where they were able to continue to engage in medical and research activities. These Investigators lost their patient bases but were able to bring their experience and knowledge to those regions and clinics where clinical trials had not been conducted previously. Principal Investigators assembled new teams and trained new specialists. Thus, such forced internal migration of specialists made it possible to increase the number of research centres and cover new territories of the country. All doctors taking part in clinical trials are not GCP certified, but according to the legislation they are obliged to have a local GCP certificate, issued by the MOH. According to Ukrainian legislation, any clinic has the right to participate in clinical trials, if they comply with MOH requirements (license, accreditation, local ethics committee).

Sponsors

During the conflict many Sponsors have moved their studies to other regions of Ukraine and have thus been able to continue study activities with few significant losses, since it remained possible to save the data and results obtained. The number of new studies, especially long-term ones, has now declined significantly since 2014.

Year	Number of CT
2012	213
2013	177
2014	188
2015	144
2016	135
2017	183
2018	178
2019	210
2020	203

Table 1. The number of positive conclusions regarding the conduct of international clinical trials in Ukraine, 2012–2020.

Information of State Expert Center on the Examination of Clinical Trials of medicinal products materials. URL: https://dec.gov.ua/. There are fluctuations in the number of clinical trials conducted over the years, which can be caused by both political and regulatory changes in certain periods. An increase in the number of clinical trials worldwide, increase of NCEs and approaches to the treatment of the same diseases have led to a return of attention to Ukraine by Pharma Sponsors.

We observe similar tendencies when analysing data from the resource https://clinicaltrials.gov/.

As shown in Table 2, an increase in the number of new studies initiated in Ukraine has taken place since 2017. This is due to multiple factors including the development of the health care system in Ukraine, the significant development of the culture of clinical trials, the opening of new research centres and the creation of specialised researchers' associations, as well as localisation of international CROs.

Year	Launched CT
2012	157
2013	127
2014	132
2015	131
2016	139
2017	170
2018	178
2019	171
2020	182

Table 2. Number of launched clinical trials in Ukraine 2012–2020.

Site Management Organisations (SMOs)
Not all clinics and study sites can adapt to the new working conditions. Representatives of the Sponsor and employees of CROs do not always have the opportunity to train site personnel in Good Clinical Practice. In these situations, clinics run by SMOs could play an important role. SMOs could take on the responsibility of training skills of study team members by internal training and providing assistance during the study. Clinics with SMO assistance are able to quickly adapt to changes in study performance, recruit additional staff and train staff in GCP. In addition, the SMO assumes the function of additional internal quality control of the study team, with a positive effect on the performance of the site.

Contract Research Organisations (CROs)
Most of major international CROs operate in Ukraine. In the past, Ukrainian offices of international CROs were focused mostly on local clinical operations.

After the two decades of conducting clinical trials, the local labour market is saturated with lots of highly qualified clinical research professionals with various specialisms.

Ukraine's labour force is widely known as well-educated and talented in natural sciences. Also, most of young Ukrainians have a professional command in English (which was not the case 20 years ago).

As a result of the war, many Ukrainians have relocated to Europe and possessed managerial roles in European offices of CRO's and pharmaceutical companies which were often higher than in Ukraine. This proves the high qualification of the Ukrainian clinical research workforce.

The Ukrainian combination of fluent English, deep technical expertise and moderate costs had looked unbeatable before wartimes. No surprise that CRO's had taken advantage. Companies were pro-active in creating global project management, medical monitoring, data management, statistical analysis, and biometrics departments in their local offices during last years.

As working skills of clinical research professionals are easy transferable internationally, we observe an intensive outflow of the qualified workforce. In the post-war future, CROs will likely face a heavy shortage of qualified personnel.

Regulatory
The regulatory system of Ukraine has made an impressive progress. There are three main regulatory bodies reviewing clinical trials.

- State Service of Ukraine on Medicines and Drugs Control: for medical device trials
- Coordination Centre for Transplantology of Organs, Tissues and Cells: for cell-based therapies and tissue-engineered products
- State Expert Centre of Ministry of Health (SEC): for medicinal products, i.e., for the majority of clinical trials.

While regulatory procedures for advanced therapy and medical device trials are still vague, State Expert Centre has created a good working regulatory framework for review of clinical trials which is quite "user friendly" and with the real zero tolerance to corruption.

Ukraine is quickly becoming a very digitally advanced country. The SEC keeps in line with this trend. Electronic submissions have been allowed. Study subjects may sign informed consents electronically. SEC has launched an online consulting service which is free of charge, any Sponsor can remotely submit their request and obtain the expert's answer within 5 working days or schedule a meeting. Submissions can be tracked online through the secure visualisation system. Electronic medical information systems are common. eCRFs are used in more than 90% of trials.

The matter of transparency in clinical trials is handled seriously. All study approvals are published on the SEC website[1] on an ongoing basis. The national register of clinical trials is available to the public online either.

Review timelines for initial applications are up to 47 calendar days according to law. Although the average review time of initial submissions was just 41 days in 2021 – considerably shorter than in 2020 (50 days) and 2019 (67 days) according to Mykhailo Babenko, Head of SEC.[2]

Ukrainian health authorities are open to the world and participate in many international collaborations. Ukraine is a part of PIC/S (member), ICH (observer), ICMRA (associate member).

Even not being a part of the EU, Ukrainian regulators closely collaborate with EMA keeping local regulations in line with EMA recommendations. This trend is long-term as Ukraine has applied to enter the EU and currently is the candidate country.

Ethics
Ukraine has no Central Ethics Commission but uses Local Ethics Committees (LECs), i.e., each site must have its own local ethics committee. EC applications can be reviewed in parallel with regulatory submissions, that shortens the start-up period. The approval time is up to 30 days. The consulting support of ethics committees seems undervalued. The authors believe that highly qualified ethics committees will make the transition to a more decentralised regulatory model possible, which might make Ukraine more competitive on a global scale.

Support of Ukrainian Clinical Trials

It is a regulatory requirement that investigators must be familiar with GCP and local CT regulations. SEC requires investigators to attend their training that combines GCP and local regulations. Without this training investigators will not be allowed to conduct a clinical trial. Sponsors do also provide training according to their SOPs. But investigators must be trained at SEC regardless of sponsor training.

Investigators are frequently trained on GCP in clinical trials. Nevertheless, gaps in study staff skills and knowledge are still observed. Areas to focus on are training, educational and consulting support of investigators and study staff members.

