

# JOURNAL FOR CLINICAL STUDIES

Your Resource for Multisite Studies & Emerging Markets

PEER REVIEWED

**The Immense Potential of Africa's  
Advantageous Landscape**

**The Global Regulatory Landscape for Clinical Trials  
Considering the COVID-19 Pandemic**

**Special Considerations for Child Psychiatric Trials  
During a Global Pandemic**

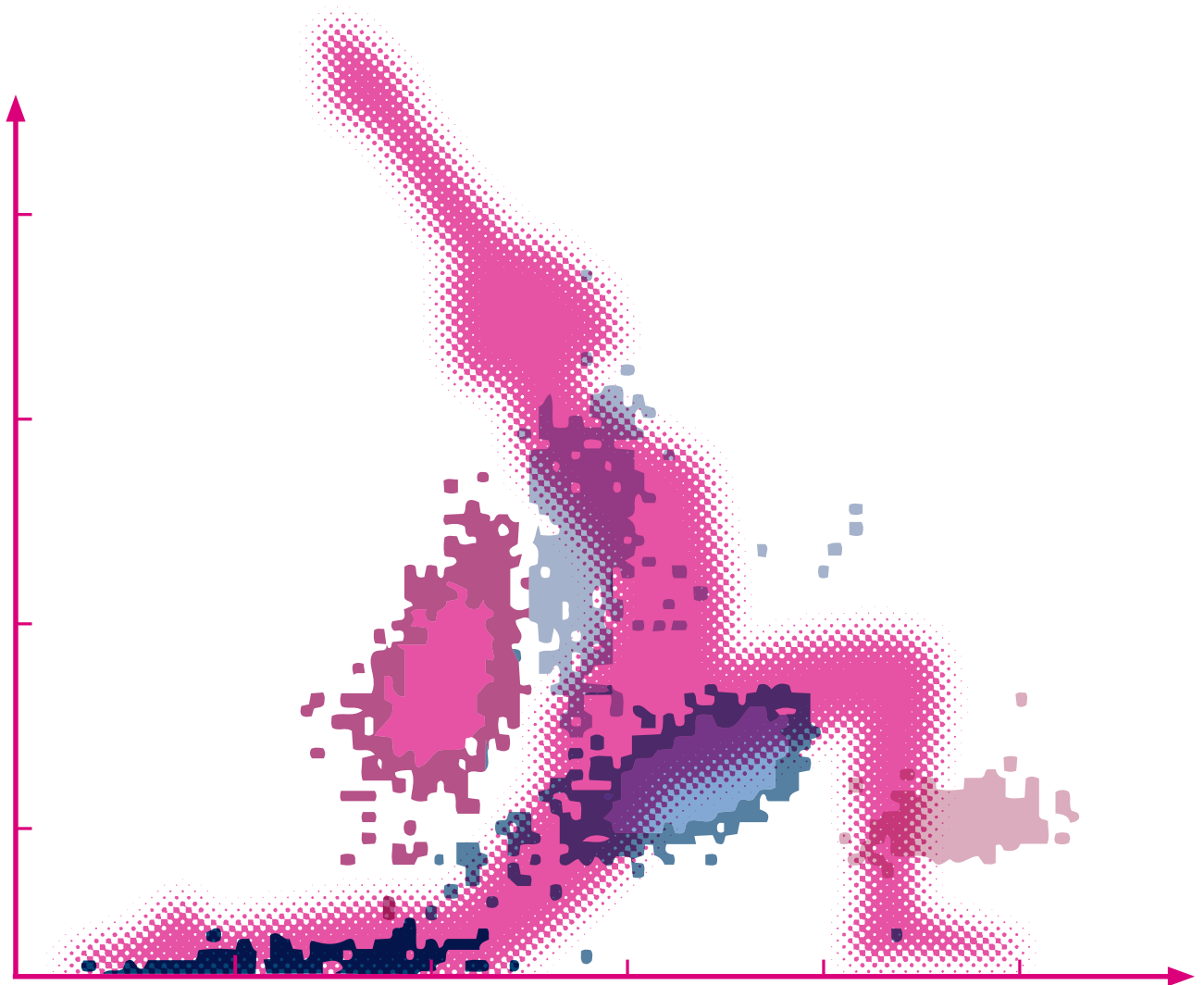
**Patients as People:**  
Operational Empathy Remains a Key Driver  
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Journal by Clinical Studies – ISSN 1758-5678 is published  
bi-monthly by PHARMAPUBS

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The current COVID-19 pandemic, caused by the novel coronavirus SARS-CoV-2, is the current focus of numerous drug therapies and vaccine candidates. We have seen swift action from regulatory authorities to fast-track clinical programmes to find a cure or treatment. However, **Bruno Speder and Robin Rogiers at SGS** question whether it would be possible that human challenge testing – or controlled infection models – could offer insights into developing therapies.

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The pressures on pharmaceutical organisations to capture, sift and process real-world adverse event data are immense – and soaring. So why are Safety & Pharmacovigilance departments lagging in their application of smart technology? **John Price at Arriello** looks at why more life science companies are not automating PV data capture and what the practical solutions are to meet demand.

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Contact-tracing apps and technologies are a hotly debated issue with legal, medical and technological implications. The most common mistake in the public debate is to put the tracing carried out by a private tech company to sell a service on the same level as the tracing carried out by governments to better manage infection risk during a pandemic. **Vincenzo Salvatore and Giulia Tenaglia at BonelliErede** offer hindsight into contact-tracing apps in Italy.

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Clinical research is a complex, expensive, and time- and resource-intensive process. Feasibility assessments play a crucial part in this clinical research planning process as it enables the sponsors and contract research organisations (CROs) to evaluate the possibility of conducting clinical research in a particular region or country. **Bee Ying Tan, Audrey Ooi and Noorzaihan Mat Radi at Clinical Research Malaysia** put together a report on the reasons behind feasibility rejection.

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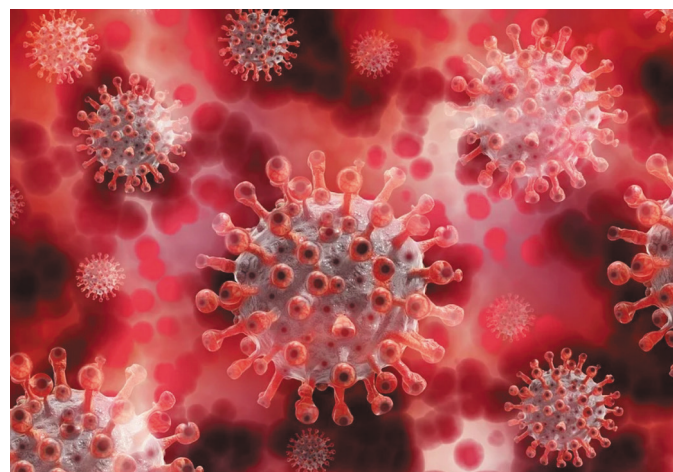
The medical device industry makes a colossal number of items ranging from invasive gloves to non-natural joints to imaging gear and assumes a pivotal job in growing new therapeutic advancements that can improve the capacity to analyse and treat disease. Like physician-endorsed drugs, medical devices are controlled by the Food and Drug Administration (FDA). **Balamuralidhara V, Kavya S Reddy, Sanhita Singha Roy and M P Venkatesh at JSS Academy of Higher Education & Research** look at clinical evaluation and post-marketing surveillance of medical devices in the USA.

## 30 The Immense Potential of Africa's Advantageous Landscape

The low representation of African countries in clinical trials is not unusual. Poor visibility of existing sites, limited infrastructure, cultural barriers, misunderstandings of requirements to work in the region, and unpredictable clinical trial regulatory timelines are some of the key issues hindering investments in this area and hence causing a burden to conducting clinical trials within Africa. **Carole Wallis and Sofie Vandevyver at Cerba Research** offer practical solutions, while highlighting the incredible potential of Africa's advantageous landscape.

## 34 Why the Development of COVID-19 Diagnostics is Far from Over

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Healthcare data comes in all shapes and sizes, just like the patients and patient population it is derived from. Data sources vary widely, for example individual metrics such as heartbeat and pulse from an Apple watch or individual EKG or genetic sequence, from patient registries, to electronic medical records, to claims data, to eCRF for patient chart review. **Douglas Drake at Clinerion LTD** looks at the complexity of finding and treating rare disease patients in a global digital haybale.

## 46 Special Considerations for Child Psychiatric Trials During a Global Pandemic

As the COVID-19 pandemic continues, many sponsors, CROs, investigators, and IRBs have modified clinical trials, moving visits from clinics to living rooms worldwide. When trial participants are children, a more complex decision process must govern when and for whom a move to virtual visits is possible. **Dr. Joan Busner at Signant Health** looks at the regulatory considerations for child psychiatric trials during COVID-19.

## TECHNOLOGY

## 50 Patients as People: Operational Empathy Remains a Key Driver of Recruitment Success

Big data, artificial intelligence and digital platforms have dramatically transformed the clinical research landscape. Yet despite these extraordinary advances in technology and communication tools, the prevailing challenge of clinical trials has remained constant for decades: recruiting and retaining qualified patients. **Tom Ruane at Parexel** explains why operational empathy remains a key driver of recruitment success, even during COVID-19.

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Medical devices play a critical role in the lives and health of millions of people worldwide. From everyday household items such as oral thermometers to complex implantables such as deep-brain stimulators, patients and the public rely on regulators to ensure that legally marketed medical devices have been shown to be safe and effective. **Shrinidh Joshi at Kolabtree** puts forward the best practices for medical devices during clinical trials.

## LOGISTICS AND SUPPLY CHAIN MANAGEMENT

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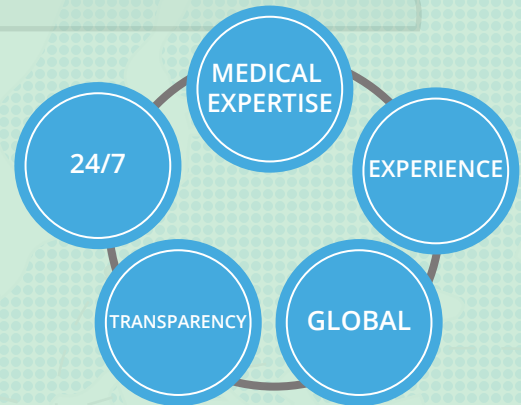
A global network used to deliver products and services from raw materials to end users through flow of information, physical distribution and cash define what a 'supply chain' is. In the healthcare sector, the end user is the patient, and the only product that they are after is improved health at the most affordable price possible. **Sharan Ashwin Mandavia** provides a guide to managing a successful and efficient supply chain in the healthcare sector.

# Medical Monitoring for your next Clinical Trial










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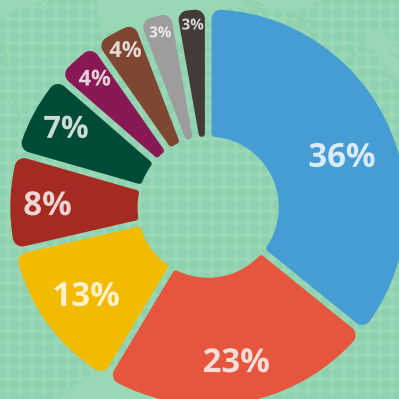
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It is safe to say that 2020 has been an unpredictable year. The outbreak of COVID-19 created unprecedented circumstances for the conduct of clinical trials across the world. While the industry has experienced challenging conditions in managing research before, for example, during political unrest or natural disasters, this type of crisis was typically local,

short-term, and contingency plans could in many cases utilise lessons learnt from past occurrences.

This is a sentiment echoed by **Marcelina Rybiańska and Aman Khera at Worldwide Clinical Trials** who explain how COVID-19 has put a huge strain on the healthcare system. The unique situation of patients placed under quarantine plus disruptions in Investigational Medicinal Product (IMP) supply made it difficult to adhere to the approved research plans and forced urgent modifications to secure data validity.

As a result, the clinical trial space has had to adapt, innovate, and explore virtual options, such as wearables, video calls and remote technology to facilitate a better patient experience. According to **Tom Ruane at Parexel**, remote technology is particularly useful for COVID-19 trials, in which patients are isolated yet there is still a need to frequently report their symptoms to clinicians. This is because the pandemic has exponentially hastened our need for accurate data in real time to help drive sound medical decisions. Remote monitoring not only provides accurate data, but it also cuts down on speed trial timelines, bringing therapies to more patients, as told by **Rik Van Mol at Veeva**.

The rise of the virtual clinical trial landscape is a growing trend, with sponsors, CROs, investigators, and IRBs modifying clinical trials, by moving visits from clinics to living rooms worldwide. With a sizeable shift in attitude and practice towards innovative remote and virtual techniques that bring trials to patients, the clinical space as we know it is changing. Special considerations must now be put in place for vulnerable age groups, such as children, to govern when and for whom a move to virtual visits is possible.

**Joan Busner at Signant Health** explains why decisions to move child psychiatric trial visits from face to face in-clinic to virtual and remote require careful deliberation and multiple special considerations. This kind of heart-felt empathy reduces fear and encourages parents to consider clinical trials in the context of helping not only their child, but other children whose parents are experiencing the same gripping fear and uncertainty.

Anxiety during clinical trials is certainly not uncommon, but is especially heightened during the pandemic, with **Vicenzo Salvatore and Giulia Tengalia at BonelliErede** showing that the government's intrusion into our personal lives has manifested into us feeling distrust and fear. When there is fear, recruiting patients for clinical trials or even new technologies becomes overwhelmingly challenging. As a result, the use of virtual technologies like contact tracing apps needs to be reevaluated to maintain regulatory compliance, whilst putting patient-centricity first.

Big data, artificial intelligence and digital platforms might have dramatically transformed the clinical research landscape, but clinical trial diversity is still somewhat lacking. Countries like Africa hold immense potential because of its size, demographic and desire to improve health and life expectancy. However, it only accounts to less than 2% of the number of clinical trials. **Carole Wallis and Sofie Vandevyver at Cerba Research** believes this is because of limited infrastructure, cultural barriers and unpredictable clinical trial regulatory timelines, which are some of the key issues hindering investments in this area and hence causing a burden to conducting clinical trials within Africa.

Although the low representation of Africa in clinical trials is not unusual, more must be done to ensure that clinical trials are not homogeneous, so that patients from all backgrounds are fairly included. Clinical trial diversity, remote monitoring and regulatory compliance will remain as hot topics throughout 2020.

I hope you all enjoy your summer and I look forward to welcoming you back in Autumn, with more enthralling articles to be included in JCS.

You may have noticed that we have changed the theme of the front cover picture of the JCS Journal. We started JCS with the unique goal of highlighting emerging countries and thoroughly analysed these countries as a clinical trial destination. Hence, we featured the national flower of one of the countries highlighted in that issue. Although we remain committed to bringing you a market analysis of emerging clinical trial destinations, JCS will now focus on therapeutic and regulatory aspects throughout 2020. The front cover picture will represent one of the therapeutic focuses that we have in this issue.

*Ana De-Jesus, Editorial Co-Ordinator  
Journal for Clinical Studies*

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## ‘First’ Therapeutic Approvals Bring Patients Hope

When novel drugs and biologics hit the market, the treatment horizon for many patients is suddenly broadened. US Food and Drug Administration (FDA) ‘firsts’ can present a vital step toward advancing the health of patients. Apart from the case of a first-ever treatment approved by the FDA in a particular disease, other firsts could include a novel category of treatment (e.g., gene therapy), the first approved new product in some time, or the first of a given treatment approved in the US.

The FDA explains on its webpage “Novel Drug Approvals for 2020” that, each year, the Center for Drug Evaluation and Research (CDER) approves a wide range of new drugs and biological products, some of which are innovative new products that never have been used in clinical practice. As of July 24, the webpage listed a total of 29 new molecular entities (NMEs) and new therapeutic biological products approved by CDER in 2020. Among firsts in the table, including several that relate to rare conditions, are:

No.	Drug Name	Approval Date	FDA-approved Use
25	Dojolvi (triheptanoin)	6/30/2020	First therapy for the treatment of long-chain fatty acid oxidation disorders
19	Qinlock (ripiretinib)	5/15/2020	First drug for fourth-line treatment of advanced gastrointestinal stromal tumour (GIST)
18	Retevmo (selpercatinib)	5/8/2020	First therapy for patients with lung and thyroid cancers with a certain genetic mutation or fusion
17	Tabrecta (capmatinib)	5/6/2020	First targeted therapy to treat aggressive form of lung cancer
14	Pemazyre (pemigatinib)	4/17/2020	First treatment for certain types of cholangiocarcinoma
12	Koselugo (selumetinib)	4/10/2020	First drug for NF1
10	Isturisa (osilodrostat)	3/6/2020	First drug to directly address cortisol overproduction in Cushing’s disease
3	Tazverik (tazemetostat)	1/23/2020	First treatment for patients with epithelioid sarcoma, a rare soft tissue cancer
2	Tepezza (teprotumumab-trbw)	1/21/2020	First drug to treat thyroid eye disease
1	Ayvakti (avapritinib)	1/9/2020	First drug specifically approved for GIST harbouring a platelet-derived growth factor receptor alpha (PDGFRA) exon 18 mutation

**Note:** This listing does not contain vaccines, allergenic products, blood and blood products, plasma derivatives, cellular and gene therapy products, or other products approved in 2020 by the Center for Biologics Evaluation and Research (CBER).

Having no treatment available is a common reality in the rare disease realm. The FDA notes on its “Rare Diseases at FDA” webpage that many rare conditions are life-threatening, and most do not have treatments. Currently, there are >7000 rare diseases affecting >30 million people in the US, the agency says.

As explained in the FDA’s *Draft Guidance for Industry: Rare Diseases: Common Issues in Drug Development (Revision 1)*, issued in February 2019, the Orphan Drug Act generally defines a rare disease or condition as one affecting <200,000 people in the US. However, most rare diseases affect far fewer people, the guidance states.

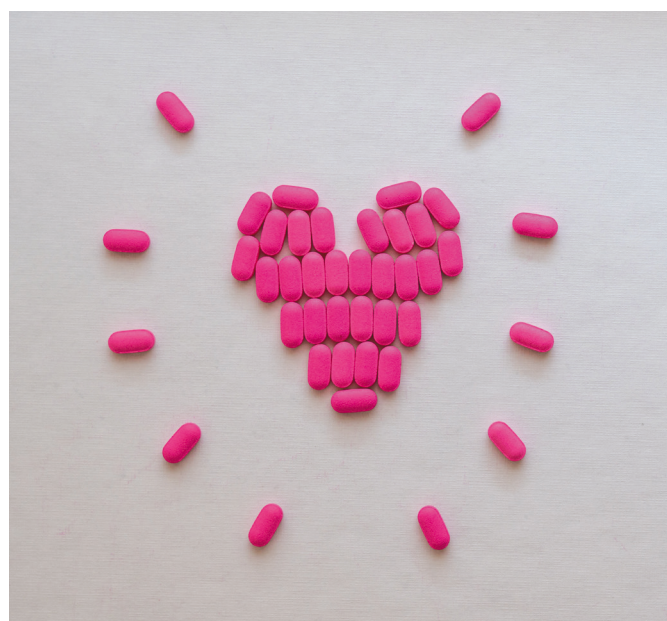
One of the recent first market entries for a rare condition, as listed above, was Koselugo (selumetinib), from AstraZeneca Pharmaceuticals LP. An inhibitor of mitogen-activated protein kinases 1 and 2 (MEK1/2), Koselugo was approved by the FDA

on April 10, 2020, for the treatment of paediatric patients aged ≥2 years with NF1 who have symptomatic, inoperable plexiform neurofibromas (PN).

NF1 affects males and females in equal numbers, affects all races and ethnic groups equally, and is estimated to occur in 1 in 2500 to 3000 births, states the National Organization for Rare Disorders (NORD). It is a genetic disorder characterised by the development of multiple benign tumours of nerves and skin (neurofibromas) and areas of abnormal skin pigmentation.

The National Institute of Neurological Disorders and Stroke (NINDS) of the National Institutes of Health (NIH) notes that symptoms of NF1 — which may be evident at birth and nearly always by the time the child is 10 years old — may include light brown spots on the skin, ≥2 growths on the iris of the eye, a tumour on the optic nerve, a larger than normal head circumference, and abnormal development of the spine, a skull bone, or the tibia. The symptoms are mild in most cases, and individuals live normal and productive lives. In some cases, however, NF1 can be severely debilitating and may cause cosmetic and psychological issues.

“Everyone’s daily lives have been disrupted during the COVID-19 pandemic, and in this critical time we want patients to know that the FDA remains committed to making patients with rare tumours and life-threatening diseases, and their unique needs, a top priority,” said Richard Pazdur, MD, director of the FDA’s Oncology Center of Excellence (OCE) and acting director of the Office of Oncologic Diseases in CDER, in the agency’s press release announcing the approval of Koselugo.







Another recently approved first drug for a rare condition was Pemazyre (pemigatinib), from Incyte Corporation. A protein kinase inhibitor, Pemazyre was granted FDA approval on April 17 as the first treatment for adults with certain types of previously treated, advanced cholangiocarcinoma, a rare form of cancer that forms in bile ducts.

In its press release about the Pemazyre approval, the FDA explained that, at diagnosis, most patients with cholangiocarcinoma have advanced disease, meaning that the disease is no longer treatable with surgery. These patients have “no other good options” after first-line chemotherapy treatment, Pazdur said in the announcement.

#### When Other Drugs Fail

An example of a first approval for patients who have exhausted all existing FDA-approved therapies is Qinlock (ripretinib), a kinase inhibitor from Deciphera Pharmaceuticals, LLC. This drug was approved on May 15 as the first fourth-line treatment for adults with advanced GIST. The indicated patient population is patients who have received prior treatment with  $\geq 3$  kinase inhibitors, including imatinib.

“Despite the progress that has been made over the past 20 years in developing treatments for GIST, including four FDA-approved targeted therapies — imatinib in 2002, sunitinib in 2006, regorafenib in 2013, and avapritinib earlier this year — some patients don’t respond to treatment and their tumours continue to progress,” said Pazdur in the FDA’s press release announcing the Qinlock approval.

As shown in the above table, the first novel product approved in 2020 — Ayvakit (avapritinib), from Blueprint Medicines

Corporation (Blueprint) — is indicated for a particular type of GIST that does not respond well to standard therapies for this condition, noted Pazdur in the press release about the approval.

On April 28, Blueprint announced that top-line results from its Phase III VOYAGER trial did not meet the primary endpoint of an improvement in progression-free survival for avapritinib versus regorafenib in patients with third- or fourth-line GIST. Based on those data, the firm discontinued plans to further develop the drug in GIST indications other than PDGFRA exon 18 mutant GIST. On May 15, Blueprint announced that it received a complete response letter from the FDA stating that the agency could not approve the new drug application (NDA) submitted by Blueprint last year seeking accelerated approval of avapritinib for the treatment of adults with fourth-line GIST.

#### Deborah Komlos

Deborah Komlos, MS, is the Senior Medical & Regulatory Writer for the Cortellis suite of life science intelligence solutions at Clarivate. In this role, her coverage centres on FDA advisory committee meetings, workshops, and product approvals. Her previous positions have included writing and editing for magazines, newspapers, online venues, and scientific journals, as well as publication layout and graphic design work.



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# Advancing Towards Human Challenge Studies with the SARS-CoV-2 Virus

The current COVID-19 pandemic, caused by the novel coronavirus SARS-CoV-2, is the current focus of numerous drug therapies and vaccine candidates. This has seen swift action from regulatory authorities to fast-track clinical programmes to find a cure or treatment; however, would it be possible that human challenge testing – or controlled infection models – could offer insights into developing therapies?

In a human challenge trial (HCT), subjects may either be inoculated with a candidate vaccine before being exposed to a live challenge virus, or dosed with an investigative therapeutic agent following experimental infection. Studies are potentially more ‘crisp’ because subjects can be infected directly, they can be cared for throughout the test period, and the tests are properly regulated and controlled. In addition, the challenge agent has been properly characterised and subjects are not exposed to a relatively unknown agent in the environment where many other types of co-infections occur.

Any step towards undertaking an HCT for SARS-CoV-2 would need to be discussed with regulators, although some of the initial considerations are discussed here.

