VaxTrials

Shorten Start-Up Timelines in Vaccine Trials

Six Factors Critical to Success

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In clinical development, speed is always of the essence. No sponsor can afford to let a trial languish in the start-up phase.

However, sponsors of trials for infectious disease vaccines are under exceptional pressure to move quickly. A combination of factors—from fierce competition to global health crises—make time-to-market especially critical to commercial success.

The industry's Herculean response to introducing vaccines during the COVID pandemic has significantly raised the bar for vaccine development. Some COVID vaccine trials were conducted from start to finish in less than a year, proving that it is possible to proceed with all due haste. And while this speed was achieved at least in part because trials for COVID vaccines were prioritized and proceeded under special waivers from regulatory authorities and ethics committees, expectations have been reset accordingly.

We believe that six areas are most significant in impacting the efficiency—and hence the turnaround time—of the study start-up phase:

Success Factor #1
Rely on in-country staff

Success Factor #2
Identify and engage key study personnel early on

Success Factor #3
Obtain regulatory and ethical approvals efficiently

Success Factor #4
Develop and implement a robust operational plan

Success Factor #5
Develop effective recruitment strategies

Success Factor #6
Harness technology to accelerate building the trial database

Licensed vaccines exist for 26 pathogens out of over 1,400 known human pathogens[1,2]

Immunization prevents 3.5 to 5 million deaths every year around the world[3]

10 manufacturers provide 75% of vaccine doses (excluding COVID-19 vaccines); more than 80 manufacturers serve the remaining market[4]

Every dollar invested in immunization programs in low- and middle-income countries yields a return of $52[5]

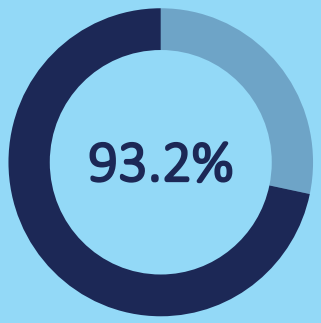
Vaccine Trials
Pose Unique Start-Up Challenges

Vaccine trials differ from treatment trials in many clinical respects. The single greatest difference affecting the start-up timeline is that vaccine trials depend on the willingness of thousands of healthy volunteers to take part. Treatment trials (beyond Phase I), on the other hand, seek patients presenting with specific symptoms and typically involve only hundreds of volunteers.

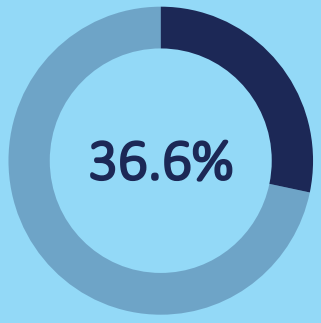
Access to the investigational treatment and a desire for care from the clinical trial staff are common motivations for their participation.[6] Thus, the risk/reward ratio of trial participation is different for healthy volunteers than for patients. Indeed, concerns over vaccine safety may make some potential participants hesitant to enroll in vaccine trials.[7,8,9]

We have also observed that the Inclusion/Exclusion (I/E) criteria for vaccine trials are becoming increasingly narrow—in effect making it harder to find participants in sufficient numbers. A trial might, for instance, seek to study vaccine response in infants who are five months old, plus or minus two weeks.

