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06 Feb 2020 |

Best Practices In Seasonal Vaccine Efficacy Studies: Tips For Successful Planning And Execution

Thought Leadership In Association With ICON

by

Classical, randomized placebo-controlled efficacy studies of vaccines for seasonal illnesses, such as influenza and respiratory syncytial virus (RSV), must conform to the calendar and run like clockwork. Typically, they are very large studies – with tens of thousands of subjects – and operate within a compressed timeframe dictated by the respiratory season. Thus, they cannot be undertaken as "business-as-usual," but rather require accelerated processes, rapid decision-making, and a different approach to risk. Here, we outline the challenges in these studies and share our recommendations for study planning, enrollment, surveillance and study closeout. With the right planning and support, these challenging studies can be completed successfully within the narrow seasonal window.

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Seasonal Studies:
A Wild, Rollercoaster Ride For Clinical Operations

While no two seasonal vaccine efficacy studies are truly alike, they all aim to prevent laboratory-confirmed disease. They also share several challenges that make for an intense and busy time for sponsors, contract research organizations and sites:

- An aggressive calendar. There is a narrow window of time during which study execution can occur. Ensuring vaccine availability, site activation and the recruitment and vaccination of thousands of subjects in a compressed timeline can there-fore be challenging. There is no "wiggle room" in the schedule, so not starting early enough and unexpected setbacks can put a study at risk for a delay. Depending on the study plan, this could mean a 6-12 month delay; six months if a two-hemisphere study had been planned and 12 months with a planned single hemisphere study.

- Rapid, competitive recruitment of thousands of subjects. Most seasonal virus studies enroll 7,000 to 10,000 subjects, and it is not unheard of to have 14,000 or more. All sites must be ready to go simultaneously, and all subjects must be enrolled in a short period of time (usually about eight weeks) and before they would otherwise be vaccinated in the case of influenza. Often, by the time the vaccine is manufactured and released, there is little time to spare. Enrollment must commence immediately and be completed within approximately two months, with hundreds to thousands of subjects enrolling every week. The sheer volume can be challenging.

- Active surveillance throughout the respiratory season. It is critical that the study captures all respiratory symptoms and that subjects be swabbed for virus identification. Subjects need to be proactively contacted and reminded to report protocol defining respiratory symptoms. The number of symptoms required may vary from study to study, so the site must be very aware of the protocol defining symptoms for the study that is conducting. Recently we have seen protocols only requiring one symptom of a certain duration, whereas prior studies typically required two symptoms – generally one respiratory and one systemic.

- Complex supply logistics. It can be difficult to have sufficient volume of the study vaccine (and/or the comparator vaccine) and ancillary study supplies (rulers, thermometers, diaries, swabs, blood collection supplies, etc.) on hand for study start and without interruption during study conduct. Vaccines must be distributed via a cold chain, and provisions need to be in place to quickly replace any product that might be affected by a temperature excursion so as to not cause recruitment delays. Ancillary supplies typically require a larger storage area, which many sites may not have. Thus, plans also need to be in place to ensure sufficient supplies are on site at all times to preclude recruitment pauses.

- High volumes of data and documents. The sheer number of subjects and the use of patient-

reported outcomes (PROs) for reactogenicity – either with paper diaries or eDiaries – produce large volumes of data that must be entered and cleaned. Sites must be prepared to enter in real time and the data management team must perform in-stream data cleaning, as any backlog magnifies quickly.

The Basics Of Study Design

Relative to influenza, in most developed countries like the US, there is a recommendation that everyone be immunized for influenza. This creates an ethical dilemma and can put high-risk subjects (infants and elderly) at risk in a placebo-controlled study. In studies of young, healthy adults, a placebo can be used since the population is generally at low risk for experiencing serious consequences from contracting influenza. However, this requires that subjects be fully informed of the recommendation that they receive a vaccine as the standard of care. They must understand that participation in the study means they may be randomized to a placebo and that their alternative to study participation is to receive the influenza vaccine. In the high-risk populations (such as in infants, young children, elderly and those with chronic disease) the study must include an active comparator vaccine for influenza. For RSV, there is currently no approved vaccine, so a placebo-controlled study is currently not an issue.

Seasonal vaccine studies can be based anywhere in the world as influenza and RSV are ubiquitous.