## Development of a SARS-CoV-2 Human Challenge Agent

The first choice is whether to use an attenuated or a homologous strain of the virus as the challenge agent, which must then be developed and manufactured. Although there are no specific guidelines for developing challenge agents, this process is similar to that of a drug or vaccine, and requires manufacturing in compliance with Good Manufacturing Practice (GMP), non-clinical testing under Good Laboratory Practice (GLP) conditions, and then a clinical development phase in the form of a first-in-human (FIH) titration study. A human challenge agent is considered to be a medicinal product, although there is no formal licensing procedure and steps such as a marketing authorisation application (MAA).

However, since these are medicinal products, the FDA requires an investigational new drug (IND) application to be filed for each new agent and, after GMP manufacture and non-clinical testing, a new agent needs to undergo a FIH Phase I titration/characterisation trial before being further studied and commercialised.

Presuming that a suitable agent can be manufactured safely, non-clinical development can begin, which takes place in two parts: an *in-vitro* cell-based characterisation assay to show the *in-vitro* infectivity properties of the agent; followed by an *in-vivo* characterisation study, carried out in an animal model (in the case of SARS-CoV-2 this would be ferret) in compliance with GLP.

There are also a number of non-clinical development human challenge agent areas that could be more condensed in comparison with traditional drug development. For example, pharmacokinetic and product metabolism studies are not usually required for human challenge agents and no formal toxicology studies are expected for this type of agent either, except if the virus is overly virulent or pathogenic, in which case the regulatory authorities may require this type of test to be carried out.

All the preclinical study results need to be described in the investigator’s brochure (IB) and the IND application dossier. This should include an ongoing stability results update from a GMP stability results programme following a classical 3-month, 6-month,

12-month reporting approach, or with an update each time the agent is used in a challenge study. Updated neutralisation assay results will also need to be reported.

## Containment and Biosafety Levels

With SARS-CoV-2 being a biosafety level (BSL) 3 organism, manufacturing and actual testing needs to be carried out in suitable facilities, therefore one regulatory discussion would be whether an attenuated challenge agent could be used and considered as a BSL2 organism. This means that the GMP development strategy for the agent is linked to the scientific strategy of the whole programme, as the choice of challenge agent could influence the practical execution of the overall programme strategy.

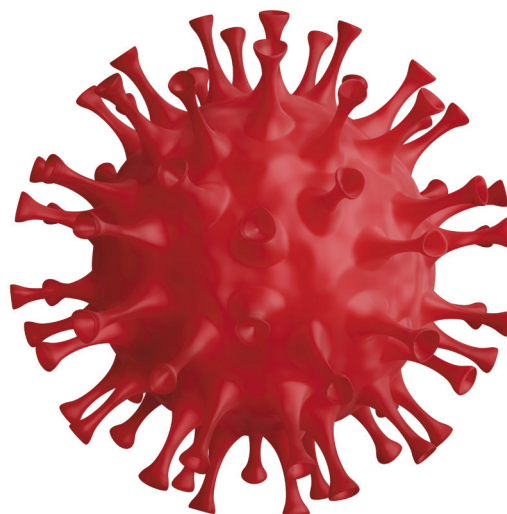
## Human Challenge Unit

Assuming that a BSL2 safety level is required, any unit undertaking a study into SARS-CoV-2 would need to hold the necessary permit and be equipped with BSL2-compliant beds, an airlock/HEPA filtered negative-pressure system and a dedicated BSL2 laboratory.

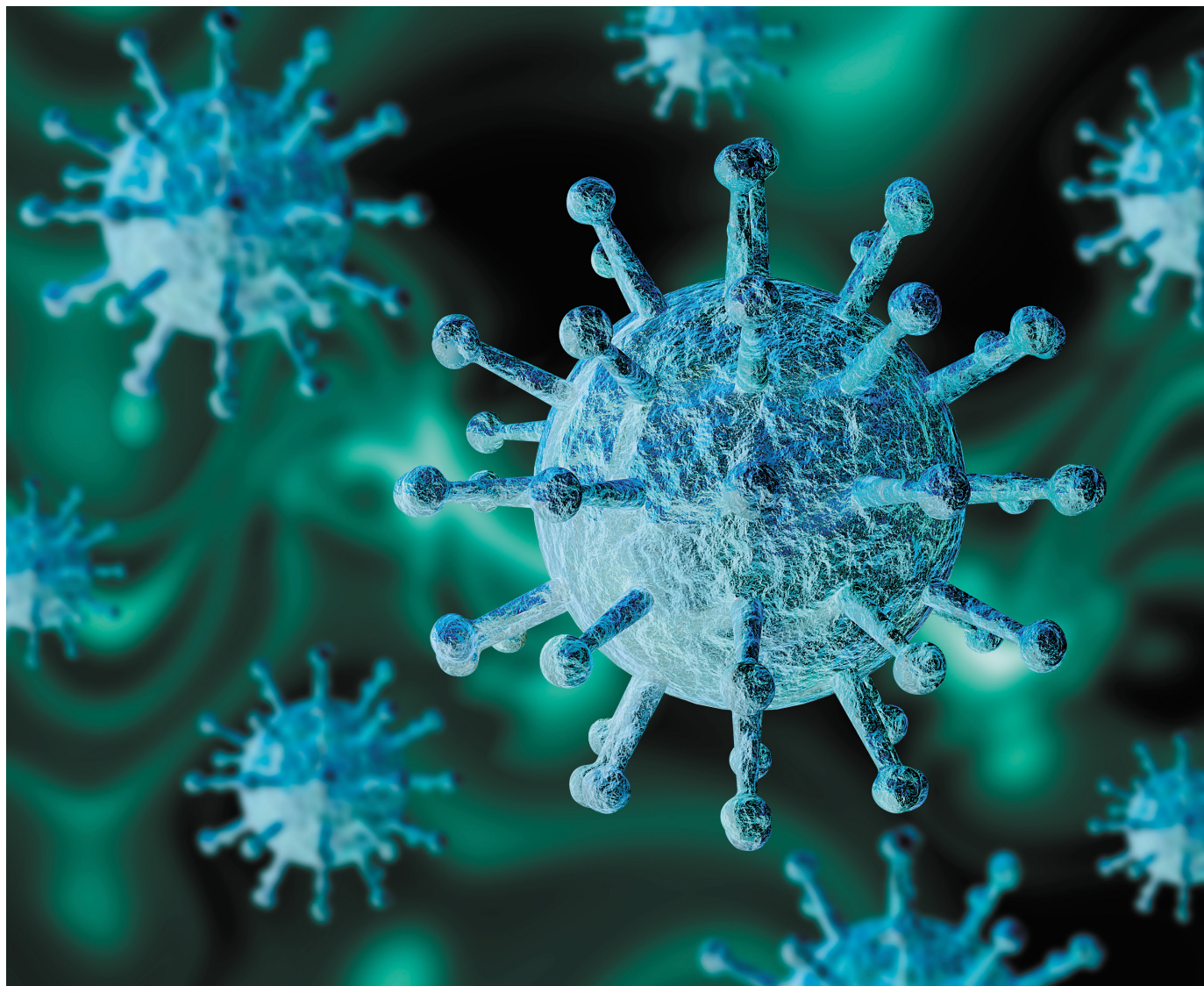
## Trial Design and Safety

For a potential COVID-19 challenge trial, as with every trial, subject safety is essential and starts with the identification of the right population to enter such a trial. Volunteers would need to be pre-screened using an accredited and validated serology screening system to avoid the dangers of shedding of virus in the community, so the length of stay of volunteers in the human challenge unit needs to be based on real-life data and data from animal studies. Any subject discharge would be predicated on achieving a negative antigen test result.

During the trial, the correct and sensitive markers need to be identified to follow a subject’s health, and the availability of intensive care units and trained staff must be ensured. The safety of the clinical trial staff and the wider community’s safety is as important as the study participants, so affected subjects will need to be adequately quarantined and clinical site staff will need to have access to appropriate PPE in order to make it impossible for the virus to infect outside the quarantine area.







When recruiting subjects, evaluating the risk factors for the virus must form part of the exclusion criteria. Age, obesity and smoking are known risk factors, while common morbidities associated with bad outcomes include diabetes, cerebrovascular disease and cardiovascular diseases such as hypertension, chronic kidney disease, and COPD. Immuno-compromised subjects should not be included in a trial.

### Stopping Rules and Further Actions

Stopping rules for HCTs must be carefully formulated based on scientific and medical rationale, which are preferably unambiguous, and based on clinical parameters that are quick and easy to obtain. These could be pulmonary function, oxygen saturation, temperature, spirometry, physical examination and the need for supportive care. As there are still many unknowns about the disease and its progression, it is essential to be very careful when following up on adverse events and to be very attentive in noting serious adverse reactions.

In conclusion, as this is a droplet infection, adequate containment of the challenge agent is required. The fact that there is currently no rescue medication available is a significant hurdle when trying to plan a COVID-19 challenge trial. In terms of PPE, European FFP2 and FFP3 and US N95 respiratory protective masks can filter out 95 per cent of particles when used correctly. These are the best available at present for use in high-risk procedures that create some type of aerosol, such as intubation or nebulisation. However, a large meta-analysis that has been conducted did not find any important benefit over general surgical masks in performing low-risk tasks such as transporting a patient, or obtaining a patient's blood pressure.

### Robin Rogiers

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### Bruno Speder

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## Remote Monitoring to Keep Clinical Trials Running Amid COVID-19

At the peak of the COVID-19 pandemic, clinical study monitors and patients were restricted from sites. Sponsors and CROs had to reassess how to keep trials on track while initiating and prioritising new trials related to COVID-19. The global pandemic forced thousands of trials to slow, stalling critical research into drugs and treatments.<sup>1</sup>

Clinical trial monitoring has been ripe for change for several years and the pandemic is accelerating an industry-wide effort to improve how trials are monitored. Regulators and industry stakeholders are now more open to this shift away from traditional on-site monitoring practices.

However, implementing a robust remote monitoring process creates new challenges. Version control issues can arise from sharing documents over email, collaboration between sites, sponsors, and CROs can suffer, and monitors may still rely on paper records – resulting in duplicated efforts. Purpose-built systems can be the answer to help companies embrace remote monitoring and transition to a virtual way of working.

Not only can dedicated systems support an organisation's shift to remote monitoring, these platforms can deliver improvements in data quality, efficiency, and overall costs of trials – along with benefits to sponsors, CROs, and sites.

### Improve Compliance with Better Data Management

Clinical trials are associated with a significant amount of paper documentation. CRAs must manually verify data contained within hundreds of files which can lead to review inconsistencies.

In an effort to share information with monitors remotely, sites often shift to sharing documents on email or enabling direct access to the electronic medical record (EMR). Not only are these methods complex, when done manually, they have the potential

to introduce errors or compliance issues. While these systems and processes may provide a temporary fix for an immediate need, they do not improve data quality or reduce compliance risk in the long term.

Purpose-built remote trial monitoring solutions, which are commonly built into a site's eRegulatory or electronic investigator site file (eISF), allow CRAs to review documents and conduct oversight activities without having to visit a physical site. Direct access to regulatory and source content enables CRAs to spot issues and trends more easily to improve quality. In addition, higher-level metrics, like safety issues or turnaround times, can be more easily identified. More specifically, the system capabilities should include:

- **Access controls** – Remote monitoring systems streamline source information sharing to authorised individuals. This prevents unauthorised access to identifiable patient information and reduces tracking and filing errors.
- **Audit trails** – All actions taken on a document are time-stamped and recorded to ensure data integrity and improve accountability.
- **Reporting** – Site- and study-level trends, such as safety issues or protocol deviations, can be more easily tracked so reviews can be prioritised and potential compliance concerns identified.

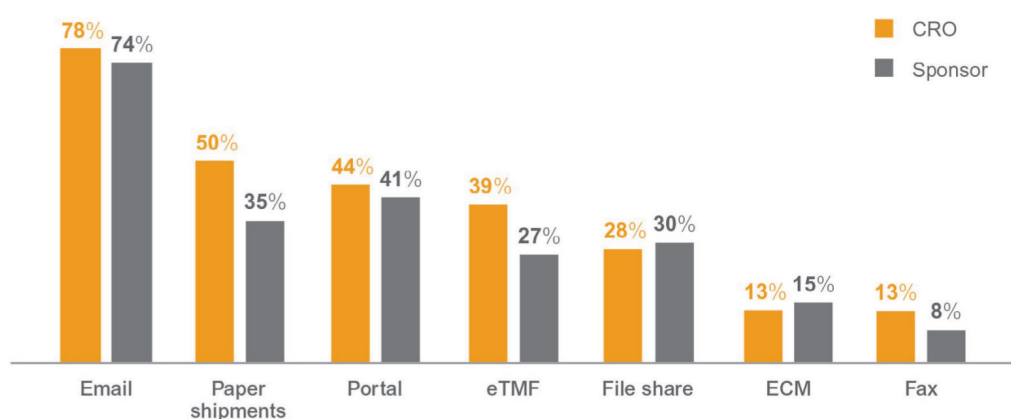
### Increase Efficiencies and Move Away from Paper

Around 90% of study-specific source forms are still created on paper<sup>3</sup>. Meaning sites and CRAs spend a lot of their time collecting and organising files, as well as tracking detailed communications via emails, attachments, and phone calls.

Remote monitoring systems can track detailed monitoring conversations in a centralised location and can automatically alert

### Methods Used by Sponsors and CROs to Exchange Information with Sites

Base: Total respondents, N=461



What methods does your organization use to exchange trial data and documents with study partners? Select all that apply per row. (Q6)

site coordinators and CRAs when feedback is needed. Not only does this improve efficiencies, it also reduces turnaround times.

Remote monitoring technology can also promote efficiency in the following ways:

- **Repeatable workflows** – With step-by-step workflows, sites can add CRAs directly into the review process. Monitors can then review documents and provide their review status before completing the next step in the workflow, ensuring nothing gets missed. Additionally, historical comments from previous reviews can be maintained, ensuring the same document is not accidentally reviewed twice.
- **Organise and prioritise work** – Documents and tasks can be automatically flagged based on their type, status, and due date to help CRAs and coordinators focus their efforts and plan their day-to-day work.
- **Support collaboration** – Alerts can notify sites and CRAs when new documents are ready for review. Upon review, monitors can flag specific text or phrases and route documents back to the site for clarification. When feedback is needed, the CRA can easily locate the document or phrase in question and respond much faster.
- **Improve standardisation** – By reducing process variation and the number of different technologies used for monitoring, sites and CRAs can become more proficient in the systems. With fewer technologies, less time is spent switching between applications, improving CRA efficiency and study quality.

## Reduce Costs and Streamline Processes

While launching and running a clinical trial is expensive overall, on-site monitoring alone can be up to 30% of total clinical trial costs. The majority of the expenses are from the travel costs of CRAs: transportation, hotel, and meals add up quickly, especially when issues or complications require the CRA to physically travel to the site many times during a trial, or with little notice.

Remote monitoring systems reduce the overall costs of launching and running a clinical trial which, in turn, means sponsors can run more concurrent trials. In addition, the time efficiencies realised with remote trial monitors helps speed trial timelines, bringing therapies to more patients, sooner. More specifically, remote monitoring reduces trial costs in the following ways:

- **Less travel** – With fewer on-site visits, monitors spend less time travelling and more time on reviewing data and supporting sites.
- **Conserve site resources** – Site staff can save time and resources, such as office space and computer equipment, that would otherwise be needed to support on-site activities.
- **Reduce turnover** – Removing the need to travel on-site can alleviate burnout and help reduce CRA turnover.

## Bring Treatments to Market Faster

The benefits of remote monitoring systems are becoming increasingly clear. Enabling sponsors, CROs, and sites to operate on a single, unified platform will further streamline clinical data collection and monitoring processes and therefore speed clinical trials.



Ultimately, reducing trial timelines is an industry imperative. Whether conducting a trial for a new cancer therapy or a COVID-19 vaccine, valuable research must be allowed to continue and be conducted faster while keeping participants safe.

By releasing oversight activities from physical sites, critically important research can continue and even accelerate. Systems that support remote monitoring can speed and simplify the data collection, oversight, and reporting processes that can keep trials on track. Most importantly, they can accelerate the development and approval of drugs and vaccines.

As the industry moves toward virtual clinical trial solutions, participants, monitors, sites, and sponsors alike will benefit. Remote trial monitoring plays a huge role in this transformation and in the future of clinical trials.

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## Rik van Mol

Rik is a senior executive with 20+ years of experience in both management consulting and cloud software in the life sciences / pharmaceutical sector. His experience has been built in assisting clients through complex transformation programmes across the life sciences value chain for most of the world's largest companies. Rik is a recognised thought leader in the life sciences industry with deep expertise in architecting, launching and implementing innovative and industry-leading strategies and solutions.



# Pharmaceutical Cold Chain Expertise – the Missing Ingredient in the CMO/CDMO Offering

Pharmaceutical supply chains continue to reach new levels of complexity that challenge even the most seasoned logistics and supply chain professionals. These complexities include:

- Innovative, advanced therapies
- Emerging new temperature requirements for products
- Expanding global supply chain to naïve patient populations
- Additional regulatory scrutiny over good distribution practices throughout the supply chain.

Within this evolving world of biopharma, it is estimated that two-thirds of biopharmaceutical manufacturing is outsourced.<sup>1</sup> Therefore, the supply chain is not only complex, but also largely virtual for pharmaceutical companies bringing their therapies through clinical development and ultimately to market. As a result of the increasing trend of virtual pharma supply chains, pharmaceutical sponsors view relationships with their contract

manufacturing partners as not only critical, but vital to the success of their therapies.

Contract manufacturing organisations (CMOs) and contract development and manufacturing organisations (CDMOs) offer expertise in manufacturing and development of therapies, allowing their pharmaceutical company customers the opportunity to focus on their core competencies. These pharma partners can provide transformational value, and effectively help pharma companies bring innovative therapies to market. However, the CMO/CDMO landscape has experienced significant consolidation – which can make it difficult for pharma companies to understand the unique, value-creating differences between competing CMOs and CDMOs.

## Challenging Forces for Clinical Trial Sponsors and their Partners

Clinical trials continue to stretch global clinical supply chains as clinical trial sponsors strive to reach naïve patient populations. This is an interesting challenge for clinical supply chain professionals as they are tasked with supporting the distribution of temperature-sensitive clinical supplies to all corners of the world, including many developing countries that potentially lack significant infrastructure to support strict temperature control of these investigational therapies.

Aside from an expanding global supply chain, emerging distribution models like direct to patient clinical trials (where therapies are delivered/administered in the patient's home) and adaptive dose clinical trials, are creating additional supply chain complexities. These added complexities can potentially drive additional cost into the supply chain as typically these situations require white glove transportation services.

In addition to increased supply costs from supply chain distribution complexity, pharmaceutical companies continue to pursue sustainability initiatives. For example, Amgen, a leader in global biotechnology, has published formal sustainability plans since 2008. Amgen is not alone in this effort as many other large pharma companies like Merck, Eli Lilly and others have large-scale sustainability initiatives as well.

As pharmaceutical companies face these challenges of: supply chain complexity, cost pressure, sustainability and temperature control, how can CMOs and CDMOs provide an innovative offering to solve these challenges?

## End-to-end Expertise

Aside from manufacturing and processing high-quality active pharmaceutical ingredients, what if CMOs/CDMOs could offer a true end-to-end solution by ensuring strict temperature control of their products in transit? What impact would these solutions have on their current and potential pharma customers?

By leading and guiding biopharma companies to effective temperature-control strategies, CMOs and CDMOs can create unique value as they act as an extension of the pharma sponsor's supply chain. After all, even the safest and most effective therapy will have zero impact on patients' lives if it does not arrive at the destination in viable condition.







### Reusable Packaging Systems

Exciting advances in thermal packaging technology have resulted in the emergence of robust and reusable packaging systems. These reusable packaging systems provide temperature assurance for a wide range of temperature ranges, and they accommodate both smaller distribution shipments as well as full pallet shipments (for bulk API/drug product/finished drug product).

With space and capacity constraints at CMO/CDMO facilities, temperature-control solutions also require the same innovation and outside-the-box thinking as today's therapies. For this reason, it is important for CMOs and CDMOs to partner with thermal packaging companies who can provide pre-conditioned and ready-to-load temperature-control packaging to their doorstep. Additionally, it's a best practice to seek thermal packaging partners who can support their needs with pre-conditioned, ready-to-load packaging throughout the CMO/CDMO network wherever they are located in the world – due to the global expansiveness of pharma supply chains.

### Reducing Costs by \$1 Million

With these new options available to CMOs and CDMOs, companies are now able to address the previously mentioned challenges for their pharma sponsor customers. For example, in working with a large pharma customer on supporting their bulk distribution supply chain, the customer has been able to reduce their thermal packaging costs by over \$1 million by switching from active systems and single-use boxes to passive, reusable parcel and pallet shippers. This project has also had a profound impact on the customer's sustainability goals. It must be noted that both the financial and environmental impact offer net value because the change in packaging systems has also assured avoidance of temperature excursions.

### Deepen Partnerships, Provide Value

In a world where biopharma companies exhaust all of their resources with innovative discovery and development of therapies, these companies are greatly impacted by customer-centric CMOs and CDMOs. The ability to not only manufacture high-quality product, but also ensure temperature control and viability to the destination, provides value that biopharma companies seek from their partners. CMOs and CDMOs already offer tremendous value to pharma customers, and now they have an opportunity to offer a true end-to-end service.

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### James Klingelhofer

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# Why Aren't More Life Sciences Companies Automating PV Data Capture?

The pressures on pharmaceutical organisations to capture, sift and process real-world adverse event data are immense – and soaring. So why are safety and pharmacovigilance departments lagging in their application of smart technology, wonders John Price, a life sciences regulatory and safety consultant and advisor to Arriello.

Pharmaceutical companies must ingest, check, interpret and report vast quantities of real-world data about any untoward effects of human medicinal products, accurately and within a tight timeframe. This substantial undertaking is growing all the time, too.

Yet, compared with other functions across the pharmaceutical product life-cycle, safety and pharmacovigilance (PV) teams are the least likely to employ smart technology to help lighten the load. This is surprising, given that life sciences companies today spend a disproportionate amount of their PV budget just amassing reports of suspected drug reactions – when many of these reports are of very low quality, meeting only minimum criteria for validity or lacking key clinical information. Crucially, any resource that goes into processing this information is time, energy and budget that is not being expended on analysing safety information – to enhance the safe use of drugs by patients.

So what is holding companies back from proactive investment in solutions that could help them?

## A Cost/Benefit Perception Bias

Organisations' lack of investment in smart solutions, certainly among organisations that lack the scale and internal IT resources to develop their own, can be put down in part to PV's perceived lack of strategic priority compared to pre-marketing authorisation activities such as clinical trials.

In the latter case, technology is seen as a means of accelerating products' speed to market, expanding the target opportunity, and bringing in new revenue. PV, by contrast, is seen as a 'cost centre'; a public health obligation which adds little value for the business.

This is lamentable, given the scope for process transformation that today's technology enables. Proven solutions exist now which could transform the efficiency, effectiveness and regulatory adherence of PV processes, without placing data at any risk of being compromised in any way.

Among the large household pharma names, technology developments probably are taking place, but internally. Typically, the major global players still prefer to build their own customised solutions, keeping these shrouded in secrecy as though they might offer some kind of strategic advantage and competitive edge. Yet this approach is perplexing. While Big Pharma clearly has the resources to develop its own solutions for adverse event (AE) case intake and processing, companies would surely be better off spreading cost, and increasing speed to effective solutions, by using ready-to-go tools which have been designed to cater for

most needs – many of which have been tried and tested many times over. Ultimately, there is little competitive differentiation in tasks that are first and foremost a public health activity designed to protect patients, as well as a regulatory necessity – so why reinvent the wheel?

## A Focus on Quantity Over Quality

To fulfil their responsibilities, stay on the right side of regulators, and maintain public trust, companies have no choice but to do PV well, and report AE cases promptly. Without technology, this is a highly labour-intensive undertaking. It also requires specialist skills. Beyond life science and healthcare qualifications, PV demands the ability to interpret complex medico-scientific data – sorting significant and meaningful findings from distracting 'noise'. The perfect blend of pharma and data science skills is relatively scarce, as demonstrated by the difficulty companies report in recruiting qualified personnel. It is imperative, then, that companies apply that expertise economically and where it is needed most: to identifying and evaluating incoming signals, and addressing safety issues.