From the practical standpoint, the following support should prove helpful:

- Assist Ukrainian regulatory bodies in the establishment of a modern regulatory framework for BA/BE, medical devices, and advanced therapy trials
- Streamlining and further digitalisation of the existing regulatory procedures
- Promotion of best practices at clinical sites, particularly in the fields of quality management, practical interpretation of GxP standards, patient centric techniques and soft skills like project management, business ethics and communication
- Support sites in development of business contingency plans
- Engage Ukrainian physicians in international scientific initiatives
- Create patient support groups helping subjects to find and get enrolled in the right study including the foreign sites
- Development and/or streamlining of clinical research procedures including writing SOPs
- Subject recruitment and retention techniques.

The Conflict

The large-scale Russian aggression in February 2022 caused lots of disruptions of logistics, concerned safety of subjects and study staff and resulted in the chaos of evacuation and massive relocations and shutdowns of vendors supporting the clinical research process.

Anyhow, industry stakeholders made incredible efforts to protect patients and research personnel and keep the integrity of ongoing studies. The lessons learned from the first, more limited conflict of 2014 and the COVID-19 pandemic have been applied widely.

The EU institutions, EMA and CTCG helped the industry with very practical and valuable recommendations on how to manage clinical trials in Ukraine during wartimes:

- CTCG recommendation to sponsors on managing the impact of the war in Ukraine on clinical trials[3]
- Advice to sponsors on managing the impact of the war in Ukraine on clinical trials (EMA)[4]
- Impact of the war in Ukraine on methodological aspects of ongoing clinical trials (EMA).[5]

Thus, analysing the events that took place in Ukraine in the period 2014–2022, it is necessary to use the experience gained and

adjust the clinical trial process to make it effective and more robust for the current circumstances.

Possible preventive measures can be:

- training of young doctors and nurses in GCP
- support of associations of study sites developing contingency plans
- formation of independent organisations for the protection of patients
- engage local CROs / SMOs with local knowledge and experience

Assessing the current experiences in Ukraine may prove helpful to positively influence the development of clinical research in the field and become a catalyst for new changes in work processes. As the situation in Ukraine improves, it should be possible to resume clinical research activities in the country in the near future.

The Future

In a post-war scenario, solid financial investments will be injected to restore the ruined Ukraine's economy and the health infrastructure will be rebuilt.

A potential economic boom may create lots of jobs which may attract work migrants from various world's regions. That may compensate demographic losses and restore the demographic basis for high recruitment rates.

Ukraine is quite successful in keeping Sponsors loyal even during wartimes. No doubt it will be easy to convince them of allocating clinical projects in peacetime.

Summing up, the post-war outlook is quite favourable in the basic scenario.

We also see an optimistic scenario in which the Ukrainian clinical trials outperform. However, the realisation of the latter scenario will require to remove bottlenecks preventing the industry development.

The main bottlenecks might probably become the lack of qualified, GCP trained workforce; unsatisfied demand for consulting support of research naïve sites, local CROs, SMOs and biotech startups; gaps in regulations; upgrade of regulations in a timely manner to catch up with innovations; transition to more flexible and decentralised regulatory model; harmonisation of local standards of care with developed countries; creating an atmosphere that would attract international life sciences investors, scientists and professionals. These tasks will demand joint and persistent efforts of the Ukrainian government, business, and academia.

Patients, investigators, and study nurses as well as local CROs and SMOs in Ukraine, have withstood the challenge in difficult times and are eager to engage in international clinical trials in the future.

In these difficult times for Ukraine, it would be highly desirable that the international scientific society takes initiatives to invest in clinical research infrastructure as well as future generations of young investigators and study coordinators in the country. Preparations for future clinical research in Ukraine should start now and could be orchestrated by international Pharma and CRO companies. Joint efforts to organise this are currently underway.

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Central Europe – Look Behind the Curtain of Trials for On The Ground Knowledge

In the last 5–10 years we have seen global sponsors and global CROs increasingly looking to open investigator sites or acquire resources in Central and Eastern Europe. Following the recent Bio Europe – where eastern Europe site options were a hot topic among execs –Pavel Marek, Managing Director of Emmes Europe, shared his view on what's ahead in the region for the next few years. In particular, he explores the growing role Central and Eastern European trial sites are now playing in early-stage trials.

To understand what's driving the region's growth you need to look at its recent history and the underlying trends. So, for example, most of the recent trial expansions have primarily benefited Central European countries. These countries joined the European Union (EU) in 2004 and fully implemented the harmonised EU directives and regulations a long time ago. So now these countries in Central Europe can offer the combination of high standards of healthcare, high quality site staff and very good access to patients with relevant diagnoses.

Delving deeper, much of this was empowered by the centralisation of healthcare in the region – whereby public healthcare grants provide access to modern therapies for the entire population. But to keep costs down, healthcare payers (like state insurance companies or state sick funds) designed specialised centres with the strong diagnostic infrastructure and highly qualified healthcare staff authorised to prescribe the expensive innovative therapy. Consequently, this clustered the experience of the newest therapies and most experienced clinicians.

However, that's not to say there are no challenges, and the difference between success and failure will be how a CRO marries this upside with solutions to overcome regional complexity.

For example, as a region of many disparate countries – despite a common regulatory framework – there are a number of hard and soft barriers. So that means often subtle differences in the implementation of EU rules – sponsors are often surprised by this – combined with local language barriers. Not surprisingly, and hardly unique to Eastern Europe, it means inevitably there is a great deal of value CROs can deliver from good hard yards on the ground and local experience – it's easier enough to open an office here but much more difficult to replicate the knowledge to seamlessly navigate eight languages, regional practices, and vagaries of receptive patient populations.

Yet operations driven from Central Europe give you the unique combination of access to: centralised hubs, the traditional big EU countries (which are attractive for global sponsors as strategic markets for future launches), as well as the very productive Central European countries generating high quality clinical data relevant for the EU population and Eastern European countries.

The other obvious advantage of the region is in its access to patients. Operations in Central Europe are an excellent base for further expansion in neighbouring Eastern European countries, where the density of clinical trials is still much lower than in other comparably regulated markets.