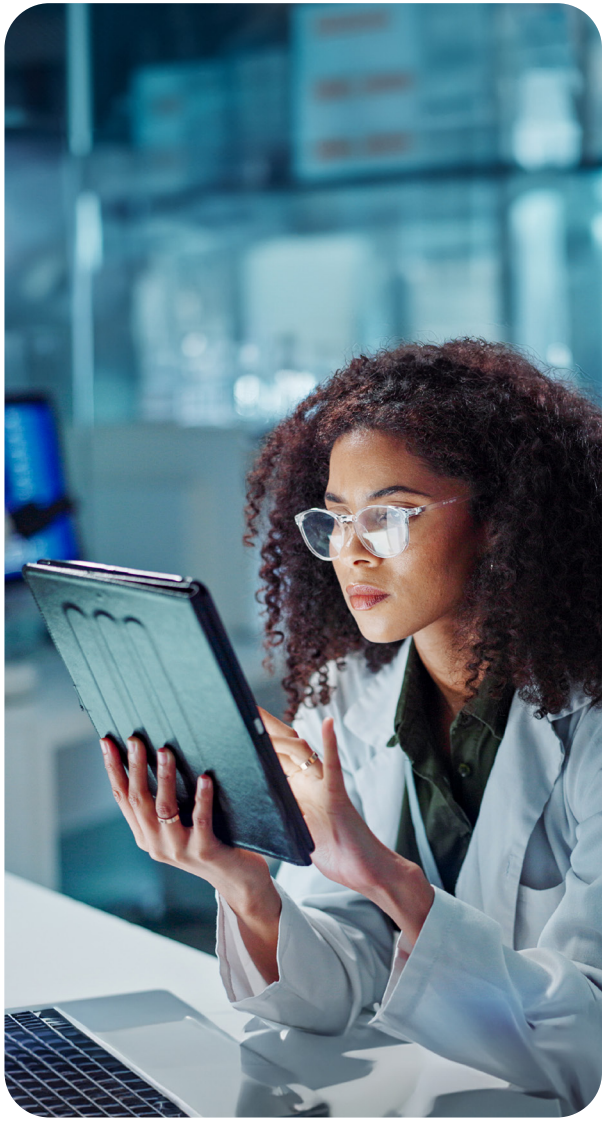
Additionally, there are seasonal and geographic considerations that complicate the launch of vaccine trials. In testing vaccines for certain diseases such as influenza, for example, sponsors must develop a testing strategy that takes into account the flu season cycle and how it varies by hemisphere.



One study has shown that altruism is the main motivator for healthy volunteers to participate in preventative vaccine trials.[10]



Fear of side effects was the primary barrier to participation.[10]



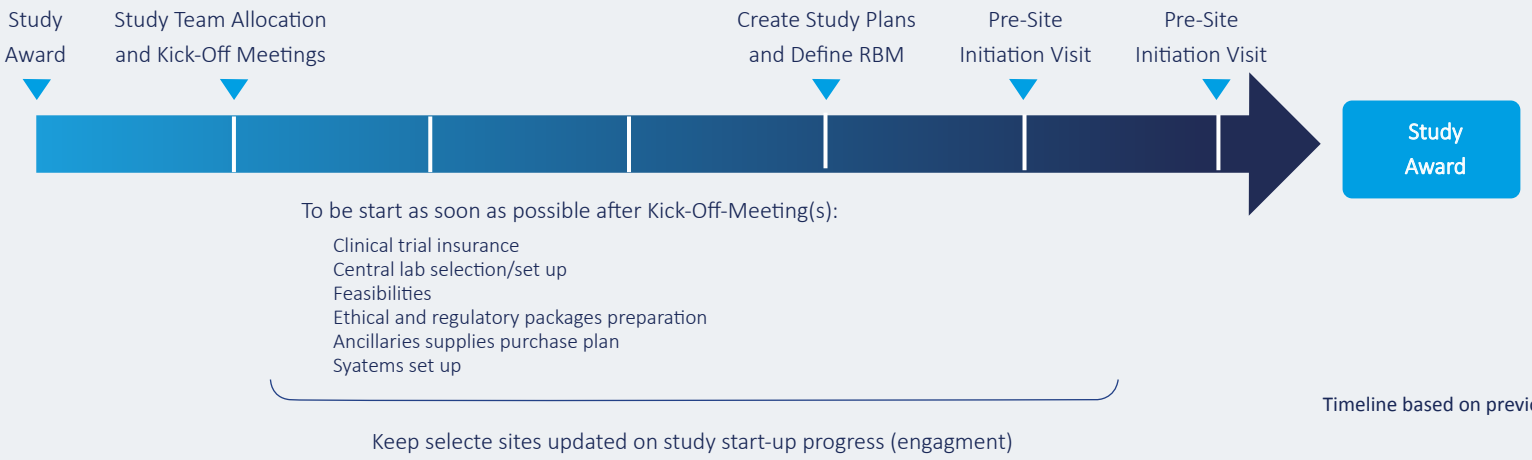
Meeting the Need for Speed
Six Imperatives

The start-up activities in a vaccine trial challenge the skills of even the most experienced project manager, as there are so many interrelated steps and confounding variables across countries that affect how long certain steps take.

Study Start-Up Activities Timeline

At VaxTRIALS, we've identified six factors that have a direct impact on the start-up timeline, and we recommend that sponsors adopt them all for the best results.

Study Start-Up Activities Timeline*



Timeline based on previous experience*

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Success Factor #1

Rely on in-country staff.

Success Factor #1
Rely on in-country staff.