Even if organisations do see PV first and foremost as a cost centre, it is one that warrants investment as a means of providing services more cost-efficiently – without compromising PV quality or integrity. To put this need into perspective, financial market watchers such as Grandview Research and Market Watch estimate that the annual global spending on external PV solutions and services – currently *\$5 billion* – is expected to more than *double* over the next few years. That's a substantial outlay, making services very expensive – and with a limited return on investment.

In an industry as competitive and cost-laden as the global pharmaceutical industry, organisations would do well to free up a healthy proportion of that resource, to channel into developing new drugs – as long as they can do so without risking patient safety; that is, without cutting corners.

## The Case for Intelligent Investment

In the right hands, advanced technology can reduce errors to drive up PV accuracy while simultaneously driving down operational costs over time. Efficiency gains of between 60–70 per cent have been predicted, where companies are targeting largely manual and resource-intensive processes with intelligent automation, and higher efficiencies are perfectly possible; the kinds of innovation which don't require a wholesale overhaul of firms' existing PV systems. This includes case intake solutions which frontline professionals can use on the go, to capture AE details for straight-through processing.

As a rule-based activity, AE case processing lends itself perfectly to automation. There is no reason why a report made by a healthcare provider, patient or drug company representative via a smartphone app, for instance, couldn't be triaged, databased and routed automatically – according to the information in the report – to company staff or regulators, with minimal human intervention. The added benefit of such an application (in-the-moment computer-aided collection of information from the reporter) would be the





promotion of 'right-first-time' capture of comprehensive, high-quality case information at source – reducing the need for case follow-up. The convenience of such a system would save time for all involved, and enable more effective PV.

## PV at a Crossroads

For now, applications that automate discrete PV activities, available from specialist PV IT providers, offer opportunities for incremental efficiencies to smaller companies with modest budgets who could otherwise be left behind in the imminent PV automation revolution.

As long as large pharma brands continue to focus their resources on developing their own customised PV solutions, mid-sized and smaller firms have a chance to peruse the market for off-the-shelf solutions or managed services which employ such aids to improve the quality and value of PV delivery.

The current window of opportunity is finite, however. Once the potential of emerging solutions has been proven, demand may already have consumed all the available capacity of technology service providers, leaving companies without the help they now

desperately need. So timing any process transformation/smarter tools use is likely to prove critical.

## John Price



John Price, owner and MD of John Price PharmaSolutions LLC, is a life sciences regulatory and safety veteran and consultant. Formerly holding leading safety roles at Alexion, Johnson & Johnson, and Pfizer, and now an advisor to PV managed service provider Arriello, John has in-depth experience of the evolution of pharmacovigilance, extending back to the late 1980s/early 1990s. This includes a rich understanding of industry best practice, and the potential of intelligent automation in the drive towards high-quality, compliant AE reporting and improved patient safety.

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# Coronavirus and Contact Tracing Apps: The Italian Case

Contact-tracing apps and technologies are a hotly debated issue with legal, medical and technological implications.

The most common mistake in the public debate is to put the tracing carried out by a private tech company to sell a service on the same level as the tracing carried out by governments to better manage infection risk during a pandemic.

The experience with COVID-19 and contact-tracing apps has shown that when the government intrudes in our private lives, our deepest anxieties of being persecuted come to the surface. This feeling harks back to the 19<sup>th</sup> and 20<sup>th</sup> centuries, but it is still very much alive and kicking. It was this kind of feeling (specifically, a desire for freedom from government intrusion) that led to the birth of personal data protection, when Brandeis and Warren theorised about “the right to be let alone” (their paper, “The Right to Privacy”, was published in the *Harvard Law Review* in 1890).

Thus, it is neither correct nor useful to compare Google’s GPS tracing (to cite one example) with contact-tracing apps used to manage the COVID-19 emergency.

Nevertheless, any analysis of contact-tracing apps must focus on:

- (a) the person responsible for the tracing (i.e., the data controller);
- (b) the purpose for which a contact-tracing app is used; and
- (c) the utility of contact-tracing apps and balancing that with people’s privacy.

## The EU’s Role

EU institutions have taken stances to encourage politicians to coordinate technologies within an EU framework of pandemic risk management. The most important documents published in this regard are:

- the European Data Protection Board’s (EDPB) first statement (19 March);
- the EDPB’s Guidelines 04/2020 on the use of location data and contact tracing tools in the context of the COVID-19 outbreak (21 April);
- the European Data Protection Supervisor’s (EDPS) Tech-Dispatch 1/2020: Contact Tracing with Mobile Applications (7 May); and
- the European Commission’s Recommendation 2020/518 on a common Union toolbox for the use of technology and data to combat and exit from the COVID-19 crisis (8 April), and its subsequent guidance and informal statement.

All these documents highlight that data protection is an indispensable part of building trust and creating the conditions needed to make any contact-tracing solution socially acceptable and ensure its effectiveness.

## The Italian Case

The Italian government and Data Protection Authority (DPA) have followed the European institutions’ same prudent approach from the outset.

Thus, even though European guidelines did not take an explicit stance on it, the Italian authorities designed a management risk framework in which **solely public health authorities are in charge of verifying and managing the infection chain and, consequently**, any contact-tracing app. Specifically, Art. 6 of Law Decree 28/2020 stipulates that the government – namely, the Ministry of Health – is the data controller and is responsible for making the contact-tracing app ‘Immuni’ available to citizens, given that it is in the public interest to manage the pandemic in the best way possible.

Data processed through Immuni **can be used exclusively by the Ministry of Health to implement safeguards to prevent and contain COVID-19, but aggregated and anonymised data can be used for public health, preventive, statistical or scientific research purposes.**

The use of Immuni is voluntary, with only approximately 3.3 million people having downloaded it to date. The app uses Bluetooth Low Energy technology (no geolocation whatsoever) – this ensures **a proper balance between the public interest of reducing infection risk and people’s privacy**. The app does not (and cannot) collect any data that would identify the user. Therefore, Immuni can determine that two users came into contact without knowing who those users are or where the contact occurred. When two phones with Immuni on them come into close proximity (under 1.5 metres), each phone sends the other random codes that cannot identify the users in any way. The phones store each other’s code for 14 days; if one of the phones’ owners is then diagnosed with Covid-19, the competent public health authority asks that person if he/she wants to alert other users he/she exchanged random codes with. In any case, alerts do not (and cannot) reveal users’ identities.

No specific instructions are currently in place regarding the behaviour to adopt if you receive an alert.

In compliance with transparency duties – and as suggested by the EDPB – the government published Immuni’s source code on the app’s website.

## Points of Discussion

One of the main sticking points concerns the voluntary basis of Immuni’s use and the lack of specific instructions to follow when an alert is received. This discussion revolves around the abovementioned balance of interests and the frequent opposition in the management of the health emergency between measures that depend on citizen responsibility and those imposed by law.

With Immuni, the Italian government has chosen – as suggested by European institutions – to adopt the responsible citizenry approach. And it is probably the best option, given that fundamental rights and freedoms and potentially high-impact technologies are involved.



The situation is different when it comes to software that enables citizens to carry out voluntary self-screening (the results of which are automatically sent to the government). In this regard, the Italian DPA stated that differentiating between the various apps used to manage the pandemic is not a good strategy to ensure the efficiency and effectiveness of contact tracing, or the security of personal data. Several Italian regions have adopted this kind of software, but it has not met with much public success.

No specific provisions permit the use of contact-tracing technologies in the private sector. Nevertheless, the DPA clarified on 6 June that the only current provision on contact tracing is that

concerning Immuni, which is managed by the government. The DPA also clarified that employers can use technologies that do not register any kind of data, such as social distancing wristbands.

#### Conclusion

The number of Immuni users is currently too low to ensure effectiveness, but public authorities are hopeful that downloads will increase this autumn – though that will require a new communication strategy.

In the meantime, private solutions such as wristbands will likely enjoy increasing success.

#### Vincenzo Salvatore

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# The Global Regulatory Landscape for Clinical Trials Considering the COVID-19 Pandemic

The outbreak of COVID-19 created unprecedented circumstances for the conduct of clinical trials across the world. While the industry has experienced challenging conditions in managing research before, for example, during political unrest or natural disasters, this type of crisis was typically local, short-term and contingency plans could in many cases utilise lessons learnt from past occurrences. Even during the previous global health emergencies, for example, the Ebola outbreak in 2013–2016 or H1N1 in 2009, questions the clinical research community faced were primarily concerning how to design and manage clinical trials for that particular disease<sup>1,2</sup>, not how to mitigate the impact of those outbreaks on existing or planned research in other indications.

The consequences of the COVID-19 pandemic reach much further, affecting trials in unrelated diseases. The strain the pandemic has put on the healthcare system, the unique situation of patients placed under quarantine or unable to travel to sites due to lockdown restrictions, and disruptions in investigational medicinal product (IMP) supply made it difficult to adhere to the approved research plans and forced urgent modifications to secure data validity and, most importantly, safety of trial participants. Regulators acknowledged the unique challenges faced by the clinical research community and the need for sponsor companies to receive guidance on how to navigate through the different choices on mitigating the impact of the pandemic on their trials, while at the same time maintaining regulatory compliance.

One of the first responses from regulators came from the UK. It was issued on the same day as the UK Chief Medical Officer raised the risk of COVID-19 outbreak in the country from moderate to high, requesting people with fever and coughing to self-isolate and announcing that more social distancing measures would be introduced in the upcoming weeks<sup>3</sup>. In the advice published 12 March 2020, the MHRA Inspectorate recognised the adverse impact COVID-19 was having on the effective management of clinical trials. The agency acknowledged the unavoidable increase in protocol and SOP deviations and emphasised that they will not per se constitute serious breach, but needed to be properly documented to allow for the trial evaluation. At the same time, the MHRA reminded sponsors that any prospective protocol waivers or bypassing eligibility criteria were unacceptable, as the safety of trial subjects remained the highest priority. While this announcement did not yet introduce any important flexibilities in the regulatory process, it reminded sponsors about the tools they already had at their disposal, such as urgent safety measures, a temporary halt to a trial, or a recruitment halt, which they could use<sup>4</sup>.

Not long afterwards, on 18th March 2020, the US FDA provided the first release of the FDA Guidance on the Conduct of Clinical

Trials of Medical Products during the COVID-19 Public Health Emergency. It included general considerations to assist sponsors in maintaining GCP compliance. Sponsors were encouraged to look at the conduct of the trial in the current circumstances, first and foremost from the perspective of the impact this situation may have on subjects' safety. For any new risks, sponsors were to consider whether these could be addressed by modifying the study or whether discontinuation of participation would be in the better interest of the subject. Moreover, FDA reminded sponsor companies that implementing protocol modifications to eliminate immediate hazards to participants (anticipated due to COVID-19) did not require prior IRB/FDA approval<sup>5</sup>.

While the main text of the FDA guidance focused on general matters, a question & answers appendix provided responses to inquiries reported by researchers and sponsors. The appendix has expanded from only ten questions in the second release of the guidance dated 27 March 2020 to twenty-four questions in the last update of 2 July 2020, covering a wide range of topics including managing protocol modifications, remote outcome assessments, alternative methods of IMP delivery and remote monitoring<sup>6</sup>. The Q&A gives practical advice for the application of FDA guidance on actual issues encountered by the clinical research community, and is therefore a helpful tool in determining the best practices in the management of the study during the current emergency.

By approximately the end of March, most agencies in North America and Europe, together with many regulators in other parts of the world, had issued some guidance for clinical studies during the pandemic. Such guidance was usually published as soon as government restrictions due to COVID-19 were announced, or soon afterwards, and tended to evolve over time, adapting to the dynamic epidemiological situation. Denmark, for example, released the first guidance on 13 March 2020, the day the lockdown restrictions became effective<sup>6</sup>. The Danish guidance has since undergone several updates and at the time of writing this article, version 6.0 was already in effect<sup>7</sup>.

The guidance in different countries varied in terms of specific topics and level of detail in the regulatory advice. The common denominating factor in all cases has been the safety of trial participants. The regulators expected sponsors, in collaboration with clinical researchers, to continuously assess the risks caused by the COVID-19 emergency, such as the reduced availability of healthcare professionals or limited access to the trial sites, and design mitigation tactics accordingly. This approach is well summarised in the guidance from the Hungarian agency OGYEI, that states: "A thorough risk assessment of ongoing investigations should be carried out considering restrictions already applied and expected (...) and measures should be put in place to prioritise patient safety and data validation. In the event of conflict between these two objectives, patient safety should be prioritised"<sup>8</sup>.



The Spanish agency, AEMPS, also emphasised that such assessment must be done together with the investigator and that critical activities need to be prioritised: “Both [sponsor and investigator] must also evaluate the application of these measures proportionately to each clinical trial considering its particularities, the organisation of each site and the epidemiological characteristics of COVID-19 at each site”<sup>9</sup>.

It is notable that the guidance documents aimed not to reinvent the regulatory framework to match the new situation, but rather encouraged sponsors to, as much as possible, use the existing regulatory approaches designed to deal with unexpected hazards to subject health, such as urgent safety measures, temporary suspension of the study or recruitment halts. Flexibilities introduced by the regulators focused on providing practical support on the management of critical trial activities. A good example of the above approaches are recommendations related to ensuring a continued supply of study medication. Most authorities, regardless of the regions, took a stand that in case of an IMP suitable for home administration, the IMP can be delivered from the site directly to a subject's home if onsite visits were not possible or would create unnecessary risk. This practical approach was applied across Europe, including non-EU countries like Switzerland<sup>10</sup> and Serbia<sup>11</sup>, as well as in Latin America (for example Argentina<sup>12</sup>, Colombia<sup>13</sup>) and the Asia Pacific region (among others, Singapore<sup>14</sup>).

The amplification of change to clinical studies during the COVID-19 outbreak could also put a strain on the agencies' resources, if they were all reported on an ongoing basis. To prevent that, regulators included in their guidance a distinction between reportable changes and those which did not require reporting and were enough to be documented in the study TMF. For example, Spain excluded certain urgent measures from the 15-day reporting requirement, allowing them to be presented along with the appropriate justification and risk assessment, within four months after the end of the COVID-19 crisis<sup>9</sup>. Interestingly, the categorisation of changes often varied even between different EU countries, which presented a challenge for the management of multinational studies and required sponsors and/or CROs to have a robust system for maintaining the country-specific intelligence on that matter.

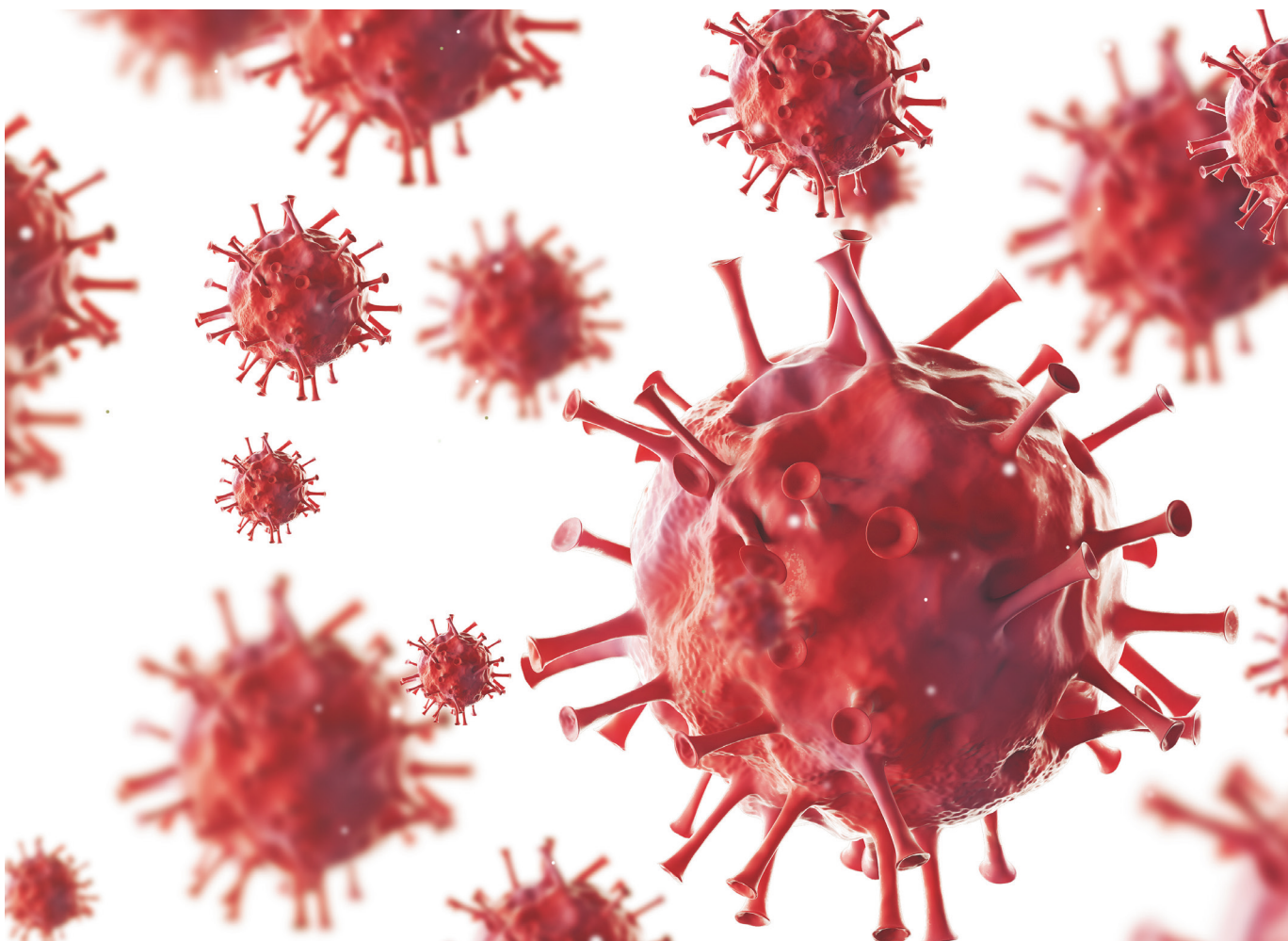
To reduce differences at the EU level, the European Medicines Agency (EMA), in collaboration with representatives of national competent authorities, prepared a harmonised list of recommendations for the trials conducted in the EU. The EMA's Guidance on the Management of Clinical Trials during COVID-19 (Coronavirus) Pandemic, first published 20 March 2020, developed from a top-level document with general considerations in version 1 to a comprehensive set of emergency measures and practical actions for sponsors and clinical researchers in version 3, dated 28 April 2020. It has covered all critical trial activities including changes to the informed consent, monitoring and IMP distribution. However, although EU countries were encouraged to implement the harmonised guidance to the maximum extent, the differences among countries have not been fully eliminated. The most notable example is the approach to remote source data verification (SDV), which was allowed by the EMA's guidance in exceptional cases, i.e. for COVID-19 studies and before database lock for pivotal trials in serious or life-threatening conditions<sup>15</sup>. Most countries fully incorporated EMA's recommendation but some took a different stand. For example, Belgium completely forbade remote SDV due to concerns over a participant's right and the burden it might create for the site. The Netherlands, on the

other hand, considered remote SDV a non-substantial change that does not require an approval prior to implementation<sup>17</sup>.

The COVID-19 pandemic has required sponsor companies to urgently design multi-level contingency plans for their studies in the conditions of a worldwide health crisis and a dynamically changing epidemiological situation. That could not be achieved without active participation of the regulators who have played a vital role in outlining the relevant considerations and providing practical recommendations and flexibilities in the process. Although the advice of the regulatory agencies in different regions has followed similar principles and focused on the safety of trial participants and data validity, the specific recommendations have varied country to country. Regulators have shown their rapid response during the pandemic and this could possibly open another area for collaboration between regulators in the future.

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# To Participate or Not Participate: Why Do Investigators Reject a Clinical Research?

Clinical research is a complex, expensive, time- and resource-intensive process. Feasibility assessments play a crucial part in this clinical research planning process as it enables the sponsors and contract research organisations (CROs) to evaluate the possibility of conducting clinical research in a particular region or country with the objective of optimising the project completion in terms of timelines, patient enrolment and cost. Investigators are the key individuals in conducting clinical research and their level of engagement has a significant impact on the success or failure of the study. Understanding the reasons of feasibility rejection among the investigators may provide insights into the internal and external factors that affect the uptake of clinical trials, while at the same time being particularly important when developing policies and interventions to promote clinical research in the country.

## Background

Clinical research is the backbone of evidence-based medicine and trial outcomes are crucial for comparing and improving the use of drugs, vaccines, medical devices, and diagnostics. The process of conducting clinical research is complex, expensive, time- and resource-intensive. Thus, clinical research feasibility assessment comes into play whereby the sponsor or contract research organisation (CRO) will be evaluating the possibility of conducting clinical research in a particular region or country with the objective of optimising project completion in terms of timelines, patient enrolment and cost.

Clinical Research Malaysia (CRM) is a site management organisation for the Ministry of Health Malaysia. It is a one-stop contact point for sponsors and CROs who plan to conduct clinical research in the country<sup>1</sup>. CRM has established an extensive database of Malaysian investigators in clinical research, as well as trial site facilities/infrastructure in the public and private healthcare sectors. This enables the company to match the clinical research with the right investigators and sites.

There are usually two types of feasibilities provided by CRM. **Pre-feasibility** assessment is information collected for preliminary, macro-level assessment to assist sponsors and CROs to decide which country is suitable to place the study. This assessment includes details on the standard of care, the clinical research registration process, epidemiology, and patient pool<sup>2</sup>. A **full feasibility** assessment is a complete documentation narrowed down to individual site, which necessitates confidential disclosure agreement, protocol synopsis and site assessment questionnaire<sup>2</sup>. It includes but is not limited to patient recruitment rate based on the study protocol, site and investigator's facilities, resources, experiences, and ethics approval.

Feasibility assessment can determine the most suitable trial sites and investigators to conduct specific clinical research. This study aims to evaluate the investigator's engagement rate in feasibility response and identify the reasons for refusal to participate in clinical research.

## Methodology

Data extraction from the CRM feasibility assessment database was carried out from 1<sup>st</sup> January 2019 to 31<sup>st</sup> December 2019. A total of 348 feasibility assessments were conducted, with 212 and 136 being pre-feasibility and full feasibility assessments, respectively.

## Results

The top three therapeutic areas from full feasibility assessment conducted by CRM in 2019 were oncology (n=35, 25.55%); followed by gastroenterology (n=18, 13.14%) and haematology (n=16, 11.68%). These full feasibility assessments were sent out to 466 investigators in 72 hospitals throughout Malaysia. CRM's database received 1059 responses from the investigators for the 136 full feasibility assessments. The majority of the investigators, 55.34% (n=586) agreed to participate in the respective clinical research; while 40.04% (n=424) declined to take part and 4.63% (n=49) did not respond.

Figure 1 shows the reasons for refusal to participate in clinical research among Malaysian investigators. The most common reason given by investigators is insufficient or lack of patient pool at the study site (n=120, 28.30%). This is followed by approached investigators referring the feasibility assessment to their colleagues (n=60, 14.15%), insufficient time to conduct clinical research due to routine clinical work (n=49, 11.56%) and investigators conducting competing clinical research (n=49, 11.56%).

Besides, about 9.43% (n=40) of investigators rejected the feasibility assessment due to study protocol which required strict inclusion and exclusion criteria. In addition, 7.78% (n=33) were not interested in the study and 6.37% (n=27) turned down the study because of the lack of resources in conducting the clinical research. Insufficient time due to other trials is also one of the reasons investigators reject the feasibility assessment (n=20, 4.72%). Other reasons, which made up 4.25% (n=18) of the total responses, are disease-/treatment-related (n=8), patient-related (n=7) and investigator-related (n=3). The remaining 1.89% (n=8) of the responses did not specify the reason for refusal.

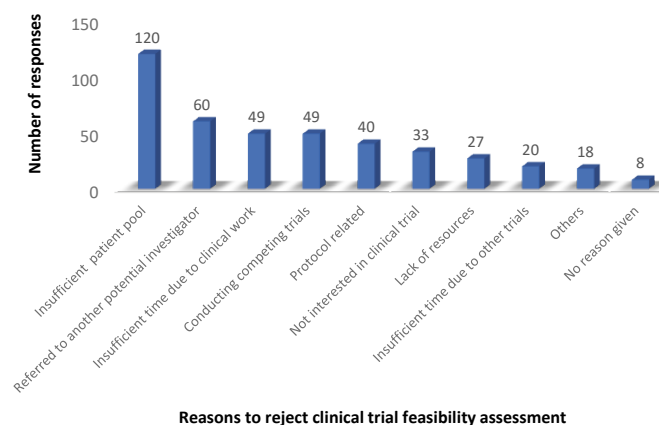


Figure 1: Reasons for feasibility assessment rejection among Malaysian investigators in 2019

## Discussion

More than half of the investigators responded positively to feasibility assessment because of the accurate mapping of



potential investigators by CRM feasibility specialists, coupled with investigators being well informed on the importance of clinical research, thus reflecting their interest to contribute to the new science of medicines. Investigators will be up to date on the latest treatment and will be able to treat patients based on scientific evidence<sup>3</sup>, thereby improving their clinical acumen.

