When I speak with pharma executives on certain topics, it’s amazing to see the difference in where companies stand in terms of implementation. Adaptive trials is one of those topics. I will talk to one executive who will tell me it is one of the trends that will most impact the pharma industry in the coming year, and then talk to another who will tell me it’s old news and something they have been doing for the past eight years. While I’m sure company size has a lot to do with that outlook, it is still interesting to see that difference in perception.

“I couldn’t agree more with that assessment,” says Sy Pretorius, M.D., SVP and Chief Scientific Officer for PAREXEL, when I discussed this topic with him recently. “Both viewpoints are correct, and it’s what we see happening in the industry as well. Taking that second perception first, this is definitely an approach that is not new. We have been performing interim analysis, as an industry, for a very long time. Adaptive design simply means adding the design element to that analysis preemptively. Specifying the changes you are going to make is the part that is new, and is necessary to ensure the trial design is still valid.”

That, Pretorius notes, segues nicely into the other opinion, which is that adaptive trials are still relatively new. He agrees with that statement as well, noting adaptive trials are certainly on the uptake, especially in Phase 2 trials, and he expects to see a lot more activity in the next 3 to 5 years. He sees a bit more reluctance by companies to tackle it in Phase 3, attributing that hesitancy to many companies not wanting to be the first movers into a new territory in a heavily regulated industry. He notes this occurs despite the fact that this approach has received positive comments and feedback from regulators.

“I often expect regulatory issues to be at the top of the list of concerns sponsors have about doing an adaptive trial,” adds Pretorius. “But that is generally not the case. The biggest concern I typically encounter is internal resistance to change. In big pharma companies, someone might like the idea of conducting an adaptive trial, but getting the protocol approved at various levels within the company can be difficult. If a protocol looks different from what individuals normally see, there may be pushback due to fear of risk and change.”

Most Suitable To Phase 2/3

Pretorius also points to research showing where the adoption is gaining ground. Data from TUFTS, ISR, and DIA show 20 to 30 percent of adoptions occurring in Phase 2 and Phase 3 trials. Most of the adaptive trials performed continue to occur in Phase 1 trials, and he sees very little in the way of adaptive approaches happening in Phase 4 at present.

At the start of a pivotal Phase 2 or Phase 3 trial, there are many uncertainties. Companies have to make a number of assumptions from the very start of a trial. With the current, more standard and inflexible design, there is really no way for companies to react if any of those assumptions are determined to be incorrect. However, if sponsors are able to get an interim look at the data, and can validate whether the assumptions are correct or incorrect, an adaptive approach might allow them to change course and get to a much better trial for both the company and its patients.

“I certainly believe, from a patient-centric perspective, that adaptive trials are more ethical,” says Pretorius. “Phase 2 and Phase 3 trials can expose a large number of patients to a treatment or dose that may be ineffective. If you have an opportunity to adjust a dose that is ineffective because of an incor-
rect assumption, it is best for the patient that you do so. Similarly, if a patient seems to be getting too much of a medicine, it is best for them if you reduce it.”

Proper Vision Assists With The Journey

Pretorius has an analogy that he likes to share that he feels accurately describes adaptive designs in trials. He notes traditional trials designs are much like a cargo plane without any windows. Without windows, we cannot see what is going on inside the plane. Similarly, without adaptive designs, researchers are often unable to see what is going on within the study. Only once the plane lands (or the study ends and the database is locked) do you get a sense of what has happened.

“Adaptive designs are much more akin to a passenger plane with windows,” he says. “During the study, you can take a look at what is going on and make any necessary adjustments that we had the foresight to plan for. We have to spell out all of those adjustments up front in the study design, and discuss your plan with the FDA; but, if we do it correctly, we can save the study and the drug, and take better care of the patients participating in the study.”

Despite the benefits, Pretorius is quick to note that adaptive trials can still be tricky to pull off. He recommends sponsors look at these trials along three dimensions. The first piece is statistical design – and that can be one of the trickiest. If sponsors do not have that experience in-house, they should work with a consultant or a partner that can provide the expertise. That experience includes being able to correctly design the adaptive study and convince regulators you are not invalidating the study as a result of the changes or adaptions that you make (for example, a type 1 error that rejects the null hypothesis when it is, in fact, true).

Second, he notes adaptive trials are difficult to execute, a dimension that is often underestimated by companies attempting them. The unique aspects of these trials require special knowledge and expertise. Third, he notes sponsors need the technology support that will allow them to make the needed adaptations.

All Companies Can Benefit

While Pretorius sees no typical company attempting adaptive trials, he does note that larger pharma companies seem to be more willing to go that route than smaller, emerg-