In vaccine trials, there is no substitute for your research partner having “boots on the ground”. In-country resources understand local healthcare systems, epidemiology, and regulatory environment which is essential to ensuring that no local issue becomes a cause of delay. Their “insider” knowledge extends beyond the basics of how things get done in each country to include cultural nuances that would be easy for non-natives to miss.

For starters, local staff can help you determine if a specific country is an optimal location for a trial based on the incidence of the disease under study, the regulatory climate, the availability of experienced sites, and the National Immunization Schedule. (While most countries tend to recommend the same kinds of vaccines for babies, children, and adults, there may be differences in the number of vaccines included, the ages at which vaccines and boosters are recommended, the number of doses recommended, and the types of vaccines recommended for the whole population and for special groups.)

In-country personnel also have intimate knowledge of investigators’ past performance, research interest, and patient base. They can, therefore, quickly zero in on the best sites to approach for a given trial, expediting the feasibility timeline.

By the same token, in-country staff will be familiar with local vendors and can recommend those that have a record of excellent performance. This is especially important in selecting logistics providers of temperature-sensitive vaccines.

A Cultural Nuance
That Turned Costly

One sponsor of a vaccine trial provided trial participants with an older model mobile device for use in patient reporting, not appreciating the value that participants in the developing country would place on the technology, outdated as it was.

This meant that some people entered the study merely for the sake of obtaining the device and then dropped out. An inordinate number of people also reported that they lost their device and needed another, further exacerbating the problem.

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Success Factor #2

Identify and engage key study personnel early on.

Success Factor #2
Identify and engage key study personnel early on.

When submitting a protocol for authorization to a local regulatory authority, you must be able to list the investigator sites that will be involved, so any delay in the latter will affect the timing of your submission. Therefore, it is most efficient to begin a feasibility exercise early in development planning.

The proper exchange with potential sites about their capabilities and the protocol requirements will not only help you identify those sites that will be able to recruit the right population for your study but will also ensure alignment on study goals and responsibilities. Through the process, sites will be alerted to the target population, and when the study starts, they may well have candidates in mind.

Often sponsors overlook the need to engage with key personnel at sites beyond the principal investigator, such as study coordinators and those in charge of data entry. Knowing how a site works—and who is responsible for what—will bear fruit in optimizing study procedures, ensuring efficient communication among team members, identifying risks, and ultimately enhancing the overall quality and success of the clinical trial.

There is often a period of months between the initial site qualification steps and the site initiation visit, and during this interim the situation at sites can change, the protocol may be amended, and sites' interest may wane. It is, therefore, important to stay in touch with sites, informing them of any changes to the study and continuing to ensure their interest and ability to take part.

Emails and newsletters to sites can serve the first purpose, and the second may be best met by a check-in visit (in person or virtual, depending on the budget) closer to the time of site activation.

Training all team members is vital to ensuring that everyone is prepared to assume their role in the study. It's especially important for clinical research associates (CRAs) to be trained on the protocol and involved early, as they will be the main point of contact with sites. Site staff should receive their training during the first site visit so that everyone is prepared to follow the protocol, and training should be refreshed as needed over the course of the study. While it is the principal investigator's responsibility to see that the site staff is trained, it is usually more prudent for the CRA to conduct the training covering all aspects of the protocol, including lab and pharmacy procedures.

Also, when sites are open to suggestions and receptive to feedback, CRAs can offer recommendations about processes that will help them in running the study.

The Importance of Proactive **Risk Mitigation**

Changing Site Capabilities after Feasibility Assessment

To qualify to take part in one vaccine trial, clinical sites had to have two ultra-low temperature freezers (a main freezer and a backup) that could maintain temperatures to-80°C. In the months between the feasibility study and site activation, one site's backup freezer needed to be repaired—a situation that was not revealed until it was time to activate the site.

The site's activation was therefore delayed until the second freezer was fully functional. This type of last-minute surprise can be avoided by maintaining a close relationship with sites that extends beyond the site qualification stage, ensuring that they remain prepared and eager to participate once the study goes live.

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Success Factor #3

Obtain regulatory and ethical approvals efficiently.

Success Factor #3

Obtain regulatory and ethical approvals efficiently.