An insufficient patient pool was the main reason for rejection. Investigators tend to reject low incidence and rare diseases studies, such as autoimmune pulmonary alveolar proteinosis, acromegaly, and low-grade glioma. Furthermore, these diseases are not commonly found among Malaysians and investigators may encounter difficulty in identifying the right patient pool to enrol in clinical research.

Next, investigators also reject feasibility assessment due to the study protocol. This includes complicated protocol, a study involving the multidisciplinary specialist team, close and long duration of follow-up, as well as strict inclusion and exclusion criteria. Oncology studies, for example, have exclusions such as prior chemotherapy, advanced stage of disease or not being newly diagnosed cancer patients. This will lead to a narrow inclusion criterion which may increase the recruitment timeline. As a result, investigators were unable to recruit enough patients for the study within the expected timeline and the sponsor may eventually need to amend the study protocol to recruit additional patients<sup>4</sup>.

A few public hospitals practise hierarchical organisational structure, whereby all the feasibility studies to those sites will have to go through the Head of Department for first-round evaluation before responding to the feasibility assessment either as a team or referring the study to other investigators. This led to the reason of referral to other potential investigators as one of the common reasons for investigators' rejection. Besides, referral of feasibility assessment to other investigators may also be an effort for experience investigators to nurture and develop new investigators in conducting clinical research.

Insufficient time due to clinical duty and conducting competing trials are among the common reasons investigators reject clinical research. In the public health sector, clinical service remains the investigator's main priority and with the high volume of patients at these hospitals, the challenge of conducting clinical research is real. Clinical research with extensive follow-up as well as those that require long discussions with patients (patient consent, protocol etc) may increase the tendency of investigators to reject the trial<sup>5</sup>. On the other hand, it is common practice in Malaysia that one investigator is dealing with multiple sites or hospitals, thus they may not have protected time to conduct clinical research.

Other reasons for feasibility rejection include patient-, disease-/treatment-, and investigator-related reasons. Patient-related reasons include ethical issues such as the targeted patient needs





to be hospitalised, is very ill, or there is a high mortality risk for patients. Investigators may not wish to subject these high-risk group of patients to the trial and thus would reject the study. Disease- or treatment-related reasons include investigational product (IP) containing pain-reducing capabilities but not disease-modifying action; IP has various drug-drug interactions and investigators are not confident with the IP mechanism of action in patients. Investigator-related refusal reasons include the transfer to a new hospital and away from work during the time when feasibility studies were conducted; these are reasons for them not being available to answer the feasibility assessments during that point in time, although they may be interested. In addition, insufficient time to answer the feasibility questionnaire within the timeline given (usually five working days) may also be a reason they refuse to participate in the feasibility assessment.

## Conclusion

The results of this study showed that more than half of Malaysian investigators that were approached by CRM are interested in participating in clinical research. Similarly, this study also presented several key refusal reasons for investigators to participate in clinical research and the reasoning behind them. The interest of investigators is influenced by numerous factors, some of which are not intrinsic to the study protocol, yet invariably play a direct role in determining the uptake of the clinical trial. The reasons for refusal in feasibility assessments are important key points to consider when engaging with them in future feasibility studies, when implementing motivational interventions to encourage more investigators to

participate in clinical research, and when developing frameworks and policies to support investigators' involvement in clinical research in the country.

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## Clinical Evaluation and Post-marketing Surveillance of Medical Devices in the USA

### Abstract

The medical device industry makes a colossal number of items, ranging from invasive gloves to non-natural joints to imaging gear, and assumes a pivotal job in growing new therapeutic advancements that can improve the capacity to analyse and treat disease. Like physician-endorsed drugs, medical devices are controlled by the Food and Drug Administration (FDA). In any case, the administrative system that the Congress has built up for medicinal gadgets is less stringent in numerous regards, due to a limited extent to fundamental contrasts between therapeutic gadgets and physician-endorsed drugs.

Most adequate gadgets can be advertised without earlier FDA audit, and most medium-chance gadgets are required to exhibit that they are "considerably equal" to a current gadget before being promoted. Not many gadgets need to show that they are protected and powerful before being showcased. Post-market surveillance is done to an abnormal degree, since the FDA and other skilled specialists will get reports from all items in their nations and reports from different nations. The FDA's surveillance of devices after they become available to the public has also been limited, although improvements are being made through initiatives such as requiring unique device identifiers on all devices.

The point of this article is to cover the clinical assessment and its requisites alongside the post-showcase reconnaissance of medicinal devices.

**Key words:** Medical devices, FDA, post-market surveillance

### Introduction

The US medical device makers' market size was estimated at USD 154.0 billion in 2017 and is foreseen to display a CAGR of 5.0% over the timeframe of Figure 1. The increasing prevalence of constant sicknesses and the expanding geriatric population in the nation are among the chief market drivers.

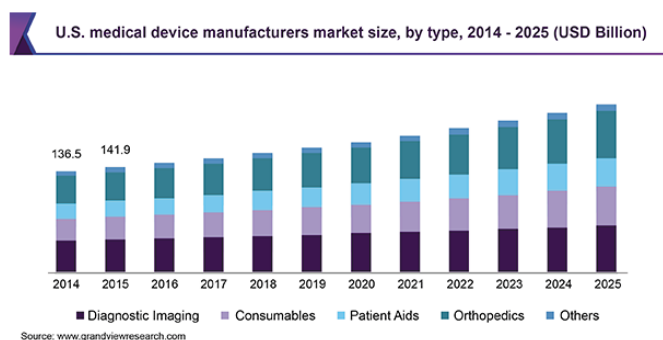


Figure 1: US medical device manufacturers market size comparison

As indicated by the US Statistics Bureau, 49 million or 15.0% of the population were classified as geriatric in 2015. The agency predicts that, by 2023, the geriatric population will represent 23.0% of the US population. The beginning of constant ailments is more regularly pervasive between the ages of 45 and 54.

Consequently, the increment in the geriatric populace is what is principally driving interest for medical device arrangements all around.<sup>1</sup>

The United States remains the greatest therapeutic gadget showcase on the planet, with a market size of around \$156 billion, and it was responsible for around 40 per cent of the overall number of restorative gadgets publicised in 2017. US payments for restorative gadgets in orders seen by the Department of Commerce (DOC) were more than \$41 billion in that year. Generally, the inspiration driving a medicinal gadget isn't cultivated by pharmacological, immunological, or metabolic techniques.

The industry is directly responsible for around 2 million jobs in the United States. Restorative advancement clearly accounts for more than 500,000 of these vocations. More than 80 per cent of therapeutic gadget associations in the United States involve under 50 agents and many new organisations have for all intents and purposes zero payment arrangements. Since progress means the therapeutic gadget sector achieves crucial better ways to deal with, treat and examine infirmities, the restorative gadget division should continue creating at a positive rate later on.<sup>2</sup>

### Classification of Medical Devices<sup>3</sup>

The Food and Drug Administration (FDA) has established classifications for approximately 1700 different generic types of devices and grouped them into 16 medical specialties, referred to as panels. The three classes and the requirements which apply to them are:

#### Device Class and Regulatory Controls

- Class I General Controls**
  - With Exemptions
  - Without Exemptions
- Class II General Controls and Special Controls**
  - With Exemptions
  - Without Exemptions
- Class III requires 510(k) and Pre-market Approval Types of applications**
  - Investigational device exemption (IDE) for clinical studies
  - Pre-market notification 510(k)
  - Pre-market approval (PMA)
  - Humanitarian device exemptions (HDE) if applicable

### Clinical Evaluation of Medical Devices

Clinical investigation of medical devices are of two types:

- Pilot clinical investigation
- Pivotal clinical investigation.

Product – Category	Medical device																		
Market filing	USA																		
Regulating agency	USFDA/CDRH																		
Regulating ministry	Department of Health and Human Services																		
Regulations	21 CFR 800-1299																		
Clinical Evaluation																			
Types of clinical investigation	Pilot & Pivotal Investigation																		
Types of device study	Device Study																		
	<div><div>Exempt low risk devices</div><div><div>Not exempt high risk devices</div><div><div>Significant risk devices</div><div>Non significant risk devices</div></div><div><div>Full requirements</div><div>Abbreviated requirements</div></div></div></div>																		
Application form Elements required	Investigational Device Exemption (significant risk devices) <ul style="list-style-type: none"><li>Name and address of support</li><li>A report of earlier examinations must incorporate reports of all earlier clinical, creature study, and research facility testing of the gadget</li><li>Investigational plan</li></ul>																		
Mode of submission	Electronic submission gateway																		
Timeline for approval	Within 30 days																		
Submission, review & approval process	<div>Submission of a complete IDE application</div> <div><div><div><div>FDA</div><div><div>Approve, approve with modification</div><div>Disapproved</div></div><div>Additional Information required</div></div></div><div><div>FDA notifies the sponsor via email receipt of an IDE application</div><div>30 days</div><div>Clinical investigation may begin if IRB approval is obtained</div></div></div>																		
Reporting of adverse events	<div>IDE reports-</div> <div>Sponsor reports</div> <div>Investigator reports</div> <div>Sponsor reports</div> <table><tr><th>What should be reported</th><th>Whom to be reported</th><th>No. of days</th></tr><tr><td>Progress reports (or annual reports)</td><td>All reviewing IRBs, FDA (for a significant risk device)</td><td>At least yearly</td></tr><tr><td>Final report</td><td>FDA and all reviewing IRBs (for a significant risk device)  All reviewing IRBs (for a non-significant risk device)</td><td>Within 30 working days. Within six months after the completion or termination of the investigation. Within six months after completion or termination.</td></tr></table> <div>Investigator reports</div> <table><tr><th>What should be reported</th><th>Whom to be reported</th><th>No. of days</th></tr><tr><td>Progress reports</td><td>Sponsor, the monitor, and the reviewing IRB</td><td>Regular intervals but no less than on a yearly basis.</td></tr><tr><td>Final report</td><td>Sponsor and the reviewing IRB</td><td>Within three months after completion or termination.</td></tr></table>	What should be reported	Whom to be reported	No. of days	Progress reports (or annual reports)	All reviewing IRBs, FDA (for a significant risk device)	At least yearly	Final report	FDA and all reviewing IRBs (for a significant risk device)  All reviewing IRBs (for a non-significant risk device)	Within 30 working days. Within six months after the completion or termination of the investigation. Within six months after completion or termination.	What should be reported	Whom to be reported	No. of days	Progress reports	Sponsor, the monitor, and the reviewing IRB	Regular intervals but no less than on a yearly basis.	Final report	Sponsor and the reviewing IRB	Within three months after completion or termination.
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Final report	Sponsor and the reviewing IRB	Within three months after completion or termination.																	



Clinical Evaluation Requirements

- Investigational Device Exemption (IDE)\***  
An investigational gadget exclusion permits the investigational gadget to be utilised in a clinical report so as to gather wellbeing and adequacy information. An IDE need not be submitted before the investigation is started.
- Significant Risk Devices**  
A huge hazard gadget exhibits a potential for genuine hazard to wellbeing, security or welfare of a subject. These gadgets require both FDA and an institutional survey board (IRB) endorsement before the instigation of a clinical report. E.g.: Sutures, cardiac pacemakers, hydrocephalus shunts and orthopaedic inserts.
- Non-significant Risk Devices**  
A non-noteworthy hazard gadget doesn't represent a huge hazard to human subjects. These gadgets require just IRB endorsement before the commencement of a clinical report. Patrons of these gadgets are not required to present an IDE application to the FDA for endorsement. E.g.: Daily-wear contact focal points and focal point arrangements, ultrasonic dental scalers and Foley catheters.

Factsheet of USA  
Post-marketing Surveillance  
(Electronic Medical Device Reporting)

Class of devices	Class II & Class III
Adverse event reporting form	Form 3500A
Timeline of reporting	Three years (basic)
Mode of submission	Electronic submission (ESG)
Software used	e-Submitter, HL-7

Table 1: Factsheet for Post-marketing Surveillance



Flowchart 1: Process of e-MDR

Conclusion

All the most at risk devices are exposed to clinical testing as they have the most extreme hazards. Be that as it may, once in a while even the most thorough clinical testing of trial gadgets will leave some security and adequacy addresses unanswered. Simultaneously, more extensive circulation of new innovation and longer clinical experience may reveal startling concerns. They

should likewise answer to the US Food and Drug Administration (FDA), giving patient statistical information, clinical data, and strategy subtleties. This shows the FDA's guideline of medical devices proceeds after they enter the market and that the guidelines for post-market surveillance are exceptionally stringent in the USA.

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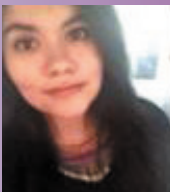
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# The Immense Potential of Africa's Advantageous Landscape

Whilst not ordinarily making the shortlist for trials in the past, Africa is an emerging as a continent based on its size, demographics, level of economic growth, and desire to improve healthcare and life expectancy. Today, Africa represents over 1.34 billion people and it is expected to surpass two billion people by 2038 and 2.5 billion by 2050. Accounting for over 17% of the global population, representing a diverse population, and carrying the highest disease burden in the world at around 25%, the African continent offers many of the best conditions for conducting clinical trials. Importantly, several diseases – particularly those defined as neglected and tropical – are endemic to the developing world, which includes Africa. Despite all these advantages, Africa contributes to less than 2% of the number of clinical trials.

### Africa Displays Incredible Amount of Genetic Diversity

The low representation of African countries in clinical trials is not unusual. Poor visibility of existing sites, limited infrastructure, cultural barriers, misunderstandings of requirements to work in the region, and unpredictable clinical trial regulatory timelines are some of the key issues hindering investments in this area and hence causing a burden to conducting clinical trials within Africa.

Africa's virtual absence from the clinical trials map poses a big problem. The continent displays an incredible amount of genetic diversity. If this diversity is not well represented in clinical trials, the trial findings cannot be generalised to large populations. Genetic analyses have clearly demonstrated that ethnic groups show variable results to various treatments, hence it is imperative to conduct clinical trials in Africa, as Africa suffers more than any other continent from diseases linked to poverty, and the interventions mainly used to cure or treat these diseases from which Africans suffer are designed elsewhere.

Cerba Research strongly believes that Africa offers an enormous opportunity for pharmaceutical, biotech companies and non-governmental organisations searching for low-cost study sites, low risk of litigation and a diverse participant population. The latter makes Africa an ideal location for research, as the diseases of affluence and poverty are prevalent. Moreover, the majority of patients to be potentially enrolled in clinical trials have not received any previous treatment for their diseases – either because it is not available, or they cannot afford it – facilitating patient recruitment.

### Challenges of Running Clinical Trials in Africa: Are They Really Challenges Still?

**Good clinical trial infrastructure in the region** – There is continuous investment and growth in the scientific base in African countries, strongly encouraged by local authorities. There are centralised healthcare institutions, well qualified, highly motivated and experienced investigators and excellent clinical trial facilities, which are comparable to the best in class globally. From a laboratory perspective, a lot of the tests are done overseas in central labs, when there is in fact the capacity to have the central lab work done in some local countries. Ideally, central lab hubs strategically placed in

Africa can help advance science and increase the knowledge pool around diseases.

**Efficient regulatory and ethics committee processes** – The regulatory approval processes in most African countries is no more complex than in Europe or the US. Faced with a sudden influx of clinical trials, many countries in Africa have been addressing the need to establish or evolve regulatory infrastructures. Some emerging markets are developing these for the first time, and many are adopting the US or European standards in a shift towards global alignment. For a product to be registered, it requires WHO approval, so one must do EMA registration of products. By now, each African country has a regulatory board, some more developed than others; for example, SAPHRA in South Africa, NAFDAC in Nigeria or TFDA in Tanzania.

**ICH/GCP the only standard** – African countries are adhering to or have already adopted the ICH/GCP guidelines in the process for regulatory and ethics committee approval. Clinical trials are conducted according to the required standard operating procedures to guide and train all the local staff, to ensure operations are carried out in compliance with ICH/GCP regulations, and to fulfil sponsor requests and requirements.

**Faster participant recruitment** – There is a large naïve population, with diseases of both the developed and developing world, which offers strong prospects for large and rapid participant recruitment.

**Cost benefits** – The majority of trials running in Africa are funded by NGOs/governments. Including investigator sites in Africa in general will help reduce the overall drug development timelines, with a higher number of participants in fewer sites. This accelerated participant recruitment allowing for fewer sites and less regulatory applications will equate to an overall lower cost for the study.

As challenging as it may seem, **Africa presents a unique profile** that interests NGOs and governmental organisations and should be equally interesting for many pharmaceutical and biotech companies. Changing requirements, the need for participant diversity and larger sample sizes in clinical trials in parallel with improved clinical research environments in African countries are resulting in a notable growth in clinical research in the region.

### There's More than TB and HIV

Until now, the focus on clinical research has primarily been on infectious diseases, particularly HIV/AIDS, TB, and malaria, as large numbers of the population are greatly affected by these diseases. There is not much focus on oncology or other lifestyle/metabolic diseases, although the prevalence of these is rapidly increasing. As such, cooperative clinical trial groups, sponsored by the National Cancer Institute, have already begun working in the Africa region, showing a large interest in bringing cancer therapies to Africa. Next to oncology, such as cervical cancer, other emerging topics are metabolic and other lifestyle diseases such as diabetes, maternal and infant health, ischemic heart diseases and strokes, and lower respiratory infections.



**COVID-19 as the Big Revealer**

Recently, the African Academy of Sciences (AAS) has launched the first iteration of the Clinical Trials Community (CTC) online platform in an attempt to increase the visibility of African clinical trial sites and investigators with the potential to participate in COVID-19 clinical trials, with an end goal of promoting the enhancement of intra-African collaboration around clinical trials.

As already indicated, few clinical trials are done in Africa: COVID-19 shows why this urgently needs to change. While there are massive movements within the industry to invest in COVID-19 vaccines, the outcomes of these COVID-19 studies will only be limited to the patient population included. These vaccines in the end might not be relevant for people in African countries, unless the studies are conducted locally. This is because responses to drugs or vaccines are complicated and can be influenced by, among other things, human genetics: different people will respond differently

to different drugs and vaccines. More countries on the African continent must urgently get involved in clinical trials so that the data collected can be representative of the whole continent.

Time is of the essence. The usual approach, of developing site- or country-specific protocols, won't work. Instead, African governments need to look at ways to harmonise the response towards COVID-19 across the continent. Now, more than ever, African countries need to work together. Every country's epidemic preparedness kit should contain funds set aside for clinical trials during epidemics or pandemics. This would require governments on the continent to evaluate their role and level of investment in the general area of clinical trials. This will augment the quality and quantity of clinical trials in the face of the constant challenge of emerging and re-emerging infectious diseases, as well as a steady rise in non-communicable diseases. On top of this, clinical trial centres and clinical research institutions on the continent should



strive to increase their visibility in the global space. This will make them easy to find in times of crisis and enhance both south-south and north-south collaborations.

## Joined-up Engagement

Cerba Research, part of Cerba Healthcare Group, has been focusing on central lab activities for the past 37 years. It has established a portfolio of customers based in Europe and the USA who need to expand to the Africa region to be able to easily enrol participants into both interventional and non-interventional studies. Cerba Research can draw on the support of the Cerba HealthCare and Lancet networks, who have joined forces to become the medical, biological and diagnostic leaders in Africa. With over 11,000 collaborators who share the same goal of providing patients, physicians, pharmaceutical and biotech companies with the best healthcare service, Cerba and Lancet ensure that patients, irrespective of their geographical location, benefit from proximity, quality and innovative biology. This joint venture follows a successful collaboration between the two diagnostic leaders and creates a network with coverage in over 23 African countries. The establishment of this joint venture and the increased resources within the group in Africa, make this the ideal opportunity for Cerba Research to also expand its activity across the African continent and become the global leader in central laboratory services in Africa.

Even before the establishment of CerbaLancet, partnering with Lancet Laboratories, Cerba Research (formerly BARC) has been able to set up and manage clinical trials in Africa for two decades. With a local team based in Johannesburg, BARC South Africa has conducted over 250 trials in a wide range of therapeutic areas. Working closely together with the US department of Health (NIH), NGOs, CROs and pharmaceutical companies, we have localised expertise which allows us to expand and execute trials in the entire Africa region, taking BARC South Africa as an example. This expansion can be seen



in the rest of Africa as the laboratory infrastructure improves and acts as a catalyst for conducting clinical trials in the entire Africa region.

## Biobanking in Johannesburg, South Africa

BARC South Africa has a **certified Sample Repository (Biobank) in Johannesburg, South Africa**. The biobanking facility in Johannesburg was launched in October 2009 and has been designed to store over seven million clinical samples (6.4 million samples at  $-80^{\circ}\text{C}$ ; a dedicated ambient storage area and 760,000 samples in the liquid nitrogen vapour phase) and is integrated into the central laboratory services. Storage conditions available include: Ambient ( $20^{\circ}\text{C}$  to  $30^{\circ}\text{C}$ ), refrigerated ( $2^{\circ}\text{C}$  to  $8^{\circ}\text{C}$ ), frozen ( $-20^{\circ}\text{C}$ ,  $-80^{\circ}\text{C}$  and  $-196^{\circ}\text{C}$ ). There are currently approximately 3.2 million clinical trial samples in storage at  $-80^{\circ}\text{C}$ , and 500,000 PBMC samples in the vapour phase of liquid nitrogen. The BARC South Africa biobank is involved in research looking at long-term storage preservation of mycobacteria in various media with the ACTG as part of the TB Quality Assurance Advisory Group. Continual internal auditing is done by the quality assurance officer on all work performed by staff to check for integrity of sample processing, storage and on source data recording, with ongoing training and development of all staff as needed. All samples are quality assured 100% on entry and prior to ship-out from the facility. Furthermore, robust methods have been developed for receipt of samples into the biobanking unit, sample processing and storage within the Biobanking unit and for sample distribution from the Biobanking unit. These methods include: pre-notification steps, shipment approvals, capturing of shipments and quality control into the laboratory management system, sample issues reported on a specimen discrepancy report (SDR), management of permits (import and export), rapid and accurate retrieval of samples. All shipping performed is done to IATA standards. The biobank therefore has the ability to disseminate frozen specimens to destinations worldwide for further research and development in accordance to international guidelines and recommendations. A system known as Citect Scada (FDA approved) is set up to ensure real-time continual monitoring of the temperature, equipment's electronic processing systems, liquid detection monitors, acceptable oxygen levels and related equipment failures within the facility. All are electronically documented with SMS notification via two independent service providers to the standby staff in case of error.

## Sofie Vandevyver

Sofie joined Cerba Research six years ago and holds a PhD in Science, biotechnology. She combines her contracts and proposals experience with her scientific background to function as the Cerba Research head of business operations & marketing.



## Carole Wallis

Carole has a PhD in molecular medicine and medical biochemistry and serves as a virologist on several different NIH protocols. Carole currently holds the position of medical director of Cerba Research (Barc) South Africa.







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# Why the Development of COVID-19 Diagnostics is Far from Over

Given the need for expanded diagnostic testing, many point-of-care tests for COVID-19 have been rapidly developed for both medical and public use. However, the pace of assay development has at times exceeded rigorous evaluation, and uncertainties still remain about the accuracy and reliability of these kits. This article explains the need for rapid point-of-care (PoC) testing, issues surrounding reliability and validation, and how the choice of reagents can affect diagnostic performance.