Less trial competition of course in itself brings a number of further advantages beyond patient recruitment as it automatically improves quality. This is because the sites can stay focused on just one or a few projects running in parallel. They can provide patients with that, all too underrated, trial benefit, increased doctor-patient time. Clinicians can therefore concentrate more on patients and become the real experts on protocol and all study-related procedures in a relatively short timeframe. Dedicating significant time for direct communication between investigator and patient, addressing all questions and concerns of the patients or their families carefully. Ultimately, this translates through to the Sponsor as an improved adherence to study protocols, with minimum dropouts and protocol deviations. Looking further ahead, this also helps deliver positive outcomes during FDA or EMA inspections at the sites who can observation this first hand.

Speaking of regulators, another previous hesitance has been the sheer number of countries here, but there is an ever increasingly harmonised environment here. In fact, all 27 EU member states now follow one legislation related to clinical research. Obviously, there are some local differences in its implementation; however, for CROS with history and local presence in these EU states, it can be relatively easy to address.

Moving to the non-member CEE countries, they have also voluntarily decided to harmonise their clinical research legislation with key EU regulations. Opening an even wider base of patients. There are challenges around language but another positive outcome from the harmonisation is that Application File and key study documents like the Trial Protocol and Case Report Form (CRF) can be submitted in either English or a local language. Its entirely at the sponsors preference. It is important to note that patient-facing materials like Informed Consent Forms or patient questionnaires, however, must all be available in local languages.

Another commonality that has implications for CROs is that both US and European markets, focus on trial allocation strategy as an integral part of registration and launch strategies. Especially in area of increasing numbers of targeted therapies, so sponsors want to be ready to submit to the relevant authorities – FDA and EMA – data generated both in the US and European environments. Yet this is even more relevant for submissions of their data to local European Health Technology assessment (HTA) agencies and HC payers. In a nutshell, they want to be ready to address all challenges regarding relevance of their clinical data for the particular population, specific lifestyle, alimentary habits, standards of care, etc.

This means it's crucial to understand the specific patient profiles, including being able to identify sites with good access to these patients. From this perspective, Central Europe provides a unique combination of important elements: a European environment and lifestyle that is similar to other EU countries, highly developed GCP environments with the strategic central role of EMA, and very good access to specific patient profiles concentrated in specialised

treatment centres. This is a very attractive combination for innovative sponsors, like dynamic biotechnological companies or pharma players focused on high-quality drug candidates.

And, surprisingly to what many expect, direct costs for things like investigator grants do not always differ that greatly. The site fees and investigators fees are around 30% lower than in the US and Western Europe, so the difference in these direct costs is not so robust as 10–15 years ago.

Instead sponsors see indirect savings generated by quicker recruitment, higher number of patients accessible on one site and generally good adherence to the protocol.

With that said, auxiliary costs in a trial, such as for monitoring, couriers, postage etc., are often significantly less expensive.

In terms of therapeutic indications, like other regions, oncology trials are always the overall biggest percentage (at around 22%) of registered trials in CEE. But we are also seeing increasing interest in neuroscience, ophthalmology, respiratory, IBD, immunology, cardiology and respiratory in CEE – and for these areas we also see some regionalisation with a trend of stronger individual country profiling. For example, the Czech Republic, where Emmes' European headquarter are located, is – from a global perspective – a very attractive place for trials in MS, Ophthalmology, IBD, and haematology.

Another area where we have seen increased growth in CEE is for orphan drug and rare disease trials. For these therapeutic areas, it's obviously beneficial to have as wide a global remit as you can and to work with national centres with concentrations of patients for these indications.

The difficulty for sponsors, particularly in Central and Eastern Europe, is finding a CRO with experience of working in this area, leveraging local expertise and cross-border coverage, and combining so called "old" western EU member states, "new" CE EU member states and Eastern European countries still outside the European Union. Consequently, Emmes' team in Europe continues to do extremely well from this perspective – it's one of those areas where there is no replacement for experience.

So, if I was asked to put all of this together, as a package of advice for a sponsor new to the region? I would say think about the culture and size of who you pick to work with. By this I mean you need that local niche aspects of regional networks but combined with cross-border coverage,and backed-up with global resources.

Ideally with early medical consultancy on protocol design and strategic trial allocation through optimum identification of sites, regulatory authority and ethics committee (RA/EC) approvals and data collection through data analysis and Clinical Study Report completion all wrapped in a package.

You also need to dig deeper and see what the depth of relations are. For example, where are clinical study managers and site monitors allocated from a geographical perspective? Could we expect that they will be experts on local conditions, i.e., will they be able to address all the potential challenges from local RA/ECs and are they ready to establish strong collaboration and cooperation with principal investigators and site staff in a reasonable timeframe?

But it you can get the right partner and manage the geographical complexity sponsors are very soon left asking why they did not enter the region sooner.

Pavel Marek

Pavel Marek, a physician by education founded Emmes Europe with his brother in 2004. Before entering the pharma industry Pavel was a Neonatologist at Faculty Hospital in Prague, Czech Republic. Now with more than 30 years in the business, Pavel remembers his previous experience of working for companies like Pfizer as a Medical Advisor and as a CRA for Quintiles (now IQVIA). Thanks to this experience and his professionalism, Pavel set a very successful start for the Emmes Europe from the beginning. His vision continues with Emmes Europe growth. We are now in most European countries, and our services are remaining high quality.

mRNA Vaccine Applications in Global Health: Promise and Challenges

The global COVID-19 pandemic has focused intense attention on the potential benefits and continuing challenges of vaccine development. In the twentieth century, a large number of important vaccines were developed empirically, without clear understanding of molecular immunology. Mass vaccination with these products successfully eliminated the scourge of smallpox, and greatly reduced and contained the global burden of other diseases such as measles, pertussis, chicken pox, and polio. Nevertheless, many important global challenges remain unresolved, and there is a tremendous unmet need for safe and effective vaccines against diseases such as AIDS (Acquired Immune Deficiency Syndrome), parasitic infections, and tuberculosis (TB).

2020 was the year when many people first became aware of mRNA vaccine technology and its potential benefits to public health. The promise of this technology is clear. Importantly, the success of those COVID-19 vaccines was only possible because of decades of foundational work by industry and academic scientists. Some of that work was specifically envisioned as the basis for a response to future pandemics. Other foundational work comes from longstanding efforts in AIDS vaccine development.