Initiating a vaccine study rapidly, of course, demands compliance with all regulatory requirements. But knowing how to proceed is far from obvious given the different regulations, approval pathways, and common practices across countries. This speaks again to the importance of working with in-country resources, who have a clear understanding of the local regulations and approval pathway. Through their experience and involvement at the local level, they can:

- Recommend the best regulatory strategy and avoid potential roadblocks in the review/approval process, reducing the need for multiple rounds of reviews. Without a local expertise, sponsors of vaccine trials might not realize, for instance, that to launch a vaccine trial in some countries they must get approval from the National Immunization Program after being cleared by the ethics committee. In another country, they may not know that signatures on some documents must be notarized. Learning of such steps too late in the process can cause unnecessary delays.
- Adopt a timeline that takes seasonal and geographic considerations into account. The start-up process must be carefully orchestrated—reflecting the approval timelines in a country—so that enrollment can begin at the appropriate time. If, for example, the right documents aren't available to submit to the authorities on time, a sponsor could miss the ideal window to launch a trial for an influenza vaccine and might have to put the trial on hold for a year.
- Expedite approvals by seeking fast-track/priority review where available and applicable. A CRO with local expertise will know when a study meets a given country's specific requirements.
- Recommend the most appropriate country mix. This should take into account a number of factors drawn from regulatory intelligence and past experience.

- Select lead or “champion” countries/sites to kick off studies in order to enroll the first patient as soon as possible. Decisions on where to focus first should be made based on knowledge of local approval timelines and sites’ past performance.
- Anticipate potential obstacles arising from local regulations. Someone without intimate knowledge of unique local regulations might not know, for example, that in Argentina, different assent forms apply to children in different age brackets. Learning this too late could jeopardize the trial timeline.
- Understand exactly how authorities want to receive packages, down to the order of specific pages in submission packages.

The right CRO can “see around corners” to anticipate and avoid issues that could cause delays and force a trial off track. Local experts have insight into how things are commonly done in a country, beyond what is spelled out in a regulation. They are aided in this by maintaining a comprehensive database of regulatory authority and ethics committee requirements by country as well as a “lessons learned” toolkit.

Such a toolkit can be very instructive in summarizing the queries that were generated in previous submissions, so that they can be anticipated and circumvented in the study in question. The entire clinical team should then be made aware of the expected approval timeline based on past history, the study type (interventional or non-interventional), and the target population.

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Success Factor #4

Develop and implement a robust operational plan.

Success Factor #4
Develop and implement a robust operational plan.

Completing study start-up steps seamlessly and efficiently is a massive project management challenge that requires structure, oversight, and a communication strategy.

The undertaking involves several different stakeholders and complex, interrelated steps, many of which must run in parallel, given their long lead times.

From our observation, sponsors are often unprepared for the length of time required to:

- Contract with a central laboratory. Setting up the contractual terms is a lengthy process (made shorter if there is a master service agreement in place) and, of course, affects the trial budget. Discussions with the lab become very detailed, especially when, as is usually the case, the lab will supply the study kit. Discussions around the contents of each kit should begin as soon as the central lab is selected because conversations around material specifications (such as the type of vials and syringes used for sample collection) will affect the primary endpoint in the study.
- Procure ancillary supplies. Once the needed materials beyond the investigational product are defined, a logistics/procurement team should begin procuring those materials locally, whenever possible. At times, the first choice is not available, and an alternative must be approved. Even material purchased locally can take many weeks or even months to procure.
- Translate documents. The regulatory package must be translated into each country's language and reviewed for accuracy.
- Obtain insurance. Insurance for the study should be sought as soon as the protocol and model informed consent form (ICF) is ready, as this is commonly a lengthy process.
- Prepare patient diaries. These must be included in the package to regulators. In the case of eDiaries, the submission must include screenshots of the application.

Study Start-Up **Activities Timeline**

ACTIVITY	TIME	COMMENTS
Central Lab selection/Set up	3-6 months	If an MSA is in place, time can be reduced by 1-2 months
Feasibility	1-2 months	It depends on the # sites the sponsor want
Reg packages preparation	1-2 months	Including translation, apostile and country-specific requirements (Central America)
Ancillaries plan	1 month	From Purchase until delivery is can take few days until 2-3 months depending on the material
Systems set-up	3-4 months	Including UAT and related documentation (guidelines, etc) eDiary: required for EC submission
Insurance	1-6 months	Long process to be started as soon as Model ICF and protocol are ready

To ensure that nothing “falls through the cracks,” VaxTRIALS has adopted a Quality Management Model that assesses risks to the trial start-up timeline by exploring various “what if” scenarios and then ensuring that mitigations are in place.

This risk-based approach should be adopted as soon as the study is awarded to a CRO, with all functions thinking through what challenges could result in delays, from regulatory approval through to the smallest details of logistics. These, along with proposed mitigations, should be discussed with the sponsor so that there are no surprises along the way and everyone involved is aligned.