## The Role of Diagnostics

Since its emergence in late 2019, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has spread to over 200 countries, infecting over 12 million individuals and resulting in at least 500,000 deaths worldwide<sup>1</sup>. While the case fatality rate of infection is relatively low (estimated at around 1%<sup>2</sup>), SARS-CoV-2 has proved to be a highly capable pathogen, combining long incubation periods with high transmissibility and a substantial proportion of asymptomatic-to-mild infections that have made it highly challenging to detect and contain. As it currently stands, there are no vaccines or specific treatments available beyond a handful of investigational therapeutics that are limited to the severest cases. As a result, non-pharmaceutical interventions have become the mainstay of disease prevention, with measures including self-isolation, travel quarantines, social distancing and personal protective equipment. Despite such implementations, many countries have been caught underprepared and as a result have faced ongoing community and nosocomial transmission. To reduce transmission to manageable levels and contain further outbreaks through contact tracing, information derived from diagnostic testing will be crucial. Not only does such data allow identification, isolation and treatment of cases, but it also provides the epidemiological variables to inform ongoing changes to public health policy on both a regional and national level.

So far, the major means of SARS-CoV-2 diagnosis has been the polymerase chain reaction (PCR), a technique that amplifies small amounts of viral RNA up to detectable levels to confirm the presence of active infection. Since the early days of the pandemic, PCR has been instrumental in diagnosing cases and has shown its strengths in both speed and diagnostic sensitivity, as swabs can be sent to a clinical laboratory to provide results within a few hours and only very small amounts of RNA are needed for amplification. However, the need to detect viral RNA is also the technique's main drawback: as our bodies begin to get a hold on an infection, the virus is quickly flushed out the body and its RNA soon becomes undetectable<sup>3</sup>. As a result, there is only a limited time window for detection, making diagnosis of asymptomatic or sub-clinical infections particularly challenging. Another major issue lies in sample collection: as viral loads in sputum are not homogeneously distributed, there is always a chance that viral RNA is not captured, which can lead to false-negative results with potentially harmful consequences<sup>4</sup>. Finally, there are some practical limitations to consider: the processing of RNA samples requires specialised biocontainment laboratories, supported by complex and resource-costly sample collection and distribution systems that typically extend turnaround times beyond

24 hours<sup>5</sup>. Combined, these factors limit the utility of PCR and make it impractical for use at scale.

## Moving to the Point of Care

To bolster diagnostic capacity and better track cases at the community level, more decentralised, rapid and “resource-lite” forms of testing are needed for use at the PoC. Furthermore, platforms that can detect antibodies raised to SARS-CoV-2 are highly desirable given their potential in epidemiological modelling, assigning so-called “immune passports”, and in the identification of convalescent patients that can provide therapeutic plasma. While there are a range of options available, one of the best-placed technologies to meet these needs is lateral flow assays (LFAs; Figure 1). In short, LFAs are paper or polymer-based immunoassays that absorb a sample and run it along the surface of a pad, binding reporter antibodies and then detector antibodies to produce a confirmatory visual signal — usually in a matter of minutes<sup>6</sup>. A well-known example of an LFA is the at-home pregnancy test.

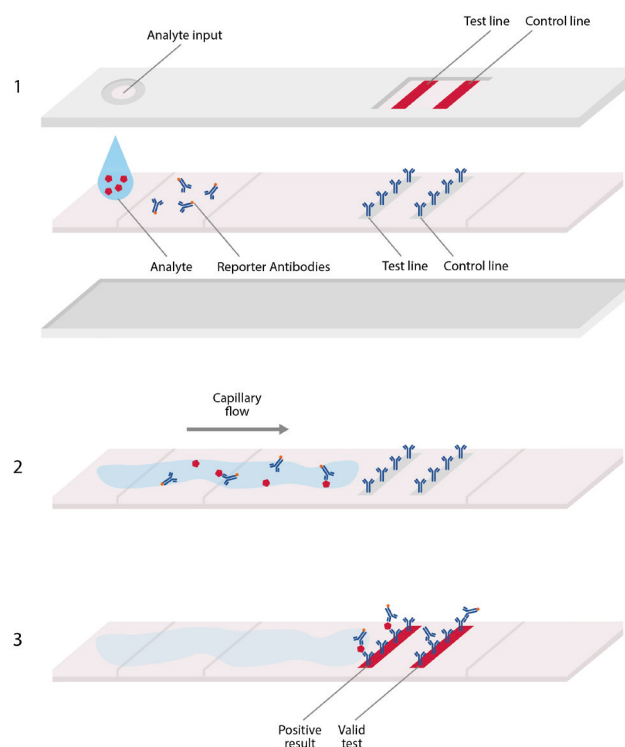


Figure 1. Basic design of a LFA. LFAs typically comprise a plastic cassette, containing a strip of absorbent material that is able to absorb and transport an analyte. 1) Analyte is first added to one end of the strip, where it is absorbed, allowing the analyte to migrate along it. 2) Analyte encounters an area of conjugate antibodies, which adhere to them, along with detectable tags. 3) Analyte continues to migrate to an area of test antibodies that are specific to the analyte and bind to produce a solid, visible line that indicates a positive result, and hence, confirms infection. Secondary control lines are used to detect migrated conjugate antibodies and ensure that the test has worked correctly.

A particularly useful feature of LFA platforms is their design flexibility, making them well-suited for different applications. For the detection of acute SARS-CoV-2 infection, virus or antigen can be collected from nasopharyngeal swab samples and detected by antibodies that are specific to the spike (S) and nucleoproteins (N). Alternatively, a range of different antibodies produced against

SARS-CoV-2 can also be measured from either sputum (IgA) or blood (IgM and IgG) to gauge the patient's immune status both during and long after infection. However, unlike antigens or RNA, antibodies appear unusually slowly in most COVID-19 patients, with a median time of 11 and 14 days for IgM and IgG, respectively<sup>7</sup> (Figure 2).

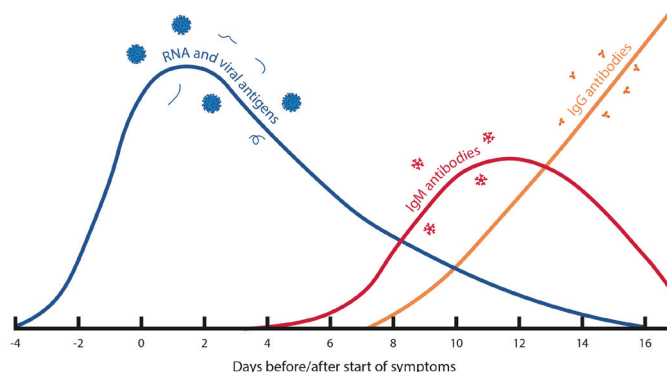


Figure 2. Graph illustrating the general levels of RNA, antigen, IgM and IgG over the time course of a SARS-CoV-2 infection.

Therefore, the application of antibody tests in acute-phase diagnosis is still uncertain and public health agencies have advised against the use of LFAs in directing healthcare, instead suggesting that they are used in tandem with other diagnostic technologies or in population-level epidemiological studies<sup>8</sup>. On the other hand, rapid antigen tests show potential in decentralised acute phase testing, especially where access to PCR is limited. Given these complementary features, the use of both antibody and antigen LFAs in combination could provide much-needed serological data, while alleviating the pressures on public testing laboratories. The secure confirmation of antibody status would allow individuals to return to work and guide policy-makers, while acute-phase status could be used to inform isolation and treatment decisions, potentially in tandem with digital approaches to contact tracing.

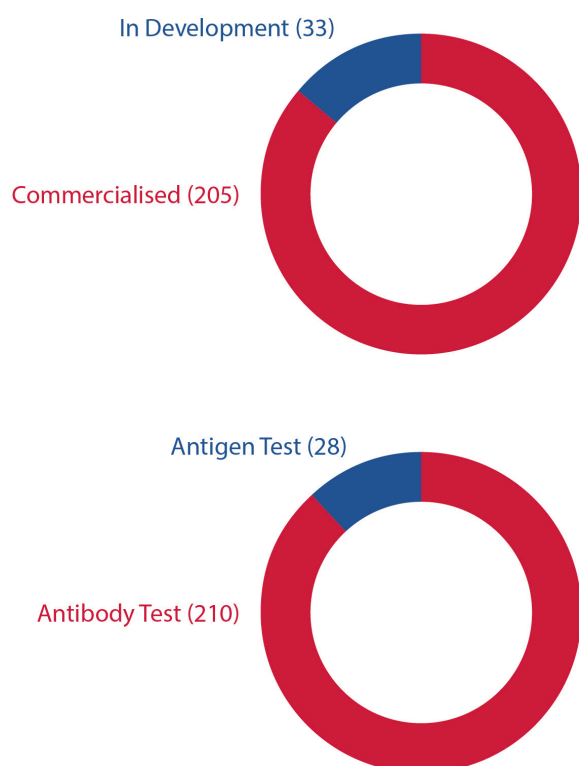


Figure 3. Pie charts showing the proportion of rapid tests that are in development or commercialised and the proportion that are antigen- or antibody-based. Data from the Foundation for Innovative New Diagnostics (FIND)<sup>9</sup>.

### Prioritising Quality

The emergence of SARS-CoV-2 and its global proliferation has spurred an unprecedented effort by diagnostic manufacturers to provide timely and effective solutions. At the time of writing, over 200 rapid tests are in development or have already been commercialised for use (Figure 3), with many being employed in small- to medium-scale serological studies<sup>9</sup>.

However, while an abundance of tests are now available, there have been several hurdles to their effective deployment. Firstly, due to the unprecedented pace at which diagnostics have been developed, the performance characteristics of many kits have not been adequately assessed for use at the PoC. The result has been a glut of low-quality diagnostics that could potentially endanger patients, waste scarce resources and compromise public trust in healthcare services. To complicate matters, the few studies assessing the performance of such tests have showed high risks of bias and heterogeneity in evaluation standards<sup>10</sup>, with further clinical investigations tending to show less favourable performance, and some tests having even been identified to have “fraudulent documentation, incomplete technical files or unsubstantiated claims”<sup>11</sup>. Finally, in the case of antibody tests, there is also still an incomplete understanding of antibody kinetics and correlates of immune protection, which limit the utility of LFAs in this application<sup>12</sup>. To remedy these problems, further research and assay validation are a clear priority. In particular, studies are needed in prospective cohorts for the intended use populations that include a range of ages and ethnicities, with transparent reporting of data.

### The Role of Reagents

While LFAs are seemingly simple devices, their development is deceptively complex. The design, optimisation and validation of an assay can take years at a time and developers will often continue improving performance characteristics after initial approval to decrease the risk of false positive and negative results. Central to an assay's performance is the development, selection and application of high-quality biological reagents. Nearly all immunoassays use recombinant proteins expressed from cell culture, which offer the advantage of improved biosafety and batch-to-batch consistency (13). For COVID-19, there are two antigens that nearly all tests are based on: the SARS-CoV-2 S and N.

The S protein (Figure 4) is found as a trimer that protrudes from the surface of SARS-CoV-2 and gives it its characteristic crown-like appearance. In addition to its three polypeptide chains, each trimer contains up to 66 glycan sugars that are post-translationally added to mediate various functions during infection<sup>14</sup>.

From the perspective of assay development, these glycans constitute many of the key surface epitopes that are recognised by host antibodies, and as a result, the use of unglycosylated S proteins risks the binding of non-specific, cross-reactive antibodies that reduce diagnostic specificity. To ensure that recombinant S protein is produced with full glycosylation patterns and proper conformational folding, developers must therefore take care in selecting and optimising their expression systems. More simplistic organisms like *E. coli*, for example, do not have the necessary cell machinery to glycosylate recombinant antigens, requiring more advanced systems such as mammalian or insect cell lines. When scaling-up protein production, factors such as yield and batch-to-batch consistency also require careful consideration. To further improve specificity, many manufacturers are also using select regions of the S protein which show greater

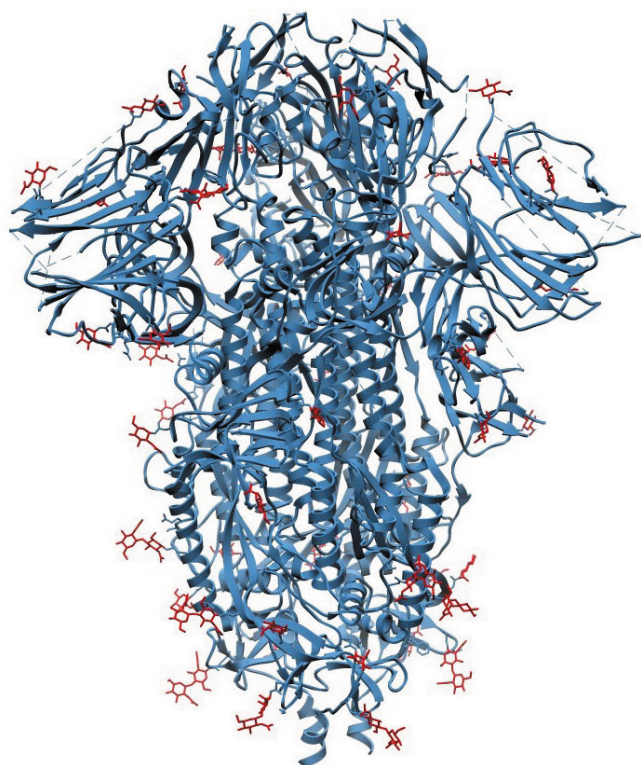


Figure 4. 3D crystal structure of SARS-CoV-2 S protein trimer. Glycans are coloured red; amino acids are coloured blue. Structure determined by Walls et al.<sup>15</sup>. RCSB#: 6VXX.

genetic variation from other coronaviruses and are therefore less able to bind cross-reacting antibodies. Popular choices are the S1 subunit of S and its receptor-binding domain, which is responsible for binding angiotensin converting enzyme 2 (ACE2) to mediate viral entry. However, this in turn brings forth new challenges, as producing and presenting these truncated proteins in their native conformation is no easy feat.

For assays that use N, the challenges are somewhat different. N is not present at the surface of the virus but are instead found within the viral capsid where they bind to genomic RNA. Unlike S, N is completely unglycosylated and shows greater genetic sequence conservation between different coronaviruses, especially at its N-terminal domain. The resulting structural similarity allows N to bind cross-reactive antibodies that have the potential to produce false-positive results. To remedy this, a popular strategy is to “ablate” cross-reactive epitopes by introducing point mutations in the N gene, while minimising structural changes to other regions. Alternatively, so-called “quenching antigens” can be introduced to “soak up” excess, cross-reacting antibodies from patient sera.

## A Balanced Approach to SARS-CoV-2 Diagnostic Testing

Balancing the need for greater diagnostic capacity and the risk of diagnostic error remains a significant challenge to public health. To achieve the promise of widespread testing, developers must take great care in designing and validating both antigen- and antibody-based assays, with a careful consideration of the critical reagents.

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## Dr. Andy Lane



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# How COVID-19 Didn't Quite Change Everything

COVID-19 has changed the world in all kinds of ways. But public perceptions of clinical trials have remained stubbornly similar. New research shows that attitudes have barely changed from before the pandemic, and that has major consequences for those recruiting for clinical trials, especially those related to COVID-19.

This article explores what lies behind these stubborn public perceptions and explores how this unique moment could help us to shift them in future.

### COVID-19 has Changed the World

CO<sub>2</sub> emissions have fallen by 8%, oil prices have crashed<sup>1</sup>, Zoom usage has soared<sup>2</sup> and our homes have become our offices.

As various exit strategies play out across the globe, we're starting to realise that the "new normal" isn't the same as the "normal" we left behind. The "new normal" is a strange place where children play in chalk boxes, restaurants serve customers in booths, and masks are compulsory on public transport. We're quickly realising that getting back to the normal we long for is only going to be achievable through medical breakthroughs like vaccinations, better treatments and cures.

But medical breakthroughs aren't cheap or quick to deliver.

### Accelerating the Slow and Winding Road to New Treatments

The path to a marketed drug is long, exhaustive and expensive. It's a journey through molecule discovery, preclinical testing and robust clinical trials and evidence gathering with all their complications and regulatory hurdles<sup>3</sup>. Typically, vaccines and novel small molecule drugs take 10 to 15 years to develop.

Even before COVID-19, efforts were being made to accelerate drug development. Better cooperation was becoming more common, with many research publications featuring collaborations between pharma, biotech and academics<sup>4</sup>. 'Patient-centricity' was taking centre-stage in efforts to improve trial efficiencies – a much-needed change in an industry where 50% of trials are delayed due to patient recruitment and 85% of trials fail to retain enough patients<sup>5</sup>. Even the traditionally rigid regulatory agencies had started introducing measures to speed up development<sup>6</sup>. Despite all these efforts, it's uncertain whether there's been any increase in new drug approvals or a reduction in total development times.

In the few months since the pandemic started, numerous novel pharmaceutical industry partnerships have been established that would have been unlikely beforehand. Regulatory bodies have eased clinical trial mandates. Processes and rule changes have been implemented within days, rather than years. There have also been unprecedented patient recruitment efforts, with heads of state repeatedly appealing to entire nations for clinical trial volunteers<sup>7</sup>.

This isn't the first crisis to shake up the clinical trial industry. In 2016, the Zika virus vaccine went from lab to first trial volunteer in 190 days, a feat that felt ground-breaking at the time<sup>8</sup>. But it's

nothing compared to the achievements of the newly-formed collaboration between Chinese researchers, Kaiser Permanente Washington Health Research Institute and Moderna Therapeutics. With their experimental COVID-19 vaccination, they've achieved the same feat in just 65 days<sup>9</sup>.

By mid-April, 598 novel coronavirus-related clinical trials had been approved in China, peaking at 32 in one day<sup>10</sup>. The FDA, a notoriously stringent and robust agency, were responding to proposals concerning COVID-19-related drug development in just one day through their Coronavirus Treatment Acceleration Programme (CTAP)<sup>11</sup>. Oxford University also recruited 1102 participants at unprecedented speed for their clinical trial investigating another experimental COVID-19 vaccination, ChAdOx1 nCoV-19<sup>12</sup>.

The initial signs are that drug developments for COVID-19 have benefited from these changes and these efforts are to be applauded. But the broader implications are yet to be quantified. Unavoidably, the development of drugs for other diseases has been affected. Nearly 100 pharmaceutical companies have reported disruption to a clinical trial as a result of the coronavirus pandemic<sup>13</sup>. Without evidence from pivotal clinical trials, new drug filings will be delayed and our understanding of treating diseases hampered. Important new medicines and scientific breakthroughs will take longer to reach health systems and patients. Research funding has also been hit. Charities like Cancer Research UK have lost a quarter of their donated income due to shops staying closed and fundraising events being cancelled. This has drastically reduced their R&D spend<sup>14</sup>.

### Breaking Down Barriers to Clinical Trials is Key

Procedural efficiencies are helping to speed up drug development, but societal barriers need to be overcome too. In 2010 the Clinical Research Scale (CRIS) was developed to measure the likelihood of people participating in a clinical trial. Using constructs from the theory of reasoned action (TRA) to understand participation in HIV vaccine trials<sup>15</sup>, TRA proposes that the strongest predictor of voluntary behaviour is a person's behavioural intention, which is heavily influenced by community attitudes and subjective norms<sup>16,17</sup>.

Current public perceptions about how 'sensible' and how 'normal' it is to join a clinical trial, may be working against efforts to recruit and retain trial participants.

Early COVID-19 trials faced all too familiar challenges with recruitment, public beliefs being one of the common barriers. China-based trials struggled to recruit the number of participants they needed. In fact, at least 40 trials had to be cancelled by mid-April<sup>10</sup>. Gilead, a major player in the race to find a treatment for COVID-19, cancelled two Phase III remdesivir trials, citing that the COVID-19 epidemic had been controlled so well in China that no eligible patients could be enrolled at the time<sup>18,19</sup>. Professor Sheng Luo, a biostatistics expert at Duke Clinical Research provided a more in-depth assessment of the reasons behind recruitment difficulties. Luo identified logistical factors around inclusion criteria, exclusion criteria and site location, before describing ingrained, cultural barriers ubiquitous to all trial designs. People in

China simply preferred to trust in their own immune systems, rather than risk the unpredictable side-effects of medicines<sup>20</sup>.

Yet fast-forward into March and the Oxford University trial of experimental vaccination ChAdOx1 nCoV-19 recruited over 1000 participants in record time<sup>21</sup>. Is it possible that the global pandemic has not only changed trial logistics, but also the public's willingness to join a clinical trial?

### Have Public Perceptions of Clinical Trials Changed?

We surveyed over 1000 British people to see if positive press around clinical trials and the pharma industry's role in tackling COVID-19 had had a positive impact on public perceptions of clinical trials<sup>22</sup>.

This new research showed that only 57% of men and 44% of women were willing to participate in COVID-19 trials<sup>22</sup>. This is comparable to numbers reported by the National Institute for Health Research (NIHR) before the outbreak (there was a 47% willingness to participate across both demographics within a UK subpopulation). Barriers to, and drivers for, trial participation also appeared to align across these samples, agreeing that motivations to participate centred on the potential benefits to one's own health or that of close friends and family<sup>22,23</sup>. The biggest barriers to participation were perceived risk of harm and receiving an 'unknown treatment', alongside concerns over time commitments and time off work. These were similar in the FAZE-led research.

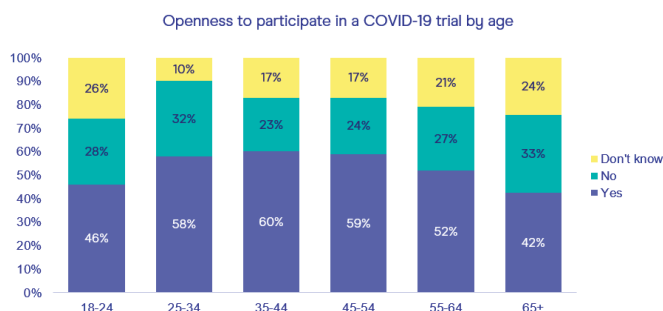


Figure 1. Breakdown of the openness to participate in a COVID-19 clinical trial by age in the UK<sup>22</sup>

Across the board, the new research consistently demonstrated that attitudes towards clinical trials have not been shifted by COVID-19. Variations in research are more easily explained by nuances in the disease than a shift in public attitudes. For example, the over-60's have often been cited as the most at-risk age group for serious/deadly COVID-19 infections<sup>24</sup>. The FAZE-led research found that over 55s were least willing to participate in COVID-19 trials, whereas the NIHR research that found over 75s were least willing to take part in clinical research<sup>22,23</sup>.

If public perceptions haven't changed, how can we explain Oxford University's recruitment success? Matt Hancock, the UK Secretary of State for Health and Social Care, took to the BBC to appeal for trial volunteers during the channel's daily COVID-19 updates<sup>25</sup>. During the pandemic, BBC viewing figures for the UK Daily Government Briefings have soared, with as many as 94% of the UK adult population (and 86% of younger people) tuning in to these updates at some point<sup>26</sup>. Mr Hancock even publicly announced that he had donated antibodies to a clinical trial investigating whether blood plasma transfusions from people who'd been infected could help treat people suffering with COVID-19. He went on to urge the public to sign up to similar trials. In many countries, this sort of direct-to-consumer trial advertising is prohibited. Even in those that do allow it, a daily audience of millions of potential viable trial candidates is

unheard of. So the success of the Oxford University's COVID-19 vaccination trial may simply be explained by the sheer reach of these daily broadcasts coupled with the collective impact of this particular infectious disease.

### Public Understanding of Clinical Trials Remains Poor

The general public have a poor understanding of how clinical trials work. They're also negatively biased towards them. As one article put it, "the only intersection between research and general interest is when things go wrong"<sup>27</sup>.

One of the most important things is the negative public perception of clinical trials.

Across the board, risk of harm is the clearest barrier to trial enrolment. But is this really justified? Let us consider actual serious adverse events (SAEs) as a direct consequence of a trial.

A systematic review of 475 Phase I studies shows that although participants on these trials can expect mild-to-moderate adverse events, there is actually a median of zero adverse events per 1000 treatment group participants per day of monitoring<sup>28</sup>. Of course, there is plenty of research which counters this, showing that expected SAE rates are higher. However, the general public's belief that trials carry an inherent high level of risk appears to be unfounded<sup>29</sup>.

### You Can Change Everything Except Public Perceptions of Clinical Trials

Recent events have proven that, in a short space of time, you can change processes, form collaborations and broadcast messages to the public. But even in a global pandemic, changing public perceptions of clinical trials is much harder.

When you look at how the media have reported trial failures in the past, and combine this with the simmering mistrust in Big Pharma, it's no surprise that the baseline perception of trials is poor. Flagship trial failures such as the 'Elephant Man' trial were latched on to by the media and have strongly influenced the way people think about trials<sup>30</sup>. Ultimately, this has left the pharmaceutical industry fighting an uphill battle to get people to participate.