Notably there are important similarities and differences in the nature of the public health need represented by acute COVID-19 infection compared to that pertaining to AIDS and TB, for example. SARS-CoV-2 infection causes an acute symptomatic infection typically followed by natural clearance of the SARS-CoV-2 virus from an infected person. In contrast, the causative agents of AIDS and TB produce long, slow latent infections. For diseases in this category, effective vaccines will probably need to provide stronger, broader, and more durable responses. In addition, the complex lifecycles and immune evasive properties of these pathogens make successful vaccine design significantly more difficult. Ongoing work is investigating the promise of mRNA in vaccine development for HIV and other infections of global importance. New RNA technologies under development, in combination with complementary vaccine approaches, will also add to the toolbox of approaches to meet the challenges of these global infectious diseases.

In infectious disease medicine, a prophylactic vaccine is a medicinal product intended to prime immunological memory and protect against infectious disease caused by specific viruses, bacteria, or other pathogens. An antigen is the molecular target of an immune response – for example a viral protein. A vaccine always includes one or more antigens or genetic material encoding such antigens. Each vaccine also needs a vehicle or vector to make sure the antigens are delivered to the correct cellular and anatomical locations. Vaccines also often include a drug substance intended to activate the immune response to the antigen, called an adjuvant.

Historically, many vaccines were developed using preparations of the target infectious agent that had been killed by heat or chemical exposure. Other vaccines incorporated live pathogen strains that were attenuated (unable to cause disease in healthy people). The Salk- and Sabin-type polio vaccines respectively are examples of killed and live-attenuated type vaccines, both still in clinical use. More recently, vaccines have been developed that incorporate artificial recombinant protein antigens plus chemically designed adjuvant compounds; examples of recombinant protein vaccines in clinical use include hepatitis B and herpes zoster or shingles vaccines.

Within the past few years, we have seen FDA approval of vaccines incorporating modern synthetic biology and gene transfer technology. This includes vaccines based on viral vectors – artificially engineered viruses that deliver and express a target antigen in a manner designed to provoke a protective immune response. This category also includes vaccines using messenger RNA (mRNA). In normal cell biology, mRNA plays the critical role of encoding genetic information transcribed from chromosomal DNA, and carrying that encoded "message" to ribosomes, which are the protein factories of the cell. Thus any properly encoded mRNA sequence can be expressed as a protein. Using synthetic biology, artificial RNA messages can be manufactured to encode any protein sequence. This allows rapid production of an mRNA product encoding any desired viral antigen sequence.

Both of the RNA vaccines with current FDA approval are comprised of mRNA molecules encoding a viral antigen, with the mRNA enclosed in a protective particle of synthetic lipid – aka a lipid nanoparticle or LNP. When a person receives one of these vaccines, the LNPs deliver the mRNA cargo into cells near the injection site, which immediately begin to synthesize the mRNA-encoded antigen. In turn, the expressed antigen is taken up by specialised immune cells to prime the antiviral immune response.

Vaccine-induced immune memory has two functional components: humoral immunity and cellular immunity. Humoral immunity is mediated by antibodies, which are complex soluble proteins secreted by B cells. Antibodies can exert a variety of antiviral effects. Antibodies that can directly block viral entry into a target cell are called neutralising antibodies. Cellular immunity is mediated by T cells, which can promote a variety of antiviral effects when they come into contact with infected cells or cells displaying fragments of viral proteins. Initiation and control of humoral and cellular immune responses depend on complex interactions among B cells, T cells, and other categories of white blood cells.

COVID-19 is caused by the SARS-CoV-2 coronavirus.[1] In most cases, a person becomes infected with SARS-CoV-2 through inhalation of airborne aerosols or droplets containing viral particles. Each viral particle is decorated with external viral spike proteins that can grab onto and bind a protein called ACE2 on the surface of human

airway cells. After binding to the ACE2 receptor, the virus can enter a human cell and hijack the host cell biology, turning the cell into a factory to make more SARS-CoV-2 particles. Upon release, these particles spread to neighbouring cells in a self-amplifying process of replication. In the upper airways, this viral replication can lead to mild-to-life-threatening flu-like symptoms. If the virus spreads to lower airways it can cause pneumonia. The extent and significance of SARS-CoV-2 spread to other organ systems is the subject of ongoing investigation. Over a period of days to weeks, an infected person's immune system learns to fight back against the virus, typically leading to clearance of the virus from the body and resolution of the acute disease. Before immune clearance, while the virus is spreading in the airways, it also becomes airborne in exhalant air, resulting in transmission to new human hosts. The degree to which SARS-CoV-2 may persist in some infected persons after acute disease is also a matter of ongoing investigation.

The primary challenge for COVID-19 vaccine designers in 2020 was to come up with a vaccine that could induce immune responses capable of slowing the viral replication process in an exposed person, to prevent the occurrence of severe acute disease. Secondary goals included: i) inhibition of SARS-CoV-2 transmission to another person; and ii) total blockade of SARS-CoV-2 infection in the vaccinated person, such that no viral replication could occur. Achievement of the primary goal was highly significant and a primary rationale for FDA approval; benefits of vaccination with respect to the secondary goals were also observed.[2]

Due to heroic efforts of vaccine developers, the medical community, government agencies, and volunteer participants in clinical trials, the primary goal of 2020 COVID-19 vaccine programs was achieved in an extraordinarily short time frame, leading to FDA approvals of two mRNA vaccines and to mass vaccination of global populations.

This historic success was made possible by a broad range of medical and social factors. On the level of immunology and virology, vaccine developers had several factors working in their favour:

1. An essential viral component to be targeted by the immune system was readily apparent: the viral spike protein. Based on prior studies of other coronaviruses, the likely role and vulnerability of the viral spike protein to immune attack was understood from the beginning.
2. Vaccine developers already had spent many years studying how mRNA could be delivered in test animals and in human research participants to generate robust antibody responses.
3. SARS-CoV-2 typically has a naturally limited, acute-clearing infectious cycle in each infected person.
4. Large numbers of participants volunteered to participate in global COVID-19 vaccine clinical trials and as the SARS-CoV-2 viral "attack rate" was high, vaccine efficacy could be measured rapidly.

The success of COVID-19 mRNA vaccine development has raised interest in ongoing efforts to apply mRNA vaccine technology to other global infectious disease challenges. There is no doubt that mRNA can play a very important role in the future of global health. However, many of the factors that allowed COVID-19 vaccines to be rapidly developed and commercialised are not equally applicable in the case of other specific global health concerns, where additional challenges are present.

