Clinicians call for greater transparency in trial recruitment

It is no secret that recruitment of patients for clinical trials is exhausting at best and downright impossible at worst. Many multicenter trials fail to enroll the desired full breadth of patients across all sites. The particulars about which centers had poor recruitment can remain hidden, hampering transparency and making it difficult to analyze the data for population biases. Because of this, an international team of clinical researchers is now calling for the recruitment inadequacies of individual investigators and institutions to be made public.

In an article published in late December, the group calls on the ClinicalTrials.gov registry to require center-specific disclosure of how many patients are successfully recruited for multi-center clinical trials (*PLoS Med.* 8, e1001149, 2011). Lead author Rafael Dal-Ré of the Pasqual Maragall Foundation in Barcelona told *Nature Medicine* that in many trials, because the majority of sites do not recruit their target number of participants, patient recruitment is skewed heavily toward a small number of trial centers. “This is a widespread issue,” he says.

Roger Lewis, an emergency physician at the Harbor-UCLA Medical Center in Torrance, California who specializes in clinical trial design, agrees that more transparency about recruitment would help, noting that the efficacy of a treatment can vary according to how many patients are being treated at a given location. For example, doctors who administer a surgical technique to a high volume of patients become more adept at the procedure, possibly making the intervention more effective. Because of this, he says that small centers may not have great success implementing results from large centers, so it’s important for them to have access to data about subject distribution in trials.

However, some researchers say there is already enough information out there about trial recruitment success for the drug companies that rely on it. “It is not immediately obvious what value public disclosures would be” for sponsors, says Richard Schilsky, deputy director of the Comprehensive Cancer Center at the University of Chicago. Schilsky points out that study sponsors, such as pharmaceutical companies, already ask that trial centers maintain recruitment logs and that the information is shared across the drug development industry.

Steven Nissen, a cardiologist at the Cleveland Clinic in Ohio, says that although

transparency is always positive, reporting center-specific recruitment data could have unintended negative effects. According to him, making it easier to do regional subgroup analyses is not necessarily productive and could lead people to focus on statistically underpowered