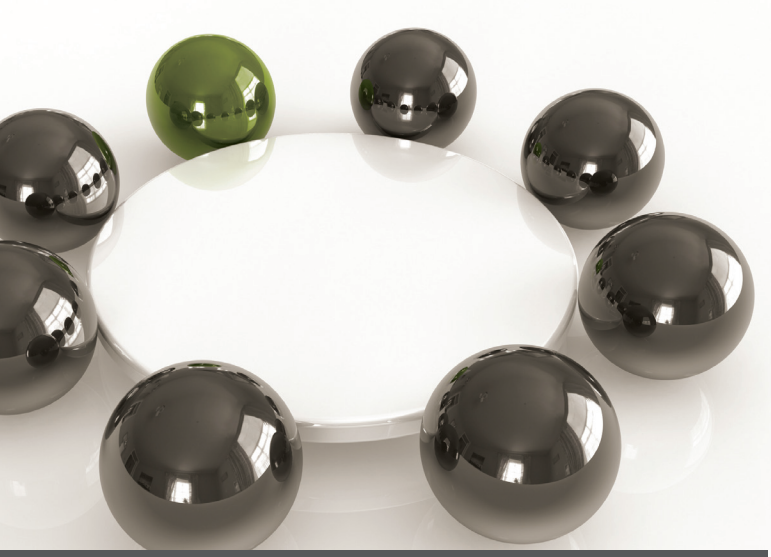

Clinical Trials Roundtable

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1. How are clinical trials growing increasingly global by nature? Discuss challenges with this movement.

EM: The forces supporting the globalization of clinical trials are powerful: universal acceptance of ICH-GCP, the saturation of research sites in the US and Europe, cost containment pressures, need for larger patient pool, and the growth of the pharmaceutical market in emerging countries. Notwithstanding, other factors act in favor of keeping the trials where they have always been, and they come in two flavors. Some are objective, such as greater logistic complexity, lack of harmonized regulations, less experienced sites, and variations in medical practices. Others are subjective and no less important; they reside in the minds of decision makers.

Global trials involve a greater deal of uncertainty. Will different countries approve and follow the protocol? Will there be unexpected costs? Will the patient population be accepted by the regulators? Will delivery be as planned? Risk acceptance and mitigation strategies are approached very differently by sponsors and CROs. These themes depend on experience, flexibility and trust. The costs involved in large trials are mind-boggling. So far, a common response to those challenges has been to concentrate decisions in headquarters or in global teams rather than investing in decentralization of knowledge and building local country experience. This approach has important implications in the development of more global development activities. As clinical development has largely moved to CROs, their success will depend on finding the right balance between short-term gains, and efficient, stable capacity building in the field.

RW: Asia is a key area of industry expansion and can add to the complexity of global trials. When we think about execution, a primary challenge is managing and supplying investigational products (IP). Obviously, logistics are a key challenge given the sheer size of the Asia Pacific region, and language differences likewise can pose obstacles if not properly understood and accommodated. A major challenge is providing sites and potentially patients the flexibility to enter data in their local languages while also aggregating the data in a single language (typically English) for reporting and statistics.

Local country regulations must also be addressed and require careful consideration when managing trial supply and local country distribution. For instance, lot country releases are directly impacted by local regulations. There may be different release timeframes for drug kits across countries based on what regulators specify, and this needs to be factored into supply and distribution plans. Many study sponsors are increasingly looking to the randomization and trial supply management (RTSM) system to provide administrative tools to manage lot disposition for multiple countries.

Another important challenge is being able to accurately forecast the volume of IP needed for the trial overall — and for individual countries. This is exacerbated by a lack of historical data in emerging markets, but getting a baseline forecast is crucial to successfully supplying a trial. To really optimize trial supply, sponsors need to consider producing and supplying 'just enough' inventory so that they minimize waste or overages, but still ensure that adequate supplies are available to meet demand.

Proactively addressing all of these issues in the planning stages can pay huge dividends later on. And considering per-patient costs, sponsors can ill afford to have patients drop out of studies due to breaches in protocols and drug administration.

ST: I'm not sure that trials over the last several years have grown more global, but rather more focused in their reason for involving many countries and for performing work globally. Sponsors are sensitive to the changing landscape in drug development and healthcare, and including ex-US countries as needed, which is why we see the value of global trials in two key areas – for positioning the product for future marketing registration, and to access patients not available in the US, primarily in later stages of development.