AIDS is a disease caused by one of two closely related viruses: Human Immunodeficiency Virus-1 or Human Immunodeficiency Virus-2 (collectively "HIV"). HIV is transmitted by exposure to body fluids from an infected individual, mostly at mucous membranes through sexual activity, by contaminated blood products, or via shared needles during intravenous drug use. Analogous to the spike protein expressed on SARS-CoV-2, HIV particles carry envelope proteins that bind to receptors on human target cells and mediate infection. HIV specifically infects a subset of white blood cells – "CD_4+ T cells" – vital for maintenance of the human immune system. After initial acute HIV infection, an infected person's CD_4+ T cells are gradually eliminated over a period of years, resulting in eventual loss of immune function and symptomatic AIDS. Without antiviral drugs to suppress HIV replication, persons with AIDS eventually die of secondary infections due to immune failure.

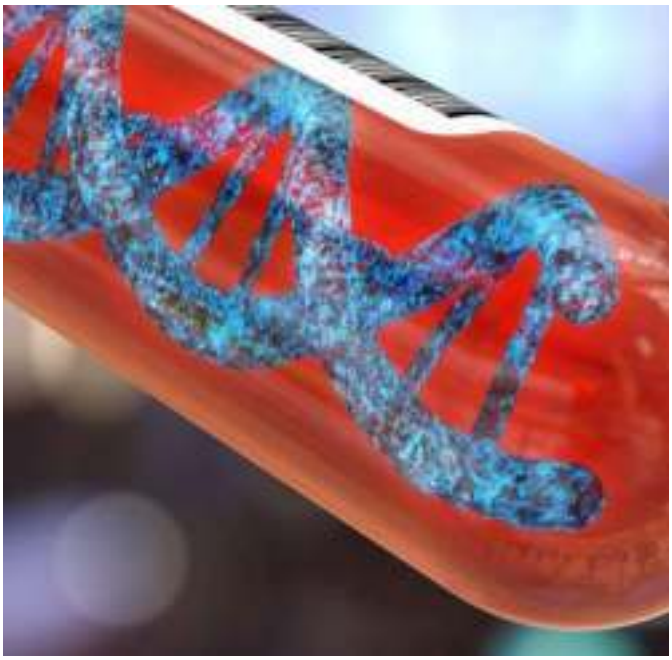
Similar to the SARS-CoV-2 spike protein binding to the ACE2 receptor on a target cell, a component of the HIV envelope protein, GP120, binds to the CD_4 protein on a target CD_4+ T cell. GP120 binding to CD_4 is followed by a complex series of molecular interactions resulting in HIV entry and productive infection of the target cell. These broad similarities in the viral life cycle, depending on specific interaction of a viral surface protein with a cellular receptor, raise the question of whether the impressively rapid success of mRNA vaccine development for COVID-19 can be replicated with AIDS. Decades of effort spent on AIDS vaccines have yielded incremental but significant advances toward a globally effective HIV vaccine. While extensive research has shown that the relatively simple type of antibody responses associated with COVID-19 vaccine efficacy are inadequate to protect against HIV infection at the population level, new findings point the way to more effective anti-HIV responses.

Some factors that make the HIV envelope protein a difficult target are as follows:

1. Globally, HIV-1 exists in genetically distinct "clades" with different susceptibility to various kinds of antibodies. In addition, replication of the HIV genetic code is intrinsically error-prone, resulting in a much greater degree of genetic diversity within replicating HIV viral populations compared to SARS-CoV-2. As a result, HIV infection takes the form of a "viral swarm" containing many genetic variants, some of which will be capable of evading any typical vaccine-induced immune response.
2. Like SARS-CoV-2, HIV incorporates a kind of sugar molecule into the envelope proteins expressed on the viral surface. These glycan sugar moieties serve as a screen or camouflage to keep host antibodies away from essential targets on the viral particle.
3. Whereas the spike proteins on the surface of SARS-CoV-2 are present in a target-rich array, the envelope proteins on HIV are sparse and spread out on the viral surface. This sparsity interferes with certain close molecular interactions of attacking antibodies that contribute to antiviral efficacy.

New approaches to mRNA vaccine design have the potential to overcome these challenges and promote production of "broadly-neutralising" antibodies against HIV.

Aside from these differences in viral particle structure, there are other important differences in viral biology that make HIV vaccine development a more difficult challenge. Importantly HIV is a retrovirus, which means that after infecting a target cell, HIV goes through a stage where the HIV genetic code is integrated into the host chromosomal DNA. This retroviral DNA functionally becomes part of the host cell genome. The latency time from integration to reactivation and production of new viral particles may be as short as a few hours or as long as many years. During these extended latency periods, the retrovirus exists essentially as a short sequence of DNA



code in the chromosome of the infected cell, functionally invisible to the immune system. Upon reactivation, even a small number of these latently infected cells is sufficient to seed active systemic infection and eventually lethal AIDS in the infected person.

This key life cycle factor makes the "victory conditions" of HIV vaccine development much more stringent than those applied to the COVID-19 pandemic. Whereas a COVID-19 vaccine can be deemed a success if it significantly inhibits viral replication during the acute disease phase and prevents severe disease, the primary goal of HIV vaccine studies generally includes prevention of latent infection that may reactivate weeks or months after initial exposure. A COVID-19 vaccine can provide significant public health benefits simply by keeping infected people out of the hospital during the acute phase of infection. To be really useful, an HIV vaccine must induce a much more suppressive antiviral immune response and prevent viral replication occurring.

As mentioned above, adaptive immunity involves more than just humoral antibody responses and the B cells that produce them. T cells also play critical roles in protection from infectious disease. Broadly speaking CD4+ "helper" T cells direct and modulate immune responses, whereas CD8+ "killer" T cells directly eliminate virally infected cells. Many lines of evidence from *in vitro* studies, animal models, and human clinical research demonstrate potentially critical roles for T cells in antiviral immune responses induced by viral infection.