Our Quality Management Model

Quality Documents

A robust system of processes described and being constantly reviewed and updated.

Quality Management

Vendors qualification and close quality oversight on projects and monitoring activities, established through a risk-based approach.

Resource Allocation

Building capabilities on our collaborators through strategic training activities.

Risk Management

Forecasting and evaluation of risks at all company levels together with the identification of procedures to avoid or minimize their impact.

Quality Strategy & Quality Analytics

Definition, measurement, and analysis of quality parameters towards company quality strategic objectives.

Continuing Improvement Process

Continuous monitoring towards the implementation of practices to mitigate new risks and/or efficiencies improvement opportunities.

In conjunction with this approach, it is important to establish clear communication channels for study team members and with site personnel to share updates and address issues.

We’ve found that weekly status calls with all functions in attendance and monthly governance meetings to discuss progress and provide oversight are invaluable.

We’ve also found that to ensure the quality of deliverables and to keep all activities on track, it is essential to task a clinical project manager with end-to-end oversight of the trial.

Expedited Study Start-Up in Public Health Emergency

The Division of Microbiology and Infectious Diseases (DMID) within the US National Institute of Allergy and Infectious Diseases (NIAID) was launching an open-label, Phase II study of a vaccine for monkeypox.

The agency was proceeding with a sense of urgency given that the director-general of the World Health Organization (WHO) had declared the escalating outbreak a Public Health Emergency of International Concern (PHEIC).

To shorten the ramp-up timeline, we set an aggressive schedule of activities and assembled a task force dedicated to streamlining processes wherever possible.

One such innovation was to release trial-related forms in a rolling fashion, as they were needed, rather than attempting to have them all prepared and approved at the start. Without compromising on quality, the group was able to:

- Review the protocol and Informed Consent Form (ICF) in one day
- Finalize the Data Clarification Form (DCF) in under 10 days (drafts were ready 5 days after receipt of the protocol)
- Draft the Manual of Operational Procedures six days after receipt of the protocol
- Launch the website four days after receipt of the initial protocol
- Hold a meeting on the Data and Safety Monitoring Board (DSMB) organizational structure 12 days after receipt of the protocol
- Deploy Advantage eClinical, Veridix integrated suite of data management applications, two days after the DCF was finalized

By working expeditiously, pursuing multiple workstreams in tandem, and developing forms on a rolling basis, we were able to prepare the study to go live in just 12 days from protocol finalization, and 2 days from CRF specification finalization.

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Success Factor #5

Develop effective recruitment strategies.

Success Factor #5
Develop effective recruitment strategies.

The first step in developing an effective recruitment strategy is to conduct a thorough feasibility assessment to ensure sites can successfully recruit participants. Artificial Intelligence (AI) can be used to mine data on sites' past recruitment performance and patient population to ensure that site selection minimizes the risk of under-enrollment and meets diversity, equity, and inclusion (DEI) targets. Additionally, we talk with the principal investigator, site coordinators, and recruitment team at sites to be sure that they have:

- Prior experience in recruiting healthy volunteers for vaccine trials
- A dedicated recruitment team that is familiar with face-to-face recruitment tactics and draws from an internal site database, social networks, and investigator networks
- Recruitment networks that extend to community leaders, nurses, referring physicians
- A call center to assist in scheduling

The second step is to set attainable targets, knowing that sites tend to be overly optimistic about their recruitment capabilities. To be realistic, recruitment forecasts should weigh an array of factors, including sites' past performance, the local context, and the burden of participation. It is important to consider such details as:

Past Performance

- Historical performance data in similar studies and a similar population
- The recruitment trend with the target population
- Lessons learned from previous studies

Local Context

- Demographics and epidemiology of the population
- The current vaccine coverage
- The public's confidence in vaccines
- Access to care
- The research environment
- Participants' likely motivations and barriers to taking part in the study

Participant Burden

- The number, spacing, and duration of visits affect participant logistics and have a direct bearing on people's willingness and ability to participate.
- The length of the study

Once participants are selected, sites are asked to characterize their patient population and offer insights into what to consider in designing participant-centered recruitment, adherence, and retention strategies that will resonate. Considerations might include, for instance, the availability of people to attend the number of visits specified in the protocol, their connectivity, and use of mobile devices. The use of decentralized study technology such as televisits can ease participant burden and make it easier to recruit. Virtual sites that partner with community healthcare settings also make it possible for people from a wider variety of geographic areas to participate, enlarging the potential participant pool.