The challenges of accessing expanded patient populations can be numerous and encompass the clinical development spectrum. For example, Sponsors working globally must account for increased protocol complexity in order to address a larger mix of diverse, globally-based patients and varying standard of care practices across countries and regions. Additionally, rising development costs in countries that were previously more economical and protracted regulatory approval timelines, may lengthen the cost, planning, and start-up of a trial. Finally, increased training and oversight of foreign-based investigators by sponsors, regulatory agencies, and patient protection programs in an effort to ensure compliance by investigators with GCP/ICH guidelines may sometimes create the need for additional oversight and time. To be sure, for trials involving large patient numbers, and those requiring access to specific patient populations, global clinical trial work can help sponsors meet their development needs.

Interestingly, one of the trends we've observed, especially as studies have grown more focused and complex, is an increased reliance on more robust Phase I and Phase II trials completed in the US before moving abroad for a large Phase III study. It will be interesting to see if this trend increases as sponsors begin incorporating more specific testing and technology that may not be standard of care or practice within the global market.

2. Which key technological advances have contributed to efficient clinical trials? How will technology continue to impact the industry?

EM: Definitively, CTMS and EDC have made clinical trials much more efficient and less costly. Ten years ago investigators complained a lot about non-user-friendly EDC systems, whereas nowadays, current web-based systems are very reliable and easy to use. The next big step will be the widespread use of EHR and its integration with study databases. Another important development will be the use of big data to locate suitable research subjects, if we can overcome the data privacy issues involved.

RW: Technology has really driven a number of efficiency gains, but many of these have been achieved independent of one another. For example, our industry has shifted from paper to electronic data capture (EDC), and from using envelopes to IVRS to web-based solutions that manage patients and supplies. There are still many opportunities to realize significant gains in efficiency and data integrity, particularly at the site level and in the overall chain of custody. However, the real opportunity is in increasing interoperability. Automating data exchanges and simplifying the integration burden are critical to seeing real advances.

Coordinating all of the complex activities involved in distributing products to trial sites and mitigating associated risks calls for a new technology solution that provides all functions visibility into the entire supply chain. Ideally, a single system could support the complete lifecycle with integrated information throughout the life of the study — from forecasting through all the downstream processes of manufacturing, packaging and labeling, drug ordering, inventory management, and product distribution. As the trial progresses, data is gathered in real time and used to modify upstream activities. This continuous cycle of information and adjustments would allow sponsors to optimize their approach to meeting actual demand — all in real time.

Adopting a sort of 'closed-loop solution' is perhaps the most significant step a company can take in improving supply efficiencies. The right system will remove information gaps that contribute to delays and added expenses, and technology is certainly a critical component of this.

ST: The shift to Electronic Data Capture (EDC) is so prevalent it is no longer a decision of electronic or paper but which system to use to perform your study. The impact of EDC has provided efficiencies in speed, quality, and cost of studies. Not far behind are the advancements in electronic submissions for IND and NDAs, improving the quality of data analysis and the speed and volume in which it can be performed. We see paper Trial Master Files as a thing of the past. Clinical Trial Management Systems (CTMS) for sponsor access to real time data to assist in study management is contributing to better decision making throughout the trial. Accelovance is currently using newer technology that we believe will impact the industry in areas of patient recruitment, patient informed consent, patient retention, and patient reported outcomes.

3. In what other ways will clinical trials evolve over the next 5-10 years?

EM: The biggest challenge we have today is fast and reliable patient recruitment. We have to work harder on this, and that means work better and smarter to help investigators. Patient-centric practices, such as research education, social support, and incentives can make a big difference in the success of a project. Attention to new technology in this area has increased with sophisticated ways to locate potential subjects however, it is human interaction that ultimately matters most. Sick patients want to interact with people and feel that site personnel care about them.

Another issue is cost containment – it cannot asphyxiate research sites. Negative cash-flow is a big problem for sites and sponsors and CROs must realize that most do not have the same financial knowledge as big companies. Payments will allow sites not only to survive, but also to develop. Honest investigators need help to succeed.

RW: Trial managers are already looking at drug pooling as a means to improve drug distribution and inventory management. This will be a critical component of trial strategy in the future and represents an opportunity to improve efficiencies. We've seen a lot of interest in pooling, but current RTSM technology may become a limiting factor. Systems are typically designed to support one study at a time, and pooling does not fit elegantly into that model. Newer architecture is necessary to make pooling an integral part of the solution.

Temperature monitoring is seeing greater demand. This is partly driven by the growth in temperature-sensitive biologics, but ambient drugs need monitoring, too. One way to support this growing demand is via emerging sensor technology, which can lead to less expensive temperature monitoring and help ensure that products arrive undamaged or uncompromised. Ultimately, this greater visibility may reduce or eliminate stock-out situations and keep trials running.

Another area to watch is in the patient-reported outcomes space. There are some really interesting devices that capture — and transmit — patient data that would eliminate data accuracy and data integrity issues. And I'm intrigued by what may happen with patient-compliance reporting as it relates to dosing instructions. I think we'll move beyond basic reminders of 'did you take your drug?' to more sophisticated directives around dosing instructions and helping people to record what's been taken and when. All of this contributes to capturing better data and supporting drug approvals.