To compound these negative, headline-grabbing stories, more and more people are being exposed to 'fake news'. Just take the UK COVID-19 vaccine trial as an example. One of the first volunteers to receive the vaccine was reported to have died and the story spread like wildfire over social media, despite it being completely untrue. Trustworthy articles, including one by The Guardian, were written to try and dispel the rumours, but there is no way of knowing how many people read and believed the lies<sup>31</sup>. If left uncontrolled, these fake news stories will only harden the attitudes that clinical trials are competing against. Indeed, the latest research on social media to date shows that false information spreads faster and further than true information – demanding better systematic approaches to tackle misinformation and key roles that scientific and medical experts may play on social media platforms<sup>32</sup>.

During a pandemic, behaviours generally lean towards self-preservation (and the preservation of your loved ones). So you'd think that clinical trials would offer hope of preservation, especially when there are no treatment options available. However, misinformation about clinical trials counters these instincts, leading to a psychological conflict. On the one hand, clinical trials offer a potential prophylactic or treatment against the disease. But on the other, they could be another failed and dangerous trial like



ones they’ve read about in the past – given the tendency to only remember bad news stories.

There also appears to be a disconnect between the concept of medical and scientific breakthroughs and the clinical research required to make one happen. It’s common for the media to report medical/scientific breakthroughs as positive news and over-promise real-world potential outcomes, but when any negative news arises, the narrative switches back to the “clinical trials” setting. In many cases, this is a distinction that does not exist. It’s important to make the public aware that many of the medical breakthroughs they take for granted are from the hard-won efforts of clinical trials.

Taking Steps Towards an Improved Public Perception

Based on the research conducted by Havas Lynx Faze and Day One Strategy, there are a number of logical strategies which, if implemented immediately, may reduce societal barriers to clinical trial recruitment and retention<sup>22</sup>.

Strategy	Why implement?
Emphasise altruistic motivators	The way COVID-19 passes from person to person has made people instinctively consider their own actions to protect other people. We can tap into these feelings of increased social responsibility and community spirit. Everyone has a friend or family member that is in a vulnerable group and this can help motivate people to act.
Build on trust	With high levels of fake news circulating, communication needs to come from reputable sources. As scientists, our voices are likely to be trusted even more than normal.
Harness fear in positive ways	Safety concerns are obviously heightened due to COVID-19. But fear can be used positively if it can be channelled into getting people to act. In a world where people feel powerless, trial participation can help them take back control.
Emphasise the role of clinical trials	It’s common for the media to report medical/scientific breakthroughs as positive news, but “clinical trials” are only ever discussed when negative news arises. We need to challenge this disconnect and emphasise that the two are intimately interconnected. We need the narrative to change so people realise that the medical breakthroughs they celebrate are the direct result of clinical trials.

Conclusion

In a short space of time, the COVID-19 pandemic has proven that people around the world can change the way they live. It’s also

proven that, in the pursuit of medical breakthroughs, you can speed up processes, form new collaborations and broadcast messages to the public. But even in a global pandemic, public perceptions of clinical trials remain stubbornly familiar.

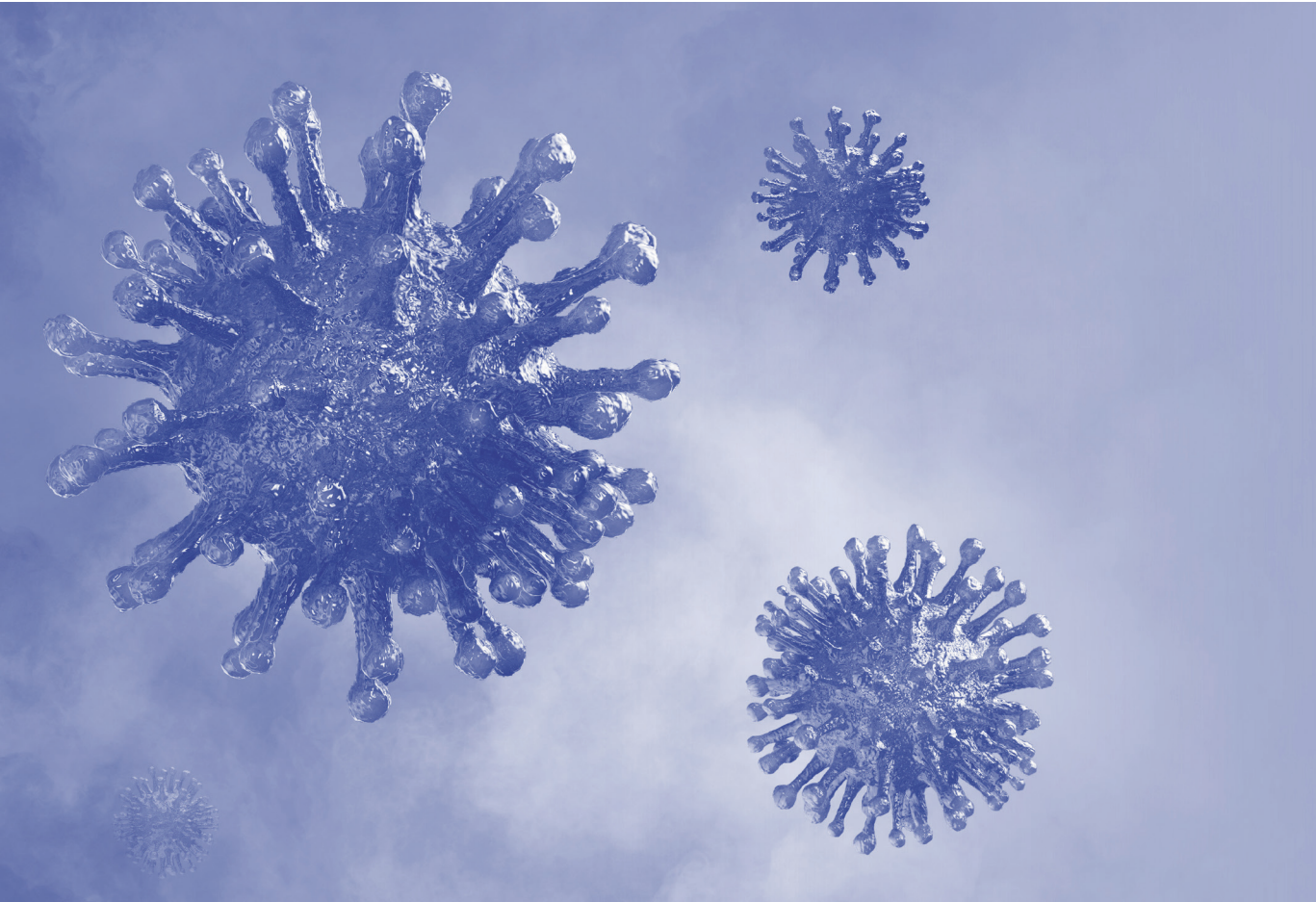
It’s become clear that to change perceptions, people need to be better informed about clinical trials. So while “health literacy” has long been considered important in improving clinical outcomes, surely “trial literacy” is also equally important.

For “trial literacy” to improve, public perceptions of clinical trials must change. And that requires a concerted effort by all of us to build on the successes and platform offered by the COVID-19 pandemic. We can foster positive perceptions of medical/scientific breakthroughs and make the argument that they can only be achieved through clinical trials.

By building positive perceptions we can help to speed up the process of fighting back against COVID-19. But more than that, we can break down barriers to future clinical trial recruitment and broadly benefit future drug development across a whole range of conditions.

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Leading clinical trial recruitment agency Havas Lynx Faze with the mission to help redesign the patient experience around patients. Regular speaker and author on the subject of designing clinical trials around patients. Evans was involved with many industry firsts, including the award-winning AIIR game, thought to be the first example of using gaming – integrated into ePRO – to motivate young clinical study participants. He was also involved in recruiting patients through Facebook in one of the first ever fully remote clinical studies, VERKKO, in collaboration with eClinicalHealth and Sanofi.

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The amount of digital data we have generated, our digital footprint on this planet, is estimated to reach 44 zettabytes sometime this year, in 2020. That is 40 times more bytes than stars in the observable universe.<sup>1</sup>

That equates to 2.5 quintillion bytes of data created each day at our current pace, 90% of this over the last two years, by and for over 3.7 billion humans on the internet, with even more data to come from increasingly connectable devices via the Internet of Things (IoT).<sup>2</sup>



*The Digital Solution has also become the problem: To quote Walt Kelly, "we have met the enemy and he is us" – and there is no off-switch. Our lives are increasingly, conveniently, digitally tethered to devices and social media, for work, as well as for news and entertainment. Source: ©Okefenokee Glee & Perloo, Inc. Used by permission. Contact: permissions@pogocomics.com*

## Healthcare: The Big Shark Tank

Our healthcare ecosystem has also gone the same way. Today, healthcare is no longer a house call by a local doctor who knows our history by simple familiarity and through their own paper records. Increasingly, our healthcare is through a network of distributed physicians and medical services that each have a puzzle piece in regard to our health status. For the services to integrate the complete picture of our healthcare journey, each of us must allow our data to be shared within this network. Multiply this across people, places, languages, regional and country regulations and one can start to envision the structural mayhem currently afoot in care as well as reimbursement.

**The issue: we are all onions with layers, and the deeper you go, the more likely someone is going cry.**

- Not all data is the same; some data is better than others.
- Raw data types give values that feed to aggregate metrics or measurements in context with other data points; that means a data hierarchy in which summary level results are derived from aggregate values which are derived from multiple single measurements.
- Data interpretation should be validated or will otherwise remain subjective. The quality, at each step (capture, analytics, and summary results generation), is critical, as garbage in will

always equal garbage out.

- Ensuring personal and private data protection is critical and legally imperative.
- Regulations and standards are important to allowing interoperability while ensuring data privacy and security relative to standards and increasing legislation.

## Healthcare Data

Healthcare data comes in all shapes and sizes, just like the patients and patient population it is derived from. Data sources vary widely; for example, individual metrics such as heartbeat and pulse from an Apple watch or individual EKG or genetic sequence, from patient registries, to electronic medical records, to claims data, to eCRF for patient chart review. Data can be classified as structured information, such as patient name, diagnosis codes and medications; or unstructured data, such as emails, audio recordings, and doctors' handwritten notes.

**Increasingly, the challenge in our lives is to filter the background noise to what is important. It is the same concept in digital data management.**

Data is therefore various and diverse. What is the best data? How is the best data acquired?

The best data is the most appropriate data, fit for the purpose intended.

- In digital biomarker development, IoT technologies are enabling objective, quantifiable, physiology and behaviour metrics through portables, wearables, and implantable and ingestible technology vehicles. As an example, AI has been used to predict heart failure hospitalisation up to ten days in advance, using data from wearables.<sup>3</sup>
- In virtual clinical trials, your smartphone, watch or glasses could link you remotely to a study, with remote sensors recording data such as body temperature and blood glucose levels automatically to the study's electronic data capture (EDC) records.
- In the US, passage of the Patient Protection and Affordable Care Act (2012) also mandated adoption of electronic medical records over traditional paper files and reports by 2014, leading to electronic health records (EHRs) now being digital and better accessible to patients and their caregivers alike.
- Real-world data (RWD) is data on observed patient outcomes, derived from sources such as electronic health records, patient surveys, clinical trials, insurance claims, billing activities, and product and disease registries. Real-world evidence (RWE) is dependent on RWD and, as defined by the FDA, is "clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD".

## Making Sense of the Mess: Real-world Data to Real-world Evidence

The volume and diversity of digital data is exploding, and, in



healthcare, the number of electronic medical records is growing exponentially as technology makes this information increasingly available. Real-world data is increasingly accessible and useful for outcomes research and regulatory purposes. While clinical trial evidence remains the gold standard for evaluation of treatment efficacy, there is increasing interest and potential for converting RWD into real-world evidence that, through analysis and interpretation, can be used to inform healthcare decision-making.<sup>4</sup> RWD offers advantages over randomised controlled trials that are particularly useful for research and can be applied to healthcare decision-making. They include the availability of timely data at reasonable cost, large sample sizes that enable analysis of subpopulations and less common effects, and the representativeness of real-world practice and behaviours outside of a clinical trial setting. While RWE offers tremendous potential, it also presents very real risks, such as biases due to lack of randomisation, data quality, and the potential for spurious results due to data mining.

### EHR Data: The Best Quality Clinically Validated Data

An electronic health record (EHR) is the systematised collection of patients' electronically stored health information in digital format. EHR systems are designed to store data accurately and to capture the statistics of a patient across time, thus relieving the need to share previous records with current and future caregivers. EHRs enable patient care to be more based on the entire healthcare network, instead of based on individual caregivers, thus allowing patients to be seen across their healthcare network and their conditions reviewed and treated by broader expertise, regardless of location.

EHRs contain patient demographic details, such as age and weight, as well as their medical history, including diagnoses, treatments, conditions, laboratory results, radiology images, and billing information. EHRs are often the best longitudinal record of a patient's journey, treatment, and diagnostic history. The upcoming 5G technology will offer the additional potential to better enable remote monitoring through wearables, telemedicine, and larger file transmission, such as medicinal images, which are often not part of medical record due to size. The challenge, with more data, is how to drink out of a firehose with increasing diameter and make utility of all the context now provided, without drowning in the data.



*Data Resolution = fit to purpose: The value of any type of digital data, including medical data, comes from its resolution. The author is shown in a digital image, revealing at higher resolution the pixelation, or individual pixel bins, much like Seurat's pointillism made of different colour values, that make up the overall image in an electronic format. Source: author's own collection.*

The exciting development which will bring us toward better healthcare is better resolution of data; digitally, specifically, but of the author, not so specifically (see picture above). Much like building a house, a foundation of digital clinical EHR data is the

solid bedrock enabling better patient metrics and better outcomes. However, issues with EHR data are often skipped over and it is important to draw out the challenges in managing EHR data for patient insights:

Firstly, even though there are many global, regional and national initiatives to harmonise data, there also still exist a multitude of coding systems that need to be managed in parallel. There is, therefore, a need for thorough mapping and translation of codes between systems so that a common search strategy can be conducted across systems.

Secondly, coding may be harmonised, but the way that the EHR data is managed for the same conditions can vary greatly because of the richness of the coding systems and the different way diseases are understood and managed in different healthcare systems.

Thirdly, the way in which systems are implemented varies greatly, so the data can be managed in different systems and harmonised in different ways, again shifting the way in which the data is managed.

Lastly, for rare diseases, the coding is often up to 70% inaccurate, due to physicians being less familiar with those conditions and their coding, so a different strategy to traditional search methods needs to be considered.

### Case Study: Rare Diseases – Enabling Better Identification and Diagnosis by Combining EHR Data Analysis and AI

Rare diseases, by nature of being rare, are often untreated, undiagnosed, or frequently misdiagnosed. In addition, rare diseases may present differentially – meaning patients don't all appear the same but are heterogenous and therefore hard to diagnose – which leads to a substantial delay in diagnosis, and makes it very difficult for patients, their families and healthcare givers to manage.

Studies show that the impact of rare disease is much wider than the individual affected and represents a significant challenge for the healthcare system itself.

In a survey of patients and caregivers in the USA and the UK, patients reported that it took on average 7.6 years in the USA and 5.6 years in the UK to get a proper diagnosis, during which time patients typically visited eight physicians (four primary care and four specialist) and received two to three misdiagnoses.<sup>5</sup> Of the 7000 known rare diseases, 90% do not have an FDA-approved medication, which means patients must go with no treatment or go with off-label use of existing medicines to treat their symptoms.<sup>6</sup> Patients with rare diseases can go up to 20 to 30 years before diagnosis, or even go entirely undiagnosed.<sup>7,8,9</sup>

Our company operates a platform on which a network of partner hospitals around the world make their patient EHR data query-able, with appropriate data privacy protections. When aiming to support the diagnosis of rare disease patients, this data is not enough to counter the data issues mentioned above. We therefore sought out technology which would identify phenotype, condition, and treatment models better.

The Swiss company Volv Global is applying cutting-edge AI and machine learning technology to highlight possible rare disease patients. Their unique methodology not only ascertains patient cohorts at risk of disease, but also helps with trial recruitment, understanding patient journeys and can make assessment of real

market size for generating rationale to create new drugs to meet these important unmet needs.

Using this technology, we can address the challenges of developing computational models capable of detecting rare disease patients in population-scale databases such as electronic health records (EHRs) while addressing all the real-world challenges highlighted in the previous section. The issues with EHRs are non-trivial as the EHR is in fact a weak proxy for a patient phenotype when we are considering rare diseases.

Typically, one would need to look across around 10,000 features in the full EHR to find relevant patients reliably. With typical machine learning methods and standard toolsets, one would expect to have to have around 50,000 “labels” (examples of patients with the disease in question) to allow the machine learning to generate a reliable model. As the reader will note, this is an impossible threshold, as, by definition, the rare disease patients are very rare. Additionally, as we have seen, they are also often misdiagnosed, so “hidden” within the system.

Volvo has overcome these obstacles with a novel, lightly-supervised algorithm that leverages unlabelled and/or unreliably-labelled patient data – which is typically plentiful – to facilitate model induction. Importantly, it can be proven that the algorithm is safe: adding unlabelled/unreliably-labelled data to the learning procedure produces models which are usually more accurate, and guaranteed never to be less accurate, than models learned from reliably-labelled data alone.

The methodology is not based on machine learning toolsets, but novel algorithm development with a validation and proof methodology built in.

This is a breakthrough for patients that are likely to be held up in a lengthy diagnostic odyssey, as the models can be adapted to the healthcare systems now on our own platform through our partnerships with hospitals around the world. Not only this, but Volvo’s remote learning and deployment capabilities mean that the combination allows us to build highly accurate and adaptive complex models reaching more and more patients as the platform expands.

Volvo’s methodology often has no examples of confirmed patients with disease to learn from (i.e. no “labels”) and it is therefore useful to get a first ‘gold-standard’ input and validation of the model performance, which is done in a specialised part of the review methodology.

Using their novel techniques with extremely small sample sizes, that are typical to rare diseases and personalised medicines, Volvo builds predictive diagnostic algorithms that outperform Human Clinical Diagnostic Performance by looking at data earlier in the patient journey and by identifying cognitive biomarkers, digital biomarkers and medical biomarkers that drive a completely new way to diagnose.

- **cognitive** biomarkers are where we are picking signals by way of things that are thought about the disease from the way it is handled or managed or classified within the clinical system
- **digital** biomarkers are where the actual data is informative in some way about the disease
- **physical** biomarkers are phenotypic features of the patients that are predictive of the disease

These biomarkers are discovered by the model learning process, and we often find them out only as the model improves and subsequently derive clinically interpretable models.

It is desirable to construct prediction models which are both accurate and interpretable, as in medical applications it is essential that clinicians understand the basis for the predictions and recommendations of decision-support systems.

One way to increase interpretability of the complex models produced by modern machine learning algorithms (e.g. deep learning, ensembles) is to identify which predictors/features are ‘important’ to the model’s predictions and to quantify this importance. Alternatively, one could trade off model performance and interpretability, adopting a less accurate but easy-to-understand model structure (e.g. linear regression, decision tree). Unfortunately, neither of these options is very useful in medical domains:

- standard feature importance assessment methods are not appropriate for many medical informatics problems, such as modelling and analysing electronic health records (EHRs);
- implementing sub-optimal prediction models in high-consequence medical settings is hard to justify.

In Volvo’s process, they “learn” an interpretable model from a proprietary good/robust model and then assess the predictive importance of the features of this new, interpretable model. This delivers a model that can be utilised by a clinician, as it is developed in their language and terminology, and it has quantifiable predictive performance, derived by specialised analysis of their complex models. Importantly, we as humans can learn new things from these models that are novel.

One of the truly interesting things about the interpretable models that Volvo produces is that they can sometimes be more than one, which may in fact mirror a clinical setting within which patients can find themselves. This is important as it means that the interpretable models are clinically relevant.

In summary, the technology collaboration with Volvo allows us to **flag potential rare disease patients correctly and then work with their treating physicians to create the outreach programmes, test the patients for rare disease, and reach a correct diagnosis.** Volvo’s methods are shown to substantially outperform state-of-the-art models in patient-finding; Clinerion’s patient data network allows healthcare systems to leverage their data in a secure and compliant manner to apply these models to the benefit of patients. Together, the two companies are enabling better healthcare for severe but undiagnosed conditions, one patient at a time.

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### Douglas Drake

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# Special Considerations for Child Psychiatric Trials During a Global Pandemic



As the COVID-19 pandemic continues, many sponsors, CROs, investigators and IRBs have modified clinical trials, moving visits from clinics to living rooms worldwide. When trial participants are children, a more complex decision process must govern when and for whom a move to virtual visits is possible. Simply by virtue of their age, children are defined by law as a vulnerable population whose safety in research receives special protection. Additional protection is needed when children have psychiatric illnesses that put them at risk of harm to themselves or others. As outlined below, decisions to move child psychiatric trial visits from face-to-face in-clinic to virtual and remote require careful deliberation and multiple special considerations.

## Regulatory Considerations

IRBs should be consulted before any formal plan to alter the trial is enacted. During the COVID-19 pandemic, IRBs have been especially responsive. The risks/benefits of retaining the child in the trial versus discontinuing the child must be weighed, suitable plans for assessing and ensuring the child's safety must be identified and means for collecting valid study data must be provided.

## Safety Considerations

Safety considerations are key in any decision to move from face-to-face to virtual visits. Is the study medication one that can be safely administered at home? How will medical emergencies be handled? How will psychiatric emergencies such as psychotic exacerbations and increased suicidality be handled? What are the specific measures in place to ensure the child is treated? Will the parent/caregiver agree to all supervision requirements imposed, including providing the address and phone number of the virtual visit site so that police or EMS can be summoned if needed? Is there a plan if the child has been exposed to COVID-19? Is there a plan if the child develops other illnesses or adverse events potentially related to the study medication? All of these questions, and more, depending on the nature of the trial, must be thought through and addressed with the overseeing IRB, participants, and parents/caregivers.

Sponsors, CROs, and investigators must evaluate closely the ability of the parent/caregiver to adhere to all protocol requirements. This is even more critical when visits move from in-clinic to virtual. In addition to supervising medication administration and accountability, the parent/caregiver must be willing and able to be present in the home throughout the virtual visit to answer questions about the child and to assist in securing emergency services if needed.

Virtual visits should not take place without a parent/caregiver present.

## Practical Considerations

In addition to safety considerations, practical considerations must be considered in any decision to move from live to virtual visits.

Telephone and internet access are required for both investigator and participants. If using video, laptops, tablets or other devices

with video capabilities may be required. If investigators and participants do not have access to equipment, sponsors and CROs may be able to supply them instead. However, all of this must be determined prior to going remote.

Assessment tools such as rating scales and diaries may be accessible to investigators and participants. Thus, the mechanics of providing these will need to be considered.

With respect to data entry, investigators and investigative staff will need a means of entering visit data into the study database. They will also need ready access to all collected data – including data from other raters at the visit, if applicable, and including past data – to make dosing and other medical decisions and to ensure the child's continued safety in the trial. A means for ensuring such data access will need to be established.

## Validity and Data Integrity Considerations The Pandemic's Effect on Children

The overall effect of the current pandemic on children is unknown. Physical effects of exposure on the brain and body systems, compounded with psychological effects of social isolation, grief, and fear of disease may exert unique effects that differ by age, study drug, psychiatric illness under study, and region of the world. For this reason, regulators have requested that data be flagged as having been collected pre or post the COVID-19 pandemic, even if there is no change in administration method.

Some investigators, in what they believe are good-faith attempts to preserve data integrity, may try to "undo" pandemic effects by adjusting their symptom ratings to try to approximate what the symptom might have been had the pandemic not occurred. This should be strongly discouraged. When it comes to psychiatric symptom assessments, investigators should "rate the symptoms as they see them" without adjusting or attempting to parse out pandemic effects. Effects of the pandemic will be examined statistically for all trials with pre and post pandemic data.

## The Effect on Data of Switching to Remote Administration Mid-study

The effect of switching to remote administrations mid-study is unclear, although one would expect to find increased variability. Attempts to maintain as much consistency as possible with in-clinic assessments should be made. For example, whenever possible the same rater should interview the child, the same assessment order should be maintained, and the same parent/caregiver should provide information. For some assessment measures there may be existing literature supporting equivalence between remote and in-person modalities. If these are available, sponsors and CROs may wish to include such citations in their regulatory submissions. In all cases, when moving from live to remote we recommend flagging the administration modality in the database. This will allow for subsequent analysis of administration type and possible effects on data.