Another pre-launch step is to work with sites to pre-screen possible participants by combing their patient database to ensure that they have ample potential volunteers (three to four times more than their assigned targets). This site preparation visit, which occurs in tandem with preparation for the start-up visit, is also an opportunity to build a stronger relationship with site staff and emphasize the study objectives.

VaxTRIALS also collaborates with sponsors and sites to design appropriate recruitment materials which may include call scripts, flyers, informed consent guides, websites, and posters—all in the local language, of course. This creation of materials and tools facilitates the understanding of the study, its objectives, criteria, etc., so that an appropriate process for participant recruitment and enrollment can be carried out.

Once recruitment begins, sites' progress against their expected enrollment quota should be monitored regularly so that the strategies can be adjusted as needed. This requires close communications between site staff, the study team, and the sponsor, regular meetings to identify risks and suggest mitigations, and, often, customized support. We've found that having a site recruitment and adherence project manager available to assist sites in developing/amending their recruitment strategies pays dividends.

Customized Strategy
Gets Recruitment Back on Track

In one study, recruitment rates were falling behind schedule, and it appeared that the social media campaign that sites were using was insufficient. VaxTrials analyzed the data and worked with sites to develop a new strategy that relied on face-to-face recruiting within the community.

Site staff who also worked in health centers, hospitals, and maternity clinics were encouraged to discuss the study with the candidates they met. Principal Investigators were urged to network with other physicians who could refer their patients to the site for potential participation. As a result, recruitment rose from a per site/ per week average of 3 enrollees to 12.

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Success Factor #6

Harness technology to accelerate building the trial database.

Success Factor #6
Harness technology to accelerate building the trial database.

Building the database that will be used for data capture and management is typically a cumbersome process involving setup and the integration of multiple systems that takes 8-12 weeks or more to complete. Much of the work is performed manually, and at times, the utility needed (such as edit checks, dashboards, and analytical tools) is not available by the start of the study.

Innovative applications of technology can change all of that, cutting the timeline by more than half for developing the database and ensuring that all the required functions launch when data collection begins. VaxTRIALS has proven success in using technology to streamline the database build process and is now incorporating AI into the process by:

1

Using Large Language Models (LLMs) and Retrieval-Augmented Generation (RAG) to digitize and structure the components of the trial protocol, a free-text document. Once the elements of the protocol are digitized, they can be fed into a study build tool.

This then automatically generates spreadsheets from predefined templates and infuses them with the protocol elements, which in turn can automate construction of electronic case report forms (eCRFs), edit checks, and automated rules in the CDMS. This method ensures adherence to the protocol requirements and facilitates the creation of CDISC-compliant data dictionaries.

2

Using AI & Machine Learning (ML) to find content across thousands of other protocols that is related and reusable. This approach can identify existing electronic case report forms (eCRFs) and edit checks which have already been qualified on other studies, speeding up the database build process.

Aside from the efficiency gained, this ensures consistency and reliability across trials as well as greater data re-use.

The approach we envision begins with the end in mind—in other words, by identifying the desired datasets from digitized protocols. The design specifications are then reverse-engineered, and AI is used to locate and leverage reusable content. The approach we are using has also equipped the AI with knowledge of CDISC data standards, enabling normalized datasets to be auto-generated in real time as data is collected through the CDMS.

Conclusion

In launching vaccine trials, the pressure is always on to “get it right the first time,” circumvent delays, and realize efficiencies. When you rely on local partners who specialize in conducting vaccine trials, you can benefit from their understanding of the local country environment, the regulatory landscape, operational best practices, and technological advances.

Their expertise and native knowledge can help ensure that your trial’s start-up phase proceeds smoothly and quickly. It will be shielded from unnecessary and unexpected delays and aided by indispensable insights, methodologies, and technology.

For additional information on our services please visit **www.vaxtrials.com.**

About VaxTRIALS

A specialized CRO, VaxTRIALS provides innovative solutions in managing and monitoring vaccine clinical trials. Part of the Emmes Group since 2023, VaxTRIALS is a recognized leader in Latin America and beyond.

The company’s local regulatory knowledge and wide network of experienced investigational sites ensures rapid trial enrollment and standards.

About the Emmes Group

The Emmes Group is dedicated to advancing public health and biopharmaceutical innovation globally. Founded in 1977, our Emmes CRO business provides tailored clinical services for public and private sector partners.

Our Veridix business delivers innovative technology solutions to power clinical trials of the future.

To learn more, visit **www.theemmesgroup.com.**

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