



## ○ Featured Article

# Immunize Your Trial against Influenza: Effective Clinical Trial Risk Mitigation in the Age of Pandemics

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Seasonal flu typically affects 5 to 20 percent of the population – but this flu season is expected to be anything but typical. With the presence of H5N1 (avian) flu smoldering in Egypt and Asia and a global pandemic of H1N1 (swine) flu underway, infection rates could reach 50 percent, according to an August 2009 report from the President's Council of Advisors on Science and Technology. Given these grim estimates, sponsors and CROs simply cannot ignore the threat of a pandemic impacting their clinical trials.

Envision half of your entire project team, investigators, vendors and study participants unable to work and/or unable to participate in your trial for two to four weeks at random points over the next six months. Even if not sick themselves, they may need to care for family members who are sick or stay at home due to health department quarantines, shutting down of mass transportation systems or school closings.

Consider the many ways this could impact a clinical trial. Study participants who get the flu may not feel well enough to make their scheduled appointments. Hospitals (sites) may be so overwhelmed by influenza patients seeking urgent care that studies are put on hold. CRA monitors may be unable to visit investigator sites. Understaffed labs may be unable to process samples...the list goes on and on.

What if the Investigational Product (IP) supplier is too short-handed to deliver study medicines as planned, or site and/or public transportation closures prevent patients from obtaining needed medications? What are the risks to patient safety of an unplanned, abrupt discontinuation of study medication?

With so many variables in play, it's easy to see why all clinical trial sponsors – not just those developing antivirals – are concerned about pandemic planning. And our teams at INC Research are concerned, too.

Figuring out the many ways a pandemic can disrupt a clinical trial, and developing risk mitigation and contingency strategies to prevent that from happening, are the kinds of considerations our Project Leaders are actively addressing. Fortunately, we've found there are many practical steps a sponsor and CRO can collectively take to minimize or dissolve the affects of a pandemic and maintain the integrity of a clinical trial.

## Protocol Best Practices

One of the most important aspects of any pandemic preparedness plan is preparation: incorporating risk management planning in the early stages of trial design is much more effective than waiting until a crisis is at hand to begin looking for viable options.

For example, sponsors may consider increasing patient enrollment targets beyond what is needed to meet study needs in order to mitigate the risk of unplanned patient discontinuations due to illness. Alternatively, a combination of telephonic interim monitoring visits or in-home monitoring by the site staff may also reduce the likelihood of patients being "lost to follow up" due to their inability to maintain the stated monitoring regime.

Trial site location and selection also is an important aspect of pandemic preparedness that should be considered early in the process. Taking a dual-hemisphere approach and including sites (even if only on stand-by) in the southern hemisphere – where flu season is counter cyclical – can ensure the availability of patients if the flu decimates trial sites and patient populations in the northern hemisphere. Additionally, selecting smaller specialty clinics (office setting) rather than large hospitals with urgent care facilities potentially overwhelmed by flu patients may help to reduce the “fear” patients may experience in going into a large hospital setting and risking exposure to the virus.

We also encourage our sponsors to consider how the flu vaccine might affect their safety and efficacy data. If some patients in a trial are likely to get the vaccine during the course of the study on their own, should the sponsor provide all patients with an influenza inoculation as part of the protocol to reduce variability as well as reduce the likelihood of patients contracting seasonal influenza, or does the addition of yet another medication increase variability?

These are just a few of the pandemic-related issues a sponsor can address proactively in their clinical trial protocol. Ideally, these questions should be considered as the trial is being designed, but there are ways to incorporate pandemic planning even when a trial is already up and running.

Changes to the protocol may take weeks to obtain approval, but they are easier to secure ahead of time than when trial execution is in jeopardy and half of the institutional review board (IRB) members are out sick and unable to review the proposed changes. Larger central IRBs, which routinely operate in a virtual environment with geographically dispersed staff, may be able to respond more reliably than local IRBs, which normally meet face-to-face and lack adequate replacement staff to ensure continuity of operations.

## Personnel Planning

In every clinical trial, there are people who play a central, critical role. But if these people are out sick for a few weeks, the trial should not – indeed it must not – come to a grinding halt.

The most important role in a trial – except perhaps for that played by patients – is the sponsor. We at INC Research understand that many of our sponsors like to maintain an active role in the conduct and decision making associated with their trial. However, we recommend that each sponsor develop an extensive internal chain of command so that decisions can still be made and the trial can still move forward even if key members of the sponsor team are unavailable.

To facilitate rapid decision-making, we recommend the sponsor and CRO dedicate time to develop detailed plans, strategies and contingency “what if” planning in a collaborative manner, similar to how we at INC Research use QuickStart™ for facilitated kick-off meetings and dedicated joint project planning periods. Decision points are identified, response plans are developed, and triggers are quantified so that if/when a certain situation presents, the team is able to act quickly, ensuring needed modifications are executed in a timely, proactive manner so that study momentum isn’t jeopardized.

If the trial’s CRO project manager or other core team member should be out sick, the benefit of working with a CRO like INC Research is that we have a deep pool of qualified professionals, using disciplined processes and standardized guidelines, enabling replacement staff to quickly come “up to speed” on the project without compromising project timelines or quality. That’s not to say the original project team member won’t be missed, even if he or she is only out for a few days – but the trial will continue to move forward because contingency plans are in place in the event they are needed.

Site monitors (CRAs) often are another key player in a trial’s success. Yet the nature of their jobs – frequent travel using public transportation to sites across a broad geographic region – puts them at high risk of exposure to influenza. INC Research teams have been working with our sponsors to come up with solutions, such as employing four part-time monitors rather than two full-time monitors. This alternate strategy allows the monitors to work regionally, avoiding travel as much as possible, and be quickly fetched home if they fall ill on the job. Additionally, having a larger monitoring team provides more people to cover for others if one gets sick.

## Technology to the Rescue

Globalization has made the modern world more susceptible to pandemics...but technology has made the modern world more prepared to deal with the situation.

Technology can prevent many of the potential problems associated with a pandemic. In fact, it can even reduce the spread of infection. A trial that uses paper for its protocols, medical records and data collection forces potentially more person-to-person contact each time documents change hands, and the paper itself can transmit germs even in the absence of face-to-face contact. Using electronic data capture and document scanning technologies reduces these risks.

Technology also can address many of the problems associated with managing a trial. For example, storing documents online in virtual project team rooms allows team members to work from home as needed. Investment in laptops and VoIP technology ensures team members can interact with no degradation when operating remotely. And technology-facilitated doctor-patient interactions, such as telephone, videoconference consultations, or electronic diary collection through IVRS or other ePRO technology can supplement on-site visits as appropriate.

## Demand the Best

This article has discussed just a few of the many factors to consider when preparing a clinical trial to withstand a pandemic. That said, the single most important thing a sponsor can do is demand the best CRO partner.

That partner should be truly global and able to execute a dual-hemisphere strategy using organic resources; tech-savvy and technology enabled to operate location independent; experienced with standardized processes to reduce variability and ensure continuity; and, most importantly, comprised of a world-class team of project professionals working with the sponsor every step of the way.

Finally, a good CRO partner needs to be honest. That may sound obvious, but some firms may tell you what you want to hear rather than what you need to hear. Pandemic preparedness isn't cheap – building redundancies into a clinical trial is bound to increase the complexity and cost of the undertaking. But as a good CRO will tell you, pandemic preparedness, though complex, is absolutely essential to ensure actionable data is delivered to the sponsor, on-time and on-budget, even in the Age of Pandemics.