## General Tips for Remote Assessment with Children During a Pandemic

Video conferencing is preferred over telephonic visits when moving

from in-person to remote visits in that these allow for an “eyes on” assessment of the child’s physical and mental status and serve as a better approximation of the “in-clinic experience”.

That said, cameras, phones, laptops, and other means of video conferencing all differ, and attention and some modifications, or even equipment provisioning, may be required to make protocol-mandated assessments. For example, close-up views may be needed to measure rashes or orofacial movements, while widescreen views may be needed to assess full-body views for some of the dyskinesia scales. The parent/caregiver may need to hold the camera during an assessment of the child to ensure correct camera positioning and image capture.

## Specific Tips for Virtual Visits in Child Psychiatric Trials

The visit should begin with both the child and the parent/caregiver in the room together. The investigator should explain that while the child and parent/caregiver interviews can be separate, it is mandatory for the parent/caregiver to be nearby to help with technical aspects and to answer questions about the child.

Before beginning any protocol assessments, it is helpful to spend a bit of time helping the child become familiar with the new setup and the fact that the visit will now be remote. Investigators should engage the child in neutral “small talk” about the child’s day as needed to promote the child’s comfort, while also introducing the trial and the technology.





Investigators should explain what will happen using simple terms and concepts. Asking the child to explain back the activities of the day and why they are being done virtually will help ensure that the child understands. Investigators should also allow the child the opportunity to express any concerns or worries about the technology or the virtual visit itself.

As noted previously, it is important that the investigator work with the parent/caregiver to ensure that the camera is positioned appropriately to capture the body parts required. This is true of scales that require visualisation of the full body to assess symptoms such as fidgetiness, tics, and hyperactivity/hypoactivity.

Finally, it's important to remember that at some point during the remote assessment (often the end), a medically responsible investigator must separately interview the child and the parent/caregiver to determine:

- Adverse events
- Dosing or discontinuation considerations
- Compliance with study medication, and
- Any known or suspected exposure to COVID-19

## Specific Guidance for Remote Administration of Commonly Used Scales in Child Psychiatric Trials

### K-SADS-PL

This scale requires separate interviews with the parent/caregiver and the child. Although the copyright holder has indicated that a phone interview is acceptable, we recommend videoconferencing of, at minimum, the child portion. This is because some disorders (e.g., ADHD, tics, and psychosis, for some typical examples) benefit greatly from visualising the child during the interview (motor activity, motor tics, and responding to internal stimuli, respectively, using the above example disorders).

### C-YBOCS

In non-remote settings, this scale is typically done with the parent/caregiver and child together in the room. Typically, the opportunity is given for either party to then speak alone with the interviewer. This approach should be maintained. Although videoconferencing is preferred, it is possible to administer the scale by phone because it is based on verbal report alone.

### CY-BOCS-ASD

In non-remote settings, the scale is often administered solely to the parent or caregiver. If this is what has occurred in the trial previously, this should be continued. As the scale does not rely on visualisation, it is possible to administer this by phone.

### YGTS

In non-remote settings, the scale is typically administered with the parent/caregiver and the child together in the room. As noted above, if this is what occurred in the trial prior to the remote assessment, this method should be continued. Videoconferencing is required to visualise any expressed tics (or demonstrated examples of tics).

### CDRS-R

This interview requires separate interviews with the parent/caregiver and the child, while also requiring visualisation of the child for some of the items. Videoconferencing is required.

### ADHD-RS

In most trials, the interview is done solely with the caregiver. Thus, telephone administration is possible.



### CGI-S/I

Regardless of the indication, the CGI-S and CGI-I requires the investigator's overall consideration of all relevant information about the illness under study. The assessment must include, in addition to a review of collected relevant data, a clinical interview with the child and a separate interview with the parent/caregiver. To best capture the full clinical picture, videoconferencing is clearly preferable to phone; for some conditions (e.g., ADHD, motor tics, among others) videoconferencing may not only be preferred but required.

### PANSS

The scale requires separate interviews with the parent/caregiver and the child. As many of the items require visualisation of the child, we strongly recommend videoconferencing for the child interview.

### In Summary

While child psychiatric trials present specific considerations and challenges during a global pandemic, they are still possible. With thought, planning, and careful oversight, many trials can be modified to successfully continue remotely.

## Dr. Joan Busner



Dr. Busner is Clinical Vice President of Signant Health, with specific scientific and clinical oversight responsibility for child psychiatric and pediatric orphan disease services including protocol consultation, rater training, endpoint quality and eCOA. Dr. Busner has over 35 years of experience as an academic clinical psychiatric researcher. She has served as Principal Investigator of 49 industry sponsored clinical trials and Sub-Investigator of an additional 35, and has directed the psychiatric clinical trials units of two major medical schools. She served continuously on University Institutional Review Boards (IRBs) for the 20 years that preceded her move to Signant Health. Dr. Busner is an active contributor to the psychopharmacology literature and has authored or co-authored over 130 peer-reviewed articles and national or international scientific presentations. Dr. Busner has trained thousands of psychiatric clinical trial investigators across the globe and lectures frequently on the application of objective rating scales in the assessment of diagnosis and efficacy in psychopharmacology, ethics in psychiatric research, the placebo effect in psychiatric research and techniques for its minimization, the role of IRBs and clinical trial methodology. Dr. Busner received her PhD in Experimental Social Psychology and her MA in General Psychology from Adelphi University. She is licensed to practice psychology in Pennsylvania, Missouri and New York.





"Our **paediatric oncology patient** would happily sit while to have her intravenous chemotherapy as long as I was dressed as a fairy, complete with tiara and wings!"

"She said that I was her **"get better fairy"** and that the trial medication was a **"magic potion"**. I was very happy to comply."  
Illingworth Research Nurse



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**Passion** for research,  
**Compassion** for patients



## Patients as People: Operational Empathy Remains a Key Driver of Recruitment Success

Big data, artificial intelligence and digital platforms have dramatically transformed the clinical research landscape. Yet despite these extraordinary advances in technology and communication tools, the prevailing challenge of clinical trials has remained constant for decades: recruiting and retaining qualified patients. According to US and UK studies, only a third of clinical trial sites meet their patient recruitment targets and around half are forced to extend their enrolment periods.<sup>1</sup>

At first glance, the COVID-19 pandemic has exacerbated these longstanding challenges, slowing or pausing recruitment and operations of large numbers of trials due to social isolation and travel restrictions. But a closer examination reveals a sizeable shift in attitude and practice toward innovative remote and virtual techniques that bring trials to patients, rather than patients to trial sites.

It's a positive trend that is long overdue and here to stay. The pandemic has accelerated the adoption of patient-centric trial models – virtual or decentralised clinical trial (DCT) models – that have historically had slower adoption into routine practice. DCTs mitigate many of the persistent barriers to trial participation: geographic distance, transportation, financial impact from missing work, scheduling conflicts and other logistical hurdles, and scientific evidence demonstrates their value. For example, drugs developed using patient-centric trial designs are 19% more likely to launch than drugs developed without this approach. Moreover, patient-centric trials take less time to recruit the first 100 participants: four months versus the average of seven months for all trials.<sup>2</sup>

But paradoxically, concepts that seem intuitive and straightforward have proven to be remarkably complex to execute, in part because they require sophisticated expertise, technology and tools, as well as the infrastructure to implement them.

### Smart Use of High-tech, Low-contact Platforms

New technology often outpaces the industry's ability to adopt and incorporate it into clinical research. But the transformative social distancing measures imposed by the pandemic have accelerated opportunities to incorporate innovative devices and platforms that remotely connect us to patients and sites.

Wearable devices, for example, have become so small as to be easily hidden under clothing, and be unobtrusive while working, exercising and sleeping. Among the latest wearables, the FDA has approved small stick-on monitors, about the size of a large key, that continuously capture vital signs and specific health events over a 30-day period. These wearables are being integrated with apps that allow patients to virtually communicate with their clinical

teams and health researchers about their experiences and even opt into clinical trials that match their health profiles. This remote technology is particularly useful for COVID-19 trials, in which patients are isolated yet there is still a need to frequently report their symptoms to clinicians.

Another new tool is a compact drug delivery device that dispenses preprogrammed doses of oral medication and reminds patients when it's time for a dose, to drink water with their medication, when the device needs to be refilled, and other tips designed to enhance compliance. The device's bluetooth function connects with wearables to capture biometric data in real time, while a small video screen enables patients to conduct telehealth visits, ask questions and stay engaged with sites from home. To help patients navigate new technology, a host of tutorials are now online to walk patients through their features in a step-by-step fashion, which aids compliance and comprehension.

There's no doubt that technology is facilitating more decentralised and patient-centric trials, but we have to remember that technology is just one tool in our arsenal. It's how we apply the technology in a patient-centric way to achieve the study objectives that make the difference.

### Real-world Evidence in a Real-time Crisis

The pandemic has disrupted life as we know it, and it has exponentially hastened our need for accurate data in real time. We need answers in days or weeks to help drive sound medical decisions for COVID-19 patients and public health policies. Real-world evidence (RWE) platforms provide an essential means for capturing this data from multiple sources to quickly assess infection rates, risk factors, symptoms, outcomes and the efficacy of investigative therapies. Even in cases where real-world evidence can't be acted upon in the short term, the data we acquire will aid our understanding of COVID-19 and ultimately help inform the future studies we design.

From the patients' perspective, RWE will serve another valuable purpose: enabling us to share the results of studies in which they've participated more quickly. According to The Center for Information and Study on Clinical Research Participation (CISCRP), almost all patients want to know the results of their trial, but few if any patients are receiving them.<sup>3</sup>

This isn't a new or emerging issue. For decades, patients have requested information on trial outcomes, according to research about patient perspectives. To accommodate their requests, we need processes that allow us to routinely inform patients about the studies. RWE accelerates data collection, which in turn speeds data analysis, which will ultimately pave the way for enhanced ways to share trial outcomes with patients. Patients who understand the value of clinical research – and the real-world impact it has on the



discovery of new drugs – will be more engaged and committed to participating.

### Connecting to Patients with Empathy

Patient-centricity, or putting patients first, is increasingly recognised as an essential element for clinical trial success, starting with the earliest stages of trial design. But as an industry, we're still missing opportunities to connect with patients as people. Recruitment is a prime example. We now have access to big data from medical claims, electronic medical records and other sources – data that help identify who and where the patients are, their demographics and disease state. But more insight is needed to gauge their willingness to participate in the study. Likewise, sophisticated digital media platforms can target patients with pinpoint precision, but additional expertise is required to translate interest into trial engagement and successful recruitment.

This is where sites play a critical role. It's essential that the doctors, nurses and physician assistants interacting with patients truly believe in the study and regard its merits with positivity and confidence. Research has clearly shown that healthcare providers refer only a small number of patients to clinical trials each year, in large part because they don't have the time to evaluate and confidently discuss clinical trial options with their patients. A Tufts study among practising healthcare physicians and nurses found that healthcare providers are "better positioned than expected as patient engagement facilitators if they have sufficient time, information, and confidence to advocate on behalf of their patients."<sup>4</sup>

Technology cannot replace operational empathy, the human element that conveys genuine compassion and which ultimately drives successful recruitment and retention. But the combination of technology and empathy has the potential to transform the patient experience.

### Building Operational Empathy

Building empathy with patients starts within an organisation's culture. With patients at the heart of everything we do, we value compassion and patient-centricity, and we model the behaviours we want our network of more than 500 alliance sites and 18,700 investigators worldwide to display. In turn, they extend those same behaviours and attitudes to study participants.

We also provide sites with the resources they need to recruit and support patients during a trial. For example, during a paediatric pulmonary study involving newborn infants, new parents were faced with a diagnosis requiring their babies to remain in the hospital. Exhausted and scared, the last thing on parents' minds was enrolling their infants in a clinical trial.

We modified the site's recruitment materials to infuse genuine sensitivity to the parents' situation, and we counselled clinicians to sit with parents, not across the table from them. We wanted parents to know that we weren't just interested in their child because they had this virus; we wanted to make sure that they were coping, too. This kind of heart-felt empathy reduces fear and encourages parents to consider clinical trials in the context of helping not only their child, but other children whose parents are experiencing the same gripping fear and uncertainty.

Additionally, recognising site pain points and asking sites for input on decisions that impact their workload, schedules and technological capabilities creates an engaged research partner, not

just a paid clinical site. The smallest of details can influence a site's perspective of a clinical trial. For instance, if multiple vendors are collaborating with a site, then providing the site with a single sign-on across multiple software platforms can exponentially reduce their burden and allow for rapid data entry in the midst of a busy private practice that's also juggling a clinical trial.

We take pride in providing hands-on training and support; for example, setting up a Facebook page for the clinic's patient community to bolster trial recruitment. For the cost of an hour-long engagement or a 20-minute walkthrough phone call, we can alleviate the burden for sites and establish a positive rapport that's the foundation of a long-lasting relationship.

Navigating informed consents is another well-known hurdle that we simplify through our Consent+ platform. From the patient's point of view, trial data and endpoints may not be their priority – they are more likely to care whether the study will ease their pain, help them sleep, minimise discomfort and improve their quality of life. No matter how much data is provided to patients, they want to understand, on a human level, what the trial means to them. We provide sites with interactive videos that explain, in patient-friendly terms, what the study involves. This reduces fear and confusion while encouraging potential participants to open a dialogue with site staff and ultimately make an informed decision about whether to participate.

In short, patient empathy in a trial setting means we always consider the trial through the lens of the patient and the site staff, and our recruitment approaches reflect their needs and preferences.

### Passive Listening and Active Engagement

On a more structured level, the industry is now routinely convening site and patient advisory groups to address specific aspects of a particular study and fully understand the patient experience. It's critical to use both passive and active listening to encourage open and constructive dialogue, and to drill down into the specific protocol requirements. For example, in an asthma study, what are the patient concerns about switching from one inhaler to another? Is a mother of three more likely to join an asthma study if a home nurse visits and takes her child's peak flow measurements before school instead of having to drive her child to the clinic? It's imperative that we obtain actionable feedback to inform real-world study designs that parents, busy professionals, grandparents, teens and kids can work into their routines without too much burden.

In other words, studies must answer critical scientific and medical questions, but patients can help tell us whether the studies will be successful in answering them.

### The Pandemic as a Teachable Moment

It's hard to think of a pandemic in terms of silver linings, but COVID-19 has given us teachable moments that we can't afford to ignore. The pandemic has brought to the surface the critical need to address emotions that drive patient behaviour: fear of the unknown, reassurance from trusted experts, altruistic versus personal motives (e.g., protecting oneself or protecting society at large). These are enduring human traits that technology and data will never overcome.

In many respects, the future of patient-centric trials has already begun. But while there are huge advancements in technology, big data and AI machine learning, we must remember that our



industry is made up of real people whose interactions with patients can demonstrably enhance recruitment and retention: Talking with patients in authentic and compassionate ways; engaging them as partners in the fight against their disease; and empowering them as advocates whose participation in clinical research gives them control over their conditions can shift their perspectives from fear and powerlessness to strength and a desire to contribute to the greater good.

### **The Comforts of Home: A Paediatric Study Keeps Kids in Their Own Beds**

In supporting a two-year study evaluating a night-time sleep aid in young patients with a rare disorder, our company recognised how intrusive it would be on patients and families to sleep away from home or require numerous site visits. Our solution was a hybrid decentralised trial that provided child-friendly actigraphy watches that unobtrusively collected sleep quality data, combined with at-home nurse visits, direct-to-patient drug shipments, eDiaries, and only three in-clinic visits over the course of two years.

The approach not only worked, but we also attracted patients from as far as 150 miles from the investigative site. Patients and their families gave us positive feedback and told us they would not have been able to participate in a traditional study. They especially appreciated the flexible visit dates and times for home nursing visits to minimise schedule disruptions.

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### **Tom Ruane**

Tom Ruane brings more than 28 years of experience in clinical research operations to Parexel. For the past 18 years, he has worked across the industry to drive innovative strategies for patient engagement and recruitment for clinical trials. Tom began his career as a registered nurse caring for patients in a critical care setting and has a keen understanding of the patient experience, drawing upon patient insights to drive successful trial outcomes. His strategic roles at biopharmaceutical companies, CROs and the UK National Health Service have provided a holistic view of the clinical trial recruitment landscape, which he applies to advance patient recruitment and retention strategies.



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# Best Practice for Medical Device Clinical Trials

Medical devices play a critical role in the lives and health of millions of people worldwide. From everyday household items such as oral thermometers, to complex implantables such as deep-brain stimulators, patients and the general public rely on regulators to ensure that legally marketed medical devices have been shown to be safe and effective.

The medical device sector has become increasingly important for the healthcare of citizens, with an immense influence on expenditure. For example, in the European Union (EU) alone, this sector employs approximately 675,000 people and generates €110 billion in sales, representing over 25,000 companies, of which 95 per cent are small and medium-sized enterprises<sup>1</sup>. While strict regulatory procedures exist for pharmaceuticals, there are rigorous regulations laid down by the US Food and Drug Administration (FDA) and EU's Medical Device Directive (MDD) only for Class IIb and Class III medical devices (i.e. medium and high-risk medical devices such as implantable medical devices or *in vitro* diagnostic devices). Regulators expect data that is provided by device manufacturers to reflect the risk profile of the device and needs more crucial clinical evaluation before market approval<sup>2</sup>. Higher-risk and innovative moderate-risk devices (approximately 4 per cent of all medical devices), which generally require the clinical evidence to show that the benefits of technology outweigh its risks, are the primary focus of this article.

Clinical evidence of medical devices is often critical, not only for showing the safety and effectiveness of the device but also for informing clinicians and patients about the preferred use of the device in the marketed clinical setting. Regulators are demanding more clinical evidence because they want to see more of it before granting market approval. Not only regulators but also payers are requiring more of it to substantiate product value claims and approve reimbursement. Even healthcare systems and physicians are asking for more of it when making purchasing decisions.

The demand for clinical evidence from various stakeholders is forcing medical device companies to amass more clinical data on their products than ever before. Companies are responding to this pressure by running more clinical trials and focus group studies, and responding in real time by making changes to the beta version of their medical devices. The latest trend is that medical device companies increasingly are turning to clinical trials to differentiate their products from competitors and improve their odds of adoption in the marketplace.

Here are five essential tips for conducting clinical trials for medical devices.

## 1. Blinding

Blinding is an important element in all clinical trials; it reduces measurement bias related to the observer's, doctor's or patient's subjectivity. For ethical or practical reasons, blinding is often more difficult to perform in randomised clinical trials on medical devices compared with pharmacological randomised clinical trials.

Medical device companies need to remember that when it is not possible to blind healthcare professionals, a blind assessment of the outcome should be planned with experienced and trained staff as outcome assessors. The data managers, the adjudication committee, the independent data monitoring, and safety committee, the statisticians, and the conclusion drawers should also be blinded<sup>3</sup>.

In case blinding is not used, medical device companies and their clinical trial correspondent need to give the reasons for not blinding, and discuss the limitations when reporting the results. As blinding of patients and trial personnel may be less often achievable in some medical device trials, objective outcomes must be chosen.

Recently, regulatory agencies have emphasised that medical device companies should search for creative methods to blind individuals in their trials; if they choose to incorporate a novel technique, they must ensure that the blinding process itself does not introduce bias by impairing the ability to accurately assess the outcome.

Any novel blinding technique should have three qualities:

1. successful concealing of the group allocation
2. no impairment in the ability to accurately assess outcomes
3. acceptance by the individuals that will be assessing outcomes<sup>4</sup>.

Despite careful consideration of methods to blind individuals in medical device clinical trials, situations will invariably arise when some or all groups of individuals simply cannot ethically be blinded. Medical device companies must accept this reality and incorporate other strategies to minimise bias when blinding is not possible.

## 2. Outsourcing Work to Experts

It is an industry-wide trend that most device makers lack the internal resources and expertise to run a complete clinical trial operation in-house. It might be possible for a large medical device company to have an in-house clinical development team which can help in facilitating the clinical trials. However, for small medical device companies, which have little bandwidth, experience, and margin for error, the success of clinical trial or failure can be very crucial and sometimes clinical trial means life or death for the small company.

As a result, we are witnessing a corresponding rise in the outsourcing of clinical services to contract research organisations (CROs). Medical device companies are turning to CROs for assistance with clinical operations management, investigator recruitment, clinical monitoring, data management, biostatistical analysis, health economic and outcomes strategy, quality assurance, regulatory approval, and other needs. The single most important factor to consider when choosing clinical service providers or a CRO is experience in the medical device clinical trials or expertise in the field.

A new way of working is outsourcing work to on-demand experts. This is particularly beneficial to small companies who cannot afford the heavy costs and management spends on working



with CROs or traditional consulting firms. Hiring individual medical device consultants can help save time and costs, while working with experts directly to customise deliverables. From FDA submissions experts to medical content writers, specialists in the medical device industry are offering their services on a freelance basis.

### 3. Outcome Assessment for Clinical Trials on Medical Devices

Defining relevant outcomes for clinical trials on medical devices is complex. This is partly due to the great variation in complexity and application for the different types of medical devices such as pacemakers, insulin pumps, operating room monitors, defibrillators, and surgical instruments, and partly due to a large variety of potentially relevant outcomes.

A barrier specifically related to the medical device industry is that a common understanding of the concept of outcomes is missing.

In clinical trials with medical devices, traditional outcomes such as survival, complication rates, or surrogates (biomarkers, imaging techniques, and omics) are used instead of the more appropriate hermeneutic outcome measures such as quality of life, autonomy, discomfort, disability, and life satisfaction. This does not mean to exclude specific outcomes for the functionality of medical devices such as device failure, device breaking, device slipping, migrating of the device or screw loosening, etc. It is important to understand that a hermeneutic outcome measure is a concept, not just a term with a mechanical definition.

Trials on medical devices funded by the industry are prone to report positive outcomes and to conclude in favour of experimental interventions when obtaining non-significant test results<sup>5</sup>. While industry involvement is necessary to improve technology and to drive innovation of MDs, it must be based on scientific grounds and be fully transparent.

Fire key characteristics of medical device clinical trials	Rationale
Fewer participants enrolment than drug trials.	End-points designed to show a “reasonable assurance of safety and effectiveness” tend to lead to modest sample sizes. In other cases, practical challenges limit the feasibility of conducting larger studies.
Device trials are less likely to be blinded or randomised than drug trials.	Blinding or randomisation is impractical owing to the nature of the device or the condition under study. For other studies, FDA experience with the device type allows for single-group studies that compare results with agreed-upon performance goals or established objective performance criteria.
Device design or procedure may be modified during the trial.	In some cases, early clinical events or feedback from physicians or patients may lead to changes in the device or the procedure. Validation of the changes may require additional clinical data beyond the original plan but may not require an entirely new study if it can be shown that data on the original device or procedure is appropriate to leverage.
In some cases, existing data can partially or fully substitute for prospective trial data.	Regulators such as the FDA consider the clinical data that are available external to prospective studies for the specific purpose of supporting marketing applications. This is particularly relevant for the consideration of expanded indications for approved devices in cases in which there is a body of evidence supporting the “off-label” use and in which it could be difficult or even unethical to randomly assign participants.
Many device trials assess iterative improvements on previous-generation devices.	Although some devices are truly new, the nature of device development is an iterative improvement on existing technologies as clinical experience grows and the science advances. In many cases, clinical data are required to evaluate the benefits and risks of the new device but not necessarily as extensive as for the original device.

Table 1: Five expert tips for medical device clinical trials

## 4. Early Scientific Advice and Expert Panels

The medical technology industry is dominated by large numbers of subject matter experts (SMEs). They are not trained in running trials or in trial methodology but have a high output of diverse and innovative products. Access to early scientific advice, especially for smaller companies and academia, needs to be as easy and affordable as possible. Early scientific advice about the clinical development strategy and clinical trials for their devices is wished for. Engaging in the relationship in a meaningful way early helps align on standard operating procedures (SOP) and technology.

## 5. FDA/MDR Regulatory Requirements for Medical Device Clinical Trials

The above tips represent only a fraction of the best practices of clinical trials for medical device manufacturers. Apart from these key tips, compliance with regulatory and ethical requirements is also very important.

The new regulation on medical devices imposes increased responsibilities and well-defined interactions between all economic stakeholders involved, like medical device manufacturers, authorised representatives, importers, and distributors. Many of Europe's and North America's medical technology companies are lacking the infrastructure to fully deal with their obligations.