However, sponsors tend to prefer conducting them in the Northern Hemisphere where the research and regulatory environment is more developed and predictable, surveillance is good and there is a season with a somewhat predictable robust peak. Closer to the equator, the RSV and influenza season tends to occur year-round with smaller peaks in the rainy season and in the winter. Several APAC countries have good infrastructure and very good recruitment, and thus can serve as additional countries if enrollment needs to be extended. Many sponsors opt to initiate their studies in North America and then to expand to APAC and/or the Southern Hemisphere, to have greater exposure and to mitigate for any unanticipated delays that may compromise the enrollment period. ICON has been very successful with the North America only or North America plus APAC models in studies ranging from 4,600 to over 14,000 subjects.

Planning

Not only is the timeline for seasonal vaccine studies extraordinarily compressed, but there are also potentially serious consequences for any delay. If the trial cannot be started within the optimal window, it will typically have to wait a full year for the timing to be appropriate once again unless a mitigation to bring on the opposite hemisphere is already in motion. The trial plan must, therefore, be comprehensive and also address possible contingencies. In order to help ensure the smooth conduct of the trial, sponsors should engage their research partners at least nine to 12 months in advance of study start for the Northern Hemisphere (NA and EU) and slightly longer for Latin America, China and Japan. US-only studies with all private sites have the shortest timeline and generally, seven to nine months is adequate.

> ***Once the protocol is stabilized, the hemisphere and countries where the trial will run should be selected. These decisions will affect the selection of the Contract Research Organization (CRO), labeling, shipping, importation and distribution requirements and timelines.***

The first critical step is to stabilize the protocol; it is difficult to prepare an extensive study plan if the protocol is still in flux. This should be completed nine to 12 months prior to the expected date of the First Subject In (FSI). The inclusion/exclusion criteria for the study should be considered carefully, recognizing that they can unnecessarily limit enrollment. Consider, for example, the impact of excluding subjects who received a flu vaccine in the last 12 months vs. the last six months, or the need to set restrictive blood pressures or body mass indices. Not only can these decisions restrict enrollment, they may affect labeling downstream. In general, the criteria should be as unrestricted as possible while ensuring that the subjects are generally

healthy, or health stable in the case of the elderly or high-risk special populations, so that the data are not confounded by issues related to chronic disease.

Once the protocol is stabilized, the hemisphere and countries where the trial will run should be selected. These decisions will affect the selection of the Contract Research Organization (CRO), labeling, shipping, importation and distribution requirements and timelines.

The monitoring plan should then be developed, along with any monitoring oversight plan. The monitoring frequency and the sponsor's involvement in monitoring oversight will affect the budget, so these factors should be settled early and communicated to the research partner.

The investigator budget will need to be developed early and will need to account for staff time, study procedures, a stipend for participants and the monitoring parameters established in the monitoring plan. Given the number of subjects typically involved, the investigator budget will be substantial, and it will be important to get it right before contract negotiations with sites begin to avoid delays.

The leading reason that studies fail to meet their FSI dates and or face enrollment challenges is a delay in supplying sites with the test vaccine and/or the comparator vaccine. The manufacturing plan should have time built in, if possible, for batch failures. If it becomes clear that supplies will be delayed, the CRO should be notified at once so that sites can be notified and can manage their plans as well.

It is also important to make sure that the selected sites have all of the necessary equipment to handle vaccines and lab specimens, which include centrifuges and refrigerators/freezers. This is rarely an issue in the Northern Hemisphere, but might be a consideration in Latin America and APAC where space or equipment may need to be rented for the study duration.

System development is also a critical part of the start-up process. Generally, it can take six to 12 weeks to set up and test study systems such as eDiaries electronic data capture (EDC), interactive response technology (IRT), electronic trial master files (eTMF) so that they are live prior to first subject randomized. All such systems need to be stress tested so that all sites can be activated at the same time. Similarly, all support systems, such as the help desk, need to be fully prepared for the volume of activity that will be required upon study start.

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matters: subject safety and the integrity of endpoint data.

And of course the statistical analysis plan (SAP) and any plans for an interim data analysis should be set prior to the FSI.

Manage The Volume

Enrollment

All sites within a hemisphere should begin competitive enrollment on or around the same day. To avoid over-enrollment, sponsors should know in advance how they will cap enrollment either at the site or the country level. Generally, with competitive enrollment, a country level cap is preferred to ensure that enrollment goals are met and that one or two slower enrolling sites do not compromise the completion of on-time enrollments.

Preferably, screen failures should be captured in the IRT or EDC. Should the screen fail rate be higher than anticipated, data will be available in real time to assess the situation so that mitigations can be put in place quickly, as appropriate.