The first mRNA vaccines to be commercialised are relatively simple and consist of an LNP encasing an mRNA strand encoding one viral protein. In some cases products of this type may not meet the challenge of protection against diseases that cause latent and chronic longterm infections, where viral replication continues to occur. Importantly, however, the potential contribution of RNA products to effective vaccines extends far beyond the current first-generation modalities. Examples of emerging concepts in development for RNA vaccines include the following:

- Utilising protein modelling and molecular engineering to create more stabilised and immunogenic synthetic antigens.
- Heterologous prime-boost vaccination plans including mRNA vaccine plus "booster" doses from other categories of recombinant or live-attenuated vaccine products. Many years of preclinical research indicate that a rationally designed mix-and-match approach with multiple types of vaccines for the same infectious agent can provide synergistic benefits in terms of maximising immune protection and minimising unwanted effects such as "immunodominant" off-target responses.
- RNA vaccines encoding multiple synthetic antigens, each optimised to promote a different branch of immune memory (antibodies, helper T cells, killer T cells).
- Whereas first-generation mRNA products are linear strands that persist for only a short time after vaccination, newer classes of mRNA products are under development, some of which have circular structures and others are capable of self-replication, or have other features designed to promote persistent antigen expression after vaccination. These approaches are intended to lead to stronger, broader, and more durable immune responses.
- LNPs currently in use do not provide targeted delivery of mRNA cargo to particular anatomical or immune compartments in the body. Rapid advances in the field of nanomaterials provide the potential for more complex, engineered nanoparticles that can deliver RNA products to specific tissues or cell types with a regulatable timing to enhance vaccine responses.
- For infections that originate from exposure at a mucosal surface, there is growing evidence that the most protective immune responses may engage special mucosal immunity functions. Vaccines designed to stimulate immune responses at a mucosal surface (such as the nasal mucosa) may promote mucosal immune responses with enhanced protective capabilities specifically for mucosal infections. Any or all of the above technologies can potentially be engaged to enhance design of mucosal vaccines.

In conclusion, the utility of RNA vaccines to provide significant public health benefit in the context of the COVID-19 pandemic health emergency has now been clearly demonstrated. The molecular design and formulation of these first-generation products produce limitations in the protective efficacy of resulting immune responses. Newer technologies and combinations of multiple vaccine approaches are likely to extend the efficacy and range of applications for RNA vaccines.

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Assent Is Not Just for Children:

Requirements and Best Practices for Assent in Clinical Research

Informed consent requires that prospective participants receive sufficient information about a research study and that they have the capacity to decide about their voluntary participation.[1] Paul Appelbaum defines capacity as the ability to understand the information provided, understand the consequences of a decision, make a decision and communicate a choice.[2] For those who do not have the capacity to provide consent, the challenge for the research community is how to balance the inclusion of these individuals in research with the requirement to protect those who may be vulnerable to coercion or undue influence.[3] In adults, significant numbers of clinical trials are exploring treatments for conditions that are causes of impaired decision-making capacity including neurologic diseases and psychiatric illnesses raising ethical considerations for the inclusion and the protection of these individuals in research.

In this paper we highlight the importance of asking prospective participants, who do not have the capacity to provide consent, for their assent to participate in research. We review the current regulatory and ethical framework for assent of both adults lacking capacity and children and offer strategies for engaging these potential participants in the assent process.

Is Assent Required of Adults Who Lack the Capacity to Consent? An Ethical Framework

Assent is the affirmative agreement to participate in research from a person who has some ability to understand but is unable to provide legally-effective consent.[4] While the United States regulations for human participant research require assent from children who cannot provide consent due to their age, they do not explicitly mandate obtaining assent from adults who lack the capacity to provide consent. Nevertheless, besides the obvious parallel for assent with children, there is support for this requirement in multiple regulatory frameworks, including the guiding principles of the Belmont Report[5] and US Food and Drug Administration (FDA) guidance on informed consent.[6]

The Belmont Report provides three basic ethical principles to guide human participants research.[7] These principles are Respect for Persons, Beneficence, and Justice. The first principle of Respect for Persons advocates for two ethical convictions, "first, that individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection." The second conviction is addressed by requiring consent be obtained from a legally authorized representative (LAR) whenever an adult participant lacks capacity to consent. The first ethical conviction is not subsumed by the second; that is, respect is not limited to legally effective consent and decisional capacity is not a binary attribute. Participants without full capacity may fall along a spectrum of capacity and awareness and deserve the respect of engagement as they are able.

Like consent, assent is an ongoing process that may evolve over time. If a participant who was unable to be consulted for assent at the time of enrollment later regains some cognitive ability, the study team should attempt to obtain assent when the participant can be consulted.

The FDA states the following in a guidance document[8] on informed consent:

"Institutional Review Boards (IRBs) and investigators should carefully consider whether the inclusion in research of individuals who lack capacity is ethically appropriate and scientifically necessary. Whenever individuals with impaired consent capacity (partial, fluctuating, or complete) are or may be enrolled in clinical studies, ethical and procedural challenges arise. Considerations that may help address these challenges, and provide additional safeguards include:

Assessing whether individuals who cannot provide legally effective consent on their own behalf may nonetheless be able to provide some form of oral agreement (e.g., assent) at the outset of the study and, as appropriate, throughout the course of the research (e.g., for subjects with progressive disorders), and how such oral agreement would be documented. In such a circumstance, an LAR would need to provide documented written consent."

Therefore, the requirement for obtaining assent from adult participants who lack the capacity to provide consent is not formally established in federal regulations. However, in order to ensure a participant's autonomy is respected, WCG IRB requires investigators to obtain assent whenever a participant is unable to provide consent for themselves, but they are capable of being reasonably consulted.

The IRB is responsible for determining the appropriate method for obtaining assent and documenting assent. A separate assent form is not recommended for adult participants. Instead, WCG IRB generally recommends documentation of the verbal assent process by including the signature of the person obtaining assent and the date assent was verbally obtained on the informed consent document, which will also be signed by the LAR providing consent.

Is Assent Required of Children? A Study-by-Study Determination

US federal regulations[9] require that the IRB determine that adequate provisions are made for the assent of children when the IRB judges the children are capable of assent. Regulations[10] define "children" as persons "who have not attained the legal age for treatments or procedures involved in the research under the applicable law of the jurisdiction in which the research is being conducted." Thus, the age of consent is determined by state or other local laws. In cases where a child is participating in research, the agreement of the parent(s) (or legal guardian) is referred to as "parental permission"[11] rather than consent.

The capacity to make voluntary, informed decisions evolves throughout childhood and adolescence and varies among individuals of the same age. The goal of the assent process is to involve children in discussions and decisions about research participation to the extent they are capable.