4. Identify some crucial steps for mitigating patient risk when conducting a clinical trial.

EM: Again, patient-centric practices are key to mitigating patient risk. During the feasibility process, it is important to gather data about patient care at the sites and identify if there is a history of issues in this area. Then, site staff must be thoroughly trained in the critical aspects of the study related to patient safety. During the recruitment period, even when cost and time pressures mount, the first priority should be to choose the right patient for the study. It seems obvious but patients must be able to reach sites and get reliable responses 24/7 throughout the study. When problems occur, they must be investigated and information shared to prevent new occurrences. It seems that most sponsors and CROs are doing a good job here. Many people compare clinical research safety with the attention that commercial aviation gives to the matter, and they are correct.

ST: Patient safety is paramount to conducting clinical trials, whether the trial involves healthy volunteers or patients seeking treatment in a specific disease state. To ensure the safest environment possible for clinical trial patients, a number of key steps are implemented.

Mitigating patient risk starts before the trial, with an early assessment of the protocol by a treating physician participating in the trial. While it's not feasible to solicit input from all participating physicians before the protocol is finalized, it's important to include a strong representative group who can examine the proposed schedule of events and compound to ensure the safest environment for the patient. The involvement and training by the sponsor company plays an important role here as well by providing complete information on the product profile and research to date.

Additionally, for investigational products with strong or unknown side effects, the use of Sentinel Patients allows the product to be administered carefully and monitored for evidence of any unknown side effects or potential drug-drug interactions that may occur.

Finally, the presence and oversight of a licensed and engaged physician at dosing and for an appropriate period following dosing in order to monitor patient safety is vital. It is crucial that this task be performed by physicians and not delegated to other site staff.

Combined with good site communication between physicians, nurses, and support staff, taking into account all of the elements mentioned above provide patients with a safe environment to participate in clinical research.

5. Discuss the elements of an effective feasibility assessment.

EM: Feasibility assessment is like Medicine: it is part science, part art and, nowadays, part law too. One faulty part will not get you what you need. The science is hard data review, patient charts, facilities, staff training, procedures in place, past recruitment reliability, etc. Law is becoming increasingly important: can the site accept your contract template? Are there any due diligence issues to be clarified upfront?

If all clinical studies were performed only at the sites with perfect historical data, fully trained staff, and excellent facilities, we would only be able to start a fraction of current studies. Here is where intuition, trade knowledge and personal relationships come together. One needs to decide which sites to support, and which ones to drop, which investigators will respond to study difficulties and which are not engaged. Here is when the technical and personal skills of the CRA can make a big difference. Going back to my answer to the first question, sponsors and CROs must develop their field personnel, and trust them. Systems and databases are important, but certainly not enough for an effective feasibility process.

ST: The site feasibility process has always been an important component of appropriate clinical trial site selection. However, over the last several years, we've noticed two major trends in the evaluation of site feasibility which have simultaneously improved protocol development and site selection while placing greater burden on sites, resulting in lower efficiency and response rates.

Earlier engagement with CROs and sites through feasibility, before the protocol has been finalized, has led to more effective and operationally feasible trials, which is good for the pharmaceutical company, the participating sites, and for patients. However, the increasing trend of attempting to capture more data and the means of capturing these electronically through surveys often results in inefficiencies in the feasibility process. How many sites have received a survey link with over 40 questions and decided either not to respond or have provided a half-hearted and quick response?

One of the ways in which Accelovance has created a more efficient and effective feasibility process is through a focused, personalized, and interactive approach using a smaller number of targeted questions through an electronic survey and then engaging the site through brief person-to-person follow up and directed discussion. The result has been a process that is easier on site personnel, which allows for greater efficiency and response accuracy as well as higher rates of participation. Our average feasibility response rate is greater than 55%, well above industry average.

6. Discuss approaches for thoroughly training clinical research professionals. Why is this so important?

EM: Clinical research is a highly regulated, high-risk environment. One mistake made by a single individual has the potential to jeopardize human lives and millions in investments. No professional should be able to perform any action before his/her ability to perform a task is assessed and confirmed. Moreover, academic titles alone are not enough to provide the skills needed to work in clinical research.

The role of employers in training employees is paramount. They not only depend on their workers' skills, but are also civil and criminally co-responsible for their employees' acts. Despite this, we still struggle to find more adequate and cost-effective ways to train clinical research professionals. A large portion of training is delivered by reading (print or online materials) only, which is highly inefficient. Another big part is hands-on supervised training, which is more efficient, but very costly too. Each company has to find the right balance, document all actions correctly, and develop embedded quality check systems.

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