Sites will be processing multiple subjects daily, and need to spend sufficient time with subjects on their first visit to make sure that they understand the study requirements, risks and benefits, and how to complete the diary. It is critical that sites review the diary requirements for collecting reactogenicity data with subjects as well as the surveillance process if diary alerts are part of the surveillance plan. Most sponsors opt for eDiaries due to the volume of subjects and the other advantages of digital data collection: real-time safety oversight, documentation of when the diary was completed and the fact that traditional, on-site monitoring of the data by a CRA is not required. Paper diaries have many shortcomings, including the workload to monitor and reconcile thousands of subjects and the resulting challenge to ensure the highest data quality.

Adverse Event Reporting

All vaccine studies collect reactogenicity data, solicited local and systemic symptoms, via an electronic or paper diary. In years past and in most studies today, it has been assumed that any local reaction is definitely related to the vaccine and that systemic symptoms were possibly related, due to temporal association. Recently we have seen a couple of sponsors request that the investigator rate the causality of each symptom recorded. This has created a large work burden

for the site and is something that requires careful thought and consideration if it is necessary. We've had two clients tell us it was requested by the FDA; however, we see that most clients do not require this assessment.

General, adverse events (AEs) or medically attended adverse events are generally captured for 28 days post vaccination, while serious adverse events (SAEs) are reported for the duration of the trial.

Data Monitoring And Study Documentation

These studies are well suited to risk-based monitoring as a way to both reduce costs and help study teams focus on what really matters: subject safety and the integrity of endpoint data. Options include targeted or randomized monitoring, reduced source document verification, and/or data analytics. Selection of the best solution is in large part driven by the risk tolerance of the client.

The eTMF, of course, is the documentation of the study and must be overseen closely with active, real- time filing and periodic quality checks throughout the duration of the study. Again, due to volume, failure to keep the filing up to date and reviewed for quality can prolong the study close and compromise the study integrity.

Stay On Top Of The Data

Because these studies move so quickly, data will be coming in very rapidly, and it is essential to clean it continuously, rather than letting it wait until just before the study closes. The same is true for serology, viral swabs and the reconciliation of SAEs.

Ideally, the final database lock is completed in two stages; safety lock followed by laboratory lock. It is usually possible to lock the safety database 21 days after the last subject visit, although this can be challenging because it is possible to have 10,000 or more subjects completing their last visit within one week. It typically takes three to four weeks, or more, for the final serology/virology results to come in, and thus, that portion of the database will be locked several weeks after receipt of the final laboratory data. Another approach taken by some sponsors is to lock the safety database and then handle the serology analysis outside of the safety database.

Closeout site visits should be conducted within four to eight weeks of the safety database lock to ensure study integrity and inspection readiness, as sites quickly move on to other studies and institutional memory starts deteriorating. Because the laboratory data may not yet be available at the time of closeout, sites must be advised of that fact and that they may receive additional queries around the lab data. Gener-ally, once the lab data are in and reconciled, sites will be advised to notify their international review board (IRB) of study closure.

Success Factors

Seasonal vaccine studies are fast-paced from beginning to end. In our experience, the keys to success include:

- Careful early planning, strong communications and close collaboration between the sponsor, the CRO, the sites and other vendors.
- Making the study a priority within the organization with internal advocates.
- Selecting sites that are experienced in vaccine studies and have proven their capabilities.
- Taking extraordinary steps to ensure the availability of the study vaccine and any comparator.
- Aggressively addressing any unanticipated delays.
- Using a robust system for tracking progress and gathering data.
- The ability to make decisions and resolve issues rapidly (ideally within 48 hours).
- Considering out-of-the-box solutions to ensure on-time site activations.

Seasonal vaccine studies present challenges for even the most experienced and prepared study managers. The scope and timeframes of these studies leave no room for error and have a steep learning curve with limited leeway to learn on the job. They call for a com-prehensive, coordinated approach that accounts for contingencies, properly manages risk, holds to a firm schedule and applies best practices developed through years of experience.

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Cindy Dukes is a therapeutic expert for vaccines and
leads ICON's Vaccine Centre of Excellence. She has over 40 years of diversified clinical experience, including infectious disease and vaccines. In a global survey by Vaccine Nation, Cindy was recognized as one of the "Top 50 Influential People in Vaccine Development" in 2014. In 2016, she received a Distinguished Alumnus Award from Baylor College of Medicine for her leadership in vaccine development. PharmaVoice recognized Cindy as one of the "Top 100 Leaders in the Industry" in 2016. Under her lead-ership, ICON received the "Best CRO" award at the Vaccine Industry Excellence Awards in 2014 and 2017.

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