### US FDA Regulations for Medical Devices

In the US, medical devices are regulated by the FDA. Medical device clinical studies in the US are divided into significant risk (SR) and non-significant risk (NSR) device studies. To conduct an SR device study, an investigational device exemption (IDE) application is required.

The sponsors must have approval from both the FDA and an institutional review board (IRB) prior to beginning the study. Although NSR device studies require only IRB approval, the sponsors must comply with the abbreviated IDE requirements, such as labelling, informed consent, monitoring, and record-keeping during the study.

There are two basic regulatory pathways within the FDA to bring advice to market: Pre-market approval (PMA) and the 510(k). Under the 510(k) process, the manufacturer needs to demonstrate that the device is 'substantially equivalent' to a predicate device. Generally, bench testing data and perhaps a very small clinical study is all that is necessary for a device to demonstrate equivalency. Approval of a PMA device, on the other hand, generally requires the manufacturer to provide data from a pivotal study. These are large, multi-centre, randomised clinical trials. These studies involve hundreds to thousands of patients and cost tens of millions of dollars to complete.

### EU MDR Regulations for Medical Devices

In the EU, the device approval process for medical devices is very different from that in the US. Medical devices are soon to be regulated by the Medical Device Regulation (MDR) (2017/745) and IVDR (2017/746), which replace the previous three EU Directives 90/385/EEC on Active Implantable Medical Devices (AIMDD), 93/42/EEC on Medical Devices (MDD), and 98/79/EC on *In Vitro* Diagnostic Medical Devices (IVDD). Despite the implementation of common regulatory frameworks in Europe, each member state has its own competent authority in charge of managing medical devices.

As part of the essential requirements in the EU, clinical evaluation must be conducted for all medical devices in accordance



with Directive 93/42/EEC Annex X or Directive 90/385/EEC Annex 7. According to MEDDEV 2.7.1 revision 4, released on July 1, 2016, manufacturers of high-risk or new devices must update their clinical evaluation reports (CER) annually, in contrast to every two to five years for other devices.

A medical device is approved for marketing in the EU once it receives a CE mark of conformity. To obtain a CE mark, a Class III medical device needs only to demonstrate safety and performance, not necessarily effectiveness. Compliance with this standard usually can be demonstrated with much simpler and cheaper clinical trials than required by the FDA<sup>6</sup>. For this reason, medical device manufacturers typically prefer to introduce products in the EU well before they seek FDA approval.

As I have mentioned above, this article only focuses on the key considerations for clinical trials involving medical devices. The table below summarises the key tips for medical device clinical trials.

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## Shrinidh Joshi

Shrinidh Joshi, an experienced clinical research consultant and medical writer, shares five of the best practices to keep in mind while conducting clinical trials for medical devices.



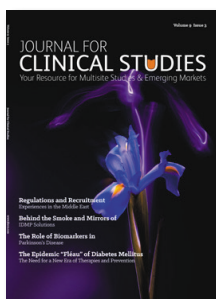




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A global network used to deliver products and services from raw materials to end users through flow of information, physical distribution and cash defines what a ‘supply chain’ is. In the healthcare sector, the end user is the patient, and the only product that they are after is improved health at the most affordable price possible.

*“Healthcare is not based on supply and demand. It can’t be stocked like it’s a traditional product, so a hospital’s supply chain is very different from a business or organisation supply chain.”*

(Mike Rip, 2019)<sup>1</sup>

Manufacturing and supply of pharmaceuticals and medical devices is now more complex than ever. Most organisations are now focused on expanding their product portfolios to be merely able to lengthen product life-cycles or, in many cases, meet the rapidly evolving market requirements. Affordable products have now become a requirement for almost every emerging economy. With greater emphasis being placed on compliance and regulatory scrutiny of the healthcare products, supply chains across the healthcare sector still remain fragmented and weak, ultimately putting more and more patients at risk. This results in a loss of billions of dollars every year and undermines the ability of the healthcare sector to stand up to the current challenges it faces.

The supply chain across the healthcare sector is now being drastically transformed through the evolution of technology. There are increasingly more opportunities that allow an organisation within the healthcare sector to increase the optimisation and the flow of products amongst different manufacturers, purchasers and suppliers. Managing a supply chain in the healthcare sector is not easy; the healthcare supply chain has been disrupted for a while now and this lack of cohesiveness has made it very difficult for organisations in the healthcare sector to seamlessly adapt to the fluctuations in both the supply and demand from various vendors, distributors and group purchasing organisations (GPOs).

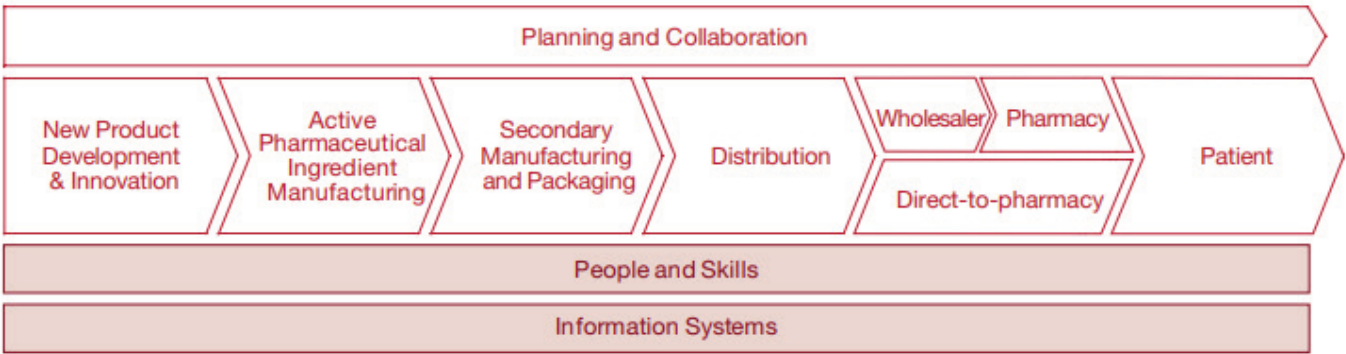
The supply chain serves as a backbone for the healthcare sector, right from the development phase, all the way through to the end user (hospitals, pharmacies or even the patients). Supply chains across the healthcare sectors are essentially supposed to cover all organisational, operational and value-adding activities that are typically needed to get these products manufactured and finally delivered to the end user.<sup>2</sup>

Transforming supply chains through limited improvement efforts will only yield poor or rather insignificant results. In order to have a healthy and fully reliable supply chain, it is important that greater focus be placed on comprehensive, integrated, complex efforts in order to automatically result in greater payoffs. Supply chains are accountable for nearly 25% of all pharmaceutical costs and nearly 40% of all medical device costs. Average spending on the global consumption of pharmaceuticals is vast – roughly \$230 billion a year and about \$120 billion on medical devices.

**Managing Shortages and Improving Safety:**

In the United States alone, drug shortages have tripled and in turn resulted in almost half a billion dollars’ worth of costs being added to hospitals worldwide since 2005. Drug shortages create a market for counterfeiters, who are quick to close in on the opportunity that arises in the event of shortages caused in the supply of legitimate and genuine pharmaceuticals and medical devices. These shortages often threaten the safety of the patients and also substantially slash the revenues for legitimate companies. There is a 33% surge each year in supply chain breaches, not just in the largest economies of the world such as China and India, but also in other developed markets across the globe.

An average of 1 in 10,000 patients falls victim to the medication errors that occur worldwide across all hospitals. Having a streamlined and efficient supply chain process is critical to the safety of the patients. Adopting the right methods and managing supply chains efficiently would result in counterfeiting being slashed by nearly 50%, resulting in nearly \$15 to \$30 billion in revenue being returned back to the legitimate companies, which could use the funds for reinvestment towards the improvement of patient care.<sup>3</sup>







## Managing a Supply Chain Across the Healthcare Sector:

### 1. Virtual centralisation of the supply chain:

Organisations that use virtually centralised systems for managing their supply chains can help hospitals and clinics to reduce/control costs as well as improve their overall levels of service. The process surrounding virtually centralised supply chains is to integrate operations from a market perspective rather than the health system. Hospitals that operate within the same region or city can opt for a consolidated service centre (CSC) that can be jointly owned and managed by different hospitals that fall in the same region. A consolidated service centre is responsible for bringing together geographically based group of hospitals and clinics to form one single entity that can work together on centralising their contracting, sourcing, distribution and logistics functions. This approach will help solve the problems that arise due to time and budget shortages. Cost reduction and conflict resolution are key aspects where

the impact of an introduction of a consolidated service centre will be noticed.<sup>3</sup>

### 2. Segmentation:

The majority of pharmaceutical and medical device organisations run a 'one-stop shop' supply chain solution. The forced movement of products through this solution of supply chain results in multiple inefficiencies – larger inventory of certain products while high demand products remain in short supply or rescheduling production demands to simply meet all and every urgent requirement that arises. Segmenting your supply chain on the basis of the requirements of the customers or on the basis of the characteristics of the products can help tackle these problems in a rather efficient manner. Segmentation can allow the pharmaceutical and medical device companies to develop different production, forecasting and distribution strategies for each product on the basis of their characteristics and demands in the market.<sup>3</sup>

### 3. Agility:

Agility is creating a model that is not just fast but also capable of responding to the fast-changing consumer demands and needs, possibly at a reduced cost. On average, the replenishment cycle of pharmaceutical products from the manufacturing plants to the distribution centres is roughly about 75 days. In comparison, FMCG (fast-moving consumer goods) can perform a similar replenishment cycle for their products in a fraction of the time taken by pharmaceutical manufacturing plants. Setting up an agile supply chain model will bring about stability in terms of production and replenishment, as well as visibility. Following a more structured and disciplined cross-



functional process, regular and more frequent communication and understanding the underlying problems facing the supply and demand of these products will help curb all bottlenecks.

#### 4. Use of RFID (radio frequency identification) applications in healthcare:

The use of radio frequency identification applications can help link up the products to the internet. These applications help in tracking and tracing the products spread across the hospitals/clinics and also shed light on data/information surrounding the products. In comparison to the old school technique of barcoding, RFID applications offer a more robust solution by eliminating the need for intervention by humans as they do not require any direct line of sight identification. An RFID application can be programmed according to the need of the user. These applications contain information about product weights and location. The use of this application reduces time spent on tracking a particular product and offers accurate information and processes that eventually provide value to services.<sup>4</sup>

The global healthcare supply chain management market is expected to reach about \$3 billion by the year 2025. This is expected to rise at a market growth rate of 7.9% CAGR (compound annual growth rate) during the forecast period.<sup>5</sup>

The transformation of the supply chain for healthcare can do much more than improve the end result. In meeting the supply chain leadership challenge, pharmaceutical and medical device companies can now provide far safer and more affordable access to medicines and medical devices that can improve or even save the lives of people across the globe. Inefficiencies that arise in the supply chain of the healthcare sector can now be made more efficient through the process of creating solutions that will increase efficiency, drive down costs and, most importantly, result in improving positive patient outcomes. Through the use of segmentation, agility and RFID applications, the healthcare sector can witness a surge in labour costs being reduced significantly, automatically resulting in pharmaceutical and medical device companies investing more of their resources directly towards the care of patients. The use of end-to-end supply chain solutions and managing the supply chain of the healthcare sector efficiently will pave the way for a brighter future of the industry.



The demand for controlling the healthcare supply chain is segmented into different categories such as manufacturers, vendors and distributors. Manufacturers must cater to their end users' growing demand for pharmaceutical products and medical devices. As a result, manufacturers are looking primarily at those supply chain management solutions that will help them to become faster, more reliable and efficient, and help reduce costs where possible. This is one of the reasons why more and more pharmaceutical and



medicine device manufacturers are opting for streamlined supply chain management solutions.

Managing a supply chain model is usually done through the achievement of three main criteria that are essential towards the successful and smooth running of these pharmaceutical and healthcare organisations. These are achieved through collaborative governance structures, implementing efficient and reliable processes and investing in information systems that will yield greater benefit and returns in the long run. The majority of the hospitals and clinics across the world are now very focused on setting up governance structures in order to be able to maintain a balance between providing the highest quality of care, and at the same time reducing costs.

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## Public Encouraged to Register for COVID-19 Vaccine Trials as 100,000 Already Sign-Up

Over 100,000 people have volunteered to take part in COVID-19 vaccine trials, helping to speed up efforts to discover a safe and effective vaccine. The government is today (Monday 17 August) encouraging more people to join the thousands of volunteers and sign up to the NHS COVID-19 Vaccine Research Registry to help the NHS in the fight against coronavirus and ensure potential candidates work for everyone. To enable large-scale vaccine studies to take place across the UK, the aim is to get as many people as possible signed up to the Registry by October.

Source: GOV.UK

## Researchers Call Out Lack of Diversity in COVID-19 Clinical Trials

Although racial minorities experience disproportionality higher rates of COVID-19 infection, hospitalization, and death, they are significantly underrepresented in COVID-19 clinical trials, according to a new perspective article. Recent Centers for Disease Control and Prevention (CDC) data reveal that Blacks, Hispanics, and American Indians are nearly three times as likely as whites to contract the virus and almost five times as likely to be hospitalized with COVID-19.

Source: Medical News Today

## AzurRx BioPharma Initiates European Arm of Phase 2b OPTION 2 Clinical Trial of MS1819 in Cystic Fibrosis

AzurRx BioPharma, Inc. a company specializing in the development of non-systemic, recombinant therapies for gastrointestinal diseases, today announced its initial European trial sites are active and screening patients for its Phase 2b OPTION 2 clinical trial to investigate MS1819 in cystic fibrosis (CF) patients with exocrine pancreatic insufficiency (EPI). A total of nine of the expected fifteen sites globally are now active and recruiting patients.

Source: Globe Newswire

## I-Mab begins Plonmarlimab Dosing in Rheumatoid Arthritis Trial

Plonmarlimab is a humanised immunoglobulin G1 (IgG1) antibody designed to act on the cytokine granulocyte-macrophage colony-stimulating factor (GM-CSF), which is associated with autoimmune and inflammatory diseases. GM-CSF neutralisation can suppress inflammatory responses and is expected to be clinically beneficially to patients with autoimmune disorders such as RA.

Source: Clinical Trials Arena

## More Than a Third of Disrupted Cancer Trials back on Track: Report

Oncology studies were some of the hardest hit in the first few months of the pandemic, but more than a third have now resumed. This is according to a new report out by life sciences analytics firm GlobalData, which found 37.8% of oncology trials disrupted by COVID-19 have resumed. "This marks the largest proportion of resumed trials since the disruptions began and the number of disrupted trials has fallen to its lowest figure in over three months," the company's report said.

Source: Fierce Biotech

## Neuroptika Completes Enrollment In Phase 2 Clinical Trial For Dry Eye Disease

Neuroptika, a privately held biotechnology company focused on the development of novel regenerative treatments for ophthalmic diseases, today announced completion of enrollment in a Phase 2 clinical controlled, double-masked trial of NRO-1 for the treatment of patients with dry eye disease. NRO-1 is a novel therapeutic with the potential to regenerate corneal nerves in ophthalmic diseases. The Phase 2 clinical trial is a multicenter, randomized clinical trial.

Source: Neuroptika

## Decentralised Trials – Aided by Tech – Could Boost Clinical Research

There's already plenty of support from regulators for virtual or 'decentralised' trials, including from former FDA Commissioner Scott Gottlieb who said last year that the agency was encouraging adoption of this approach to make trials more "agile and efficient", as well as patient-centric. Since the coronavirus pandemic interest in decentralised or hybrid trials that can include a combination of in-home clinical visits from healthcare professionals, direct to patient support and digital healthcare has been renewed, says CRO ICON in a new white paper.

Source: Pharma Forum

## THREAD Lands \$50M for Decentralized Clinical Trial Research Platform

THREAD receives an additional \$50 million capital commitment from Water Street and JLL Partners to expand its decentralized clinical trial research platform. THREAD is an innovative technology and service provider that increases participant engagement by enabling pharmaceutical companies and contract research organizations to remotely capture data from participants and sites during, in between and in lieu of in-clinic visits. This comes at a time of major exponential growth.

Source: Hit Consultant

## NIH Launches Clinical Trial to Test Antibody Treatment in Hospitalized COVID-19 Patients

Patients admitted with COVID-19 at select hospitals may now volunteer to enroll in a clinical trial to test the safety and efficacy of a potential new treatment for the disease. The Phase 3 randomized, controlled trial is known as ACTIV-3, and as a "master protocol," it is designed to expand to test multiple different kinds of monoclonal antibody treatments. It also can enroll additional volunteers in the middle of the trial, if a specific investigational treatment shows promise.

Source: National Institutes of Health (NIH)

## Bayer Expands Women's Health Pipeline with KaNDy Acquisition

Bayer has announced plans to acquire UK-based biotech company KaNDy Therapeutics, in a move to expand its drug development pipeline in women's healthcare. This includes KaNDy's investigational compound NT-814, which recently completed a Phase IIb study which showed positive findings for the treatment of moderate-to-severe vasomotor symptoms due to the menopause. A Phase III study is expected to begin in 2021, and if approved, the drug could generate peak sales of more than €1bn globally, according to Bayer.

Source: Pharma Times

## Roche Takes on Alexion, Viela Bio with Newly Approved NMOSD drug Enspryng

Treatment for neuromyelitis optica spectrum disorder (NMOSD) has transformed over the last year with FDA approvals for Alexion's Soliris and Viela Bio's Uplinza, but now pharma giant Roche is entering the fray. Roche's Enspryng, formerly known as satralizumab, scored FDA approval Friday to treat AQP4 antibody-positive NMOSD, a "devastating" neurological disease that can lead to blindness, paralysis, nerve pain, respiratory failure and more, and it's sometimes mistaken for multiple sclerosis, Kathleen Hawker, neuroscience group medical director at Roche's Genentech, said.

Source: Fierce Pharma

## Coronavirus: Protein Treatment Trial 'a breakthrough'

The preliminary results of a clinical trial suggest a new treatment for Covid-19 reduces the number of patients needing intensive care, according to the UK company that developed it. The treatment



from Southampton-based biotech Synairgen uses a protein called interferon beta which the body produces when it gets a viral infection. The protein is inhaled directly into the lungs of patients with coronavirus, using a nebuliser, in the hope that it will stimulate an immune response.

Source: BBC News

### **Galapagos Signs Deal with Scipher for IBD Drug Development**

Belgium-based biotech Galapagos has signed a collaboration deal with Scipher Medicine to advance novel drug targets for the treatment of inflammatory bowel disease (IBD). Scipher uses its proprietary Network Medicine Platform in combination with molecular patients data and AI-based methods to identify novel targets and pathways in autoimmune disease such as IBD.

Source: Pharma Times

### **Russian University Completes Clinical Trials of Covid-19 vaccine**

Russia has become the first country to have completed clinical trials of a Covid-19 vaccine candidate, after Sechenov University said that it had concluded its study. According to Sechenov University Center for Clinical Research on Medications head and chief researcher Elena Smolyarchuk, study data showed the vaccine candidate's effectiveness, reported Russian news agency TASS. Smolyarchuk was quoted by the news agency as saying: "The research has been completed and it proved that the vaccine is safe. The volunteers will be discharged on 15 July and 20 July."

Source: Clinical Trials Arena

### **Rapid Change COVID-19 & UK Clinical Research**

Since the pandemic, the UK research community mobilised with unprecedented speed to develop multi-agency collaborative systems that enabled accelerated setup and rapid delivery of high priority research. This approach required government bodies, clinical academic research experts, regulators and the life science industry all working together in extraordinary ways. The National Institute for Health Research (NIHR) has played a critical role in all of this. Through a collaborative process led by NIHR, COVID-19 studies assessed as having the highest potential to deliver evidence with the greatest impact within 12 months have been prioritised as urgent research.

Source: Pharma Field

### **Stakeholders Call for Regulatory Clarity in Rare Disease Research Network**

Stakeholders weighing in on a proposed rare disease clinical trials network called for regulatory clarity, smart use of existing resources, and a move toward harmonized trial standards and assessments. As part of the launch of the US Food and Drug Administration (FDA)'s Rare Disease Cures Accelerator, the agency asked for stakeholder input on how FDA and other agencies can achieve a more cooperative approach in supporting the drug development pipeline for rare diseases. By the 30 July deadline, over 60 comments had been received from individuals and family members affected by rare diseases, from pharmaceutical companies and trade associations.

Source: RAPS

### **FDA Approves Treatment for Rare Disease Affecting Optic Nerves, Spinal Cord**

The U.S. Food and Drug Administration has approved Enspryng (satralizumab-mwge) for the treatment of neuromyelitis optica spectrum disorder (NMOSD) in adults with a particular antibody – patients who are anti-aquaporin-4 or AQP4 antibody-positive. NMOSD is a rare autoimmune disease of the central nervous system that mainly affects the optic nerves and spinal cord. Enspryng is the

third approved treatment for the disorder. Until last year, there were no FDA-approved treatments.

Source: FDA

### **How does HTA for Orphan Drugs Differ Across Europe?**

New research looks at the factors that speed up and slow down HTA appraisals for rare disease medicines across Europe. Rare diseases drugs have always faced challenges when it comes to HTA approvals, even as governments bring in more regulatory policies that make their path through assessment easier. Several factors make it difficult for HTA bodies often to assess orphan drugs, including a lack of robust trial data due to difficulties in finding relevant patients.

Source: Pharma Phorum

### **Hollywood Multitasker Queen Latifah Boosts Boehringer's Scleroderma Awareness Campaign**

Two years ago, Queen Latifah's mother died of systemic sclerosis-associated interstitial lung disease. This week the well-known rapper, actress and producer joins the Boehringer Ingelheim "More than Scleroderma" campaign as spokesperson. Latifah appears in a video on the campaign website talking about her mother's diagnosis and care. Her cousin, Kristina, who served as caregiver to Latifah's mother, Rita, also talks about "Team Rita" and the importance of a care team and support. In the video, Latifah says she's involved in the campaign to raise awareness about scleroderma and let patients and caregivers know they're not alone.

Source: Fierce Pharma

### **Clinical Trials of Coronavirus Drugs Are Taking Longer Than Expected**

As the coronavirus pandemic continues to wreak havoc in the United States and treatments are needed more than ever, clinical trials for some of the most promising experimental drugs are taking longer than expected. Researchers at a dozen clinical trial sites said that testing delays, staffing shortages, space constraints and reluctant patients were complicating their efforts to test monoclonal antibodies, man-made drugs that mimic the molecular soldiers made by the human immune system. As a result, once-ambitious deadlines are slipping.

Source: New York Times

### **Positive Interim Safety Review of Phase 2b Clinical Trial of Lead Asset XF-73 in the Prevention of Post-Surgical Bacterial Infections**

Destiny Pharma plc (AIM: DEST), a clinical stage biotechnology company focused on the development of novel treatments for hospital infections that address the global challenge of antimicrobial resistance (AMR), announces a positive interim safety review has been completed by an Independent Data Monitoring Committee (IDMC) of the Company's ongoing Phase 2b study of its lead asset XF-73 in the prevention of post-surgical bacterial infections.

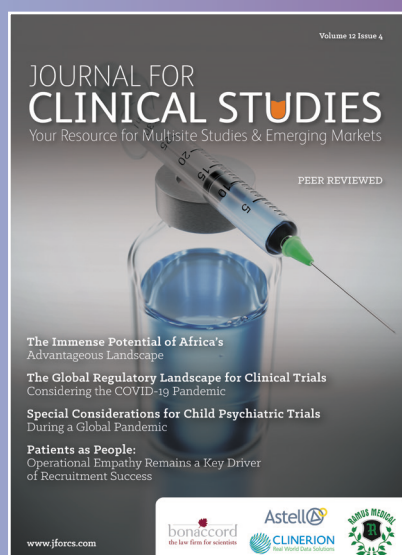
Source: Pharmiweb

### **Reify Raises \$30M in Series B round for Clinical Trial Cloud Computing System**

A company that markets cloud computing systems for the biopharma industry has raised \$30 million in a Series B funding round. Boston-based Reify Health said Wednesday that it had closed the round, led by Battery Ventures, with participation from Sierra Ventures and Asset Management Ventures. The company's software, StudyTeam, is designed to upgrade the computer systems that healthcare staff at clinical trial sites use to run studies, thereby helping to accelerate enrollment and reduce workloads, it said.

Source: Med City News

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