Clinical research can be a high-pressure, fast-paced environment fraught with challenges. Contract research organizations (CROs) provide expertise for navigating through the maze of regulatory and other important considerations.

Advice on how to tackle clinical trial-related issues was on offer at the recent Association of Clinical Research Professionals (ACRP) 2014 Global Conference. At this event, sessions covered how and when to plan for clinical trials, how to complete them with greater enrollment accuracy, how to achieve greater efficiency in motivating sites and patients, and how best to handle studies involving rare diseases or unique ethical issues.

Clinical trial difficulties usually start early, during site selection, when feasibility is the key issue, or should be.

“One of the biggest problems in the feasibility process is that sponsors, CROs, and clinical trial sites do not connect early enough to establish an accurate feasibility for the trial,” said Rebecca Little, associate director of business development at RxTrials, a site-management consultant. The company maintains what it calls an integrated site network, or ISN.

Little explained that “feasibility” has different meanings among sites, sponsors, and CROs: “For a site, this is a moment to stand out and possibly get selected to move to the next steps for that particular trial. In turn, sites may try to stand out by arbitrarily exaggerating their patient numbers. For sponsors and CROs, feasibility considerations include a variety of factors, such as geographic location for the trial, timeline, number of sites needed, and patient enrollment targets. A lot of this information can be based on the feedback they received from the sites.”

Why don’t sponsors/CROs engage sites earlier to perform feasibility studies? “Often sponsors/CROs are reluctant to guarantee they will give the work to the site and thus assume it is best to engage sites later in the process. We try to explain to the client that we are happy to perform an in-depth feasibility study without a commitment. This is a very important step in the planning process for all parties.”
Little concluded with this take-home message: “Sponsors and CROs need to engage with sites earlier in the process to perform a more accurate feasibility assessment that will result in a more realistic recruitment plan in order to meet timelines faster and to avoid recruitment issues that might not be identified until later in the trial process.”

**Informatics and Modeling**

One of the best ways to arrive at accurate forecasts for clinical trial enrollment is to use the power of statistical modeling, suggested Otis Johnson, vp of clinical research at inVentiv Health, a CRO that offers clinical, commercial, and consulting services.

“Many times investigators arrive at projections that are too optimistic only to fall behind later,” said Johnson. “We use state-of-the-art feasibility and clinical informatics tools to accurately model trial enrollment based on the current environment as well as comparable historic trials. This comprehensive, data-driven approach allows us to optimize trial planning and reduce enrollment cycle time while at the same time mitigating risk.”

Once they are gathered, the necessary details are converted into useful data, quantitative inputs that are run through a model that estimates the probability of successfully completing enrollment within the given time frame.

“For enrollment modeling, we use Monte Carlo simulation technology running up to 5,000 virtual iterations of the trial with parameters such as geographic footprint, enrollment rate, site failure, and screen failure,” explained Johnson. “We also factor in uncertainties and estimated errors to finally derive a model that displays an enrollment period distribution curve with accurate probabilities and estimated risks.”

According to Johnson, informatics modeling provides an up-front way to more accurately plan enrollment, creating an opportunity to implement mitigations from the outset: “Instead of the historically seen wrong timelines, we are better able to establish trials that proceed to completion on time with greater accuracy.”

**Cultural Shift Needed**

Another industry challenge is more than corporate cultural lines, according to Dirk Reitsma, M.D., vp and head of oncology global product development at Pharmaceutical Product Development (PPD): “It can be difficult for a pharmaceutical company to step away from a project and hand over some of the decision making to a CRO, for example. But, in an era of shrinking resources, it becomes much more efficient to collaborate with a trusted CRO that can bring depth of experience, knowledge, and innovation to the table.”

Dr. Reitsma advises pharmaceutical companies and their CRO partners to think outside traditional roles: “What is needed now is the early engagement of CROs to enhance efficiency, but also to develop trust in the collaborative process. Whether it is pharma with CROs, pharma with pharma, or CROs with CROs, we need to determine ways to enhance drug development in a more timely and cost-efficient manner.”

Dr. Reitsma noted that while pre-competitive collaborative trials should help make drug development more efficient and advance the testing of novel-novel combinations, they may be more appropriate for CROs to conduct because few pharmaceutical companies have portfolios large enough to justify those trials: “CROs are the most natural place not only to establish shared control groups, but also to develop an output profile for collaborative trials.”

**Big Datasets and Ethical Issues**

Big Data has arrived in healthcare, bringing golden research opportunities as well as a unique set of challenges. The challenges were outlined by David Vulcano, assistant vp and responsible executive for clinical research at Hospital Corporation of America (HCA).

“We can now generate so much data that it can be hard to really get your arms around it,” said Vulcano. “Information technology (IT) people can easily combine health records and a variety of plain data to create massive e-records. However, with this comes lots of noise and regulatory considerations. It is easy to want to charge ahead, but often the IT person has limited knowledge of the fine details of individual protections, privacy issues, and how to use the data.”

One example, explained Vulcano, is use of genomic data: “Although in-
vestigators say they de-identify data, often this de-identification is rather unclear and not in compliance with HIPAA regulations. If you gather a dataset under one set of conditions and then want to use it for another, you are potentially in violation. Personnel must have knowledge themselves or easy access to an individual who is well versed in regulatory and ethics requirements.

“It’s not just a matter of an IT person combining datasets, such as if Amazon bought Google and you are looking for shopping behavior,” continued Vulcano. “Healthcare issues are sensitive and have individual privacy considerations, as well as ethics for research and healthcare practices. This should be set up early in the design of research as part of a steering or planning committee. The idea of ‘First, do no harm’ is appropriate here, and of course the second major idea is how to maximize the outcome of dataset analysis.”

Gamification: Game On

Achieving goals and gaining recognition are two important innate responses driving human behavior, according to Niki Kutac, director of product management at Datatrak, a provider of trial design and management software.

“We employ a motivational strategy called gamification to monitor, report, and incentivize clinical trial sites for the purpose of enhancing efficiency,” said Kutac, who explained that gamification is defined as the use of game-thinking and game mechanics in non-game contexts to engage users and to solve problems. To do this, recognition and optional rewards for accomplishments are provided.

“Gamification has long been utilized in the context of sales to monitor progress by individuals,” continued Kutac. “When we used this technique internally to assess task completion needed for a milestone, we found a 300% increase in daily activities. We decided to apply this motivation technology to clinical trial settings.”

“First we determine what behaviors need to be improved, such as patient adherence, visit scheduling, data entry, timeline adherence, quality of work, or education (from staff to patient). We then advise on the development of reports for the selected behaviors, automating the creation of reports that reflect the real-time results of the measured activity. The status is displayed for all participants to see, using our cloud-based eClinical system.”

Besides demonstrating how its software technology can provide these measurements, the company recommends that users determine suitable forms of recognition—status levels, awards at meetings or events, or even monetary prizes.

“The game ‘Candy Crush’ is a great example of the effort participants expend in trying to rise to different levels,” remarked Kutac. “Our technologies show visible and concrete metrics that enhance clinical trial site efficiency and productivity. Our ultimate goal is to use such motivational tools to shorten the time it takes for performing clinical studies to bringing the product to market.”