The IRB is required to determine whether assent will be required on a study-by-study basis. The IRB must consider several factors, including the characteristics of the patient population (developmental status and capacity, medical history, and amount of experience with the medical system, etc.) and the potential for direct benefit to the

participants resulting from study participation. The IRB may waive the requirement for assent in situations where the intervention may be important to the health or wellbeing of the participant, or in situations where the child is not capable of assent given their cognitive and emotional maturity and psychological state.

The Assent Process: What is Required?

While the federal regulations require the assent of the child for certain kinds of research, these regulations do not elaborate on the specific elements of assent. In his essay on the ethical dimensions of research involving children (written in 1995 but still applicable today), William Bartholome[12] identified the following elements of assent to guide the assent process.

According to Bartholome the investigator should:

1. Help the child "achieve a developmentally appropriate understanding of the nature of [their] condition."
2. Disclose to the child "the nature of the proposed intervention and what [they are] likely to experience."
3. Assess the child's understanding of the information provided.
4. Secure "the child's willingness to accept the proposed intervention."

When research involves younger children, the investigator should focus on providing basic information about what will happen, and on responding to questions and concerns. For older children and teenagers, the assent process may be similar to the consent process for adults, especially if the teenagers have chronic illnesses and experience with medical procedures. In some cases, a prospective participant may feel more comfortable asking the research team questions without their parent present.

How is Assent Documented?

The regulations do not provide a set age threshold for assent and place responsibility on the IRB to decide whether to require an assent form so the requirement for assent forms and documentation of assent may vary across IRBs.

Assent requires that participants have a basic understanding of what might be asked of them, and what might happen. The information appropriate to the individual child's cognitive level and situation may vary widely across studies and between children. For that reason, the individual assent discussion is more important than what, if any, forms are used. Whether documenting an assent discussion on the consent form/parental permission form, or using an assent form, the basic elements of consent should be addressed at the level appropriate for the child. If the sponsor or the researchers wish to use an assent form, the form should be appropriate for the likely capabilities of the children enrolled considering their age, physical and cognitive condition (which may be impacted by the disease being studied), and situation (such as where the assent discussion would occur).

The IRB uses guidance from both the FDA and Office for Human Research Protections (OHRP) to make their determinations for the requirements of documentation of assent:

FDA recommends:

"Older children may be well acquainted with signing documents through prior experience with testing, licensing and/or other

procedures normally encountered in their lives. Signing a form to give their assent for research would not be perceived as unusual and would be reasonable. Younger children, however, may never have had the experience of signing a document. For these children requiring a signature may not be appropriate, and some other technique to verify assent could be used. For example, a third party may verify, by signature, that the assent of the child was obtained."[13] From this guidance, the IRB may determine no assent form is required and documentation that the assent process occurred is appropriate. For research that enrolls children across a large range of ages (e.g., from infant to adolescent), it may be appropriate to have different versions of the assent form written in a language tailored to the participant's level of cognitive development. Because the ability of each participant may vary even among children of the same age, it is preferable to have these assent forms written for different levels of development rather than specific age ranges.

OHRP notes that:

"…the IRB has the discretion to decide what form of documentation is required for a study; but offers the following as guidance: If adolescents are involved in research where a consent form would have been used if the subjects were adults, it would generally be appropriate to use a similar form to document an adolescent's assent. If young children are involved who are as yet unable to read, documentation should take a form that is appropriate for the purpose of recording that assent took place. The IRB may also decide that documentation of assent is not warranted."[14]

Assent: General Best Practices

While researchers and IRBs focus much attention on the documentation of assent, research suggests that assent is most effective when it occurs as an ongoing/iterative process as opposed to the one-time act of signing of a written document.[15] When possible, prospective participants should be given time to think about whether they want to enroll in the study. They should also be afforded the opportunity to speak with others before making a decision. Discussions should allow sufficient time for questions and further explanations. These discussions may take place over several visits.

In general, the practices that apply to informed consent also apply to the practice of assent:

Assent should still be obtained, even when the requirement for signature documentation of consent for adult participants has been waived, although assent may be verbal.

If the informed consent or parental permission document is updated with new information during the study, any assent documents should also be appropriately updated, and a "re-assent" discussion should occur whenever a "re-consent" discussion would occur.

Conclusions

The need to improve conditions that are causes of impaired decision-making capacity including neurologic diseases, psychiatric illnesses, or diseases that affect children highlights the importance of developing effective strategies to ensure both the inclusion and the protection of these individuals in research.

The guiding principles of the Belmont Report, and FDA guidance on informed consent recognise the importance of obtaining assent in the informed consent process. Assent should be sought in a manner that considers the participant's age, cognitive development, and capacity to make decisions. This will ensure the participant is involved in the consenting process to the extent they are able, thereby respecting their rights and autonomy.

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Critical Considerations when Designing Shipper Solutions for Clinical Trials

The shipping of high value, potentially lifesaving clinical trial pharma payloads requires expertly engineered, specialist solutions to ensure the precious products are protected and maintain their efficacy end to end. Due to this there are numerous components and challenges to consider.

Designing the products deployed for clinical trials requires several critical considerations to meet necessary criteria including:

- High performing materials and insulators
- High performing, stable coolants, for example using PCMs
- Ability to meet regulatory requirements
- Packing efficiency for the pharma client
- Volumetric consideration
- Be lightweight
- Be user/patient friendly
- Demonstrate sustainability and recyclability capabilities

Before engineering a packaging product, which must meet the exacting requirements of a specific clinical trial, it is important product designers have an in-depth understanding of the marketplace the product will operate within and how it will be utilised within a designated clinical trial.

With a pandemic there is an accelerated rise in patient-centric clinical trials, it's important to consider the end user or participant, alongside the warehouse teams that will handle the packaging, in addition to the latest regulatory requirements within that market space. There are also cost considerations, which when collectively combined, will help set the design boundaries for product engineers to work within.

When designing packaging products for deployment within the clinical trials space, it's essential to acknowledge the often vastly varying timescales involved within different trials. It can often take an extended length of time for a pharma product to be at the stage when it is ready for transportation and distribution, which might be due to the trial progress, necessary research, or issues within the trial project space.

In clinical trials it's imperative any risks are mitigated to help ensure the pharma product is delivered to the end user in its correct and safe state. With this consideration we acknowledge that performance stability during transit is a very prominent consideration for the design process due to how long it might have taken a specific trial to get to the position of transporting the pharma product to trial participants/patients.

Product performance stability requirements can relate to temperature stability, to mechanical stability and temperature duration in conjunction with any of the travel and transportation considerations, whether that be routing or customs considerations or transit times – they all need to be fully understood and appreciated specifically for clinical trial requirements.

From a design standpoint, budget must also be a key consideration, because often within clinical trials, the funding route is a sensitive consideration. Therefore, from a technical design point of view it's essential to achieve a balance between the product performance and stability with the cost, otherwise the product may not be successful.

Clinical Trial Challenges

When producing packaging for clinical trials and the pharma logistics sector there are several potential challenges.

When developing temperature-controlled packaging (TCP) it can be easy to get drawn into solving all design challenges that have ever been experienced but it is quite important that the boundaries enable the engineer to deliver an excellent product but not to over engineer and risk missing the original issue.

The product design needs to focus on meeting the crucial needs first and if it isn't a problem in the real world, it shouldn't be assumed it is a problem because a product designer has seen it in the design space. If this isn't managed carefully during the project process the proposed product could then end up being too expensive or too heavy for example.

Clinical trial packaging product development must meet regulatory requirements, so it is vital design teams understand all the latest regulations that need to be adhered to. The product must also meet the necessary mechanical and thermal requirements, particularly within clinical trials.

For example, you may have a precious vial of drug product, which could have taken years to develop and if its packaging isn't handled carefully within the transportation process, it can damage the payload. The protective packaging must be robust enough to ensure the pharma product within remains in its correct state, whatever the external stresses.

Any design development process needs to also be cost considerate, not only in relation to the price of the TCP box – it is also about the total cost of ownership. A clinical trial client will want to adhere to a designated budget; therefore, it can make more commercial sense for them to purchase a reusable shipper solution and then utilise that same solution for multiple trials.

It is important to know whether the TCP customer have a transit loop uses a closed loop transit programme? Which enables them to get the reusable packaging product back from its end destination. Product designers need to understand how the customer wants to

buy as well as how it will be used. There are a lot of configurations which need to be dealt with and the more detail available about the end user the better, as this enables engineers to design the product tailored to their needs.

Within clinical trials, tailored, bespoke shipper solutions are often needed, however, it's not the case that off the shelf systems will always be the right solution to meet all clinical trial challenges or requirements as such trials can be extremely specialised.

Having stability data relating to a specific medicine or therapy is beneficial for a designer to understand the parameters you can design within. It can allow some freedom within the design boundaries and assist when deciding on insulation components and achieving cost budgets.

Within clinical trials there are a lot of unknowns, which is where assessing potential risks is imperative with a comprehensive understanding of what will happen if that pharma payload goes out of temperature range.

If that drug stability data is not readily available, designers will need to consider the insulation and coolants required to minimise the risk, which can push the process in a different design direction.

With all these considerations when designing for the complex clinical trials market space it is extremely exciting and rewarding to solve the customers challenges and deliver a successful product that is fit for purpose and integrates smoothly in the customer and patient space too.

Patient-centric Clinical Trials Driving Design

When engineering a TCP product for deployment within a clinical trial, it is vitally important to consider the end user/ the patient and understand the overall user experience, as small efforts can have a large impact.

TCP designers want to better understand the user experience, the end goal, the transit and customs process. Whether that relates to visual instructions rather than written instructions, whether considering processing or return instructions, all those pieces can be interrogated to help create a deeper brief which should result in a better, more secure product that will enable the patient to have an easier experience, which is a crucial consideration to a successful clinical trial.

If the collaborative customer conversations aren't held upfront, the packaging product produced potentially won't hit the right mark with the end user. So, taking a consultative approach can make the entire design process much smoother. If sending someone a trial medicine, you want the TCP deployed to be user friendly and easy to use.

With transport and handling, it's important to look at the TCP product's journey from a customs perspective and how it gets transported from origin to destination. If we better understand those routes, what happens when the TCP reaches those touchpoints, whether that's customs, warehousing, or onward processing, the more information that's available and accessible the better. It will help ensure the transported pharma product is less at risk, which is what collectively everyone is aiming for- risk reduction in every case.

The pandemic highlighted how some TCP vendors were better equipped, from a broader product portfolio perspective, which enabled them to respond and adapt or re-engineer existing products to meet the needs of the global vaccine roll out.

Within the TCP industry it reiterated how important it is to offer a breadth of packaging products and to achieve a wider product

portfolio requires investment in an agile, experienced engineering team.

There is a longevity in what the product designers are providing within the industry, and it is important companies operating within the pharma logistics sector invest in engineering experts within their company structure.

Industry Trends

Sustainability in the sector is an emerging and increasingly important trend, whether that be sustainability in single use products in terms of material choices or sustainability in product choice including reusable products.

Determining how sustainability works with the design brief process and what is a successful sustainable product will change depending on what the TCP product is being used for and by who.

When it comes to sustainability the industry is going in the right direction and there is more that could be done. We are seeing an increase in 100 percent recyclable or compostable materials, but the challenge for us in the pharma solutions sector is that the current performance of the insulation isn't at a level that we can utilise to minimise the risk.

When considering reusable product selection, serviceability is key and the ability to access a global network of hubs where products can be cleaned, conditioned, and maintained is a rising requirement.

Within the sector there is a greater desire in the marketplace for serviceability and rental options for those organisations that don't have that infrastructure in place, a global network where products can be serviced. The increasing variety of rental options offer the opportunity to invest in a reusable TCP asset with the bolt-on of services and product maintenance that comes as part of a rental program. This offers cost saving and convenience to customers allowing them to select a tried, tested, high performing product direct from the manufacturer, thus minimising risk in the cold chain.

Going forward we will continue to see a requirement to order online, a climate of consumer convenience cultivated by the pandemic and numerous global lockdowns.

Within product solutions for clinical trials a collaborative, consultative approach will ensure the most reliable, high performing shipper solution is selected which best meets the complex clinical trial requirements and delivers payload protection throughout transit to the end user, ensuring efficacy of the lifesaving pharma product.

Karen Adams

Karen Adams is the Engineering Manager at Peli BioThermal. Karen is responsible for the development and qualification of Peli BioThermal products and has collaborated with key customers over her time with the business to ensure that products perform as they are intended in the field. Her areas of responsibility include product development, qualification, technical and customer support. Prior to her role in Peli BioThermal Karen comes from a Pharma and FMCG background and she holds a degree in Mechanical Engineering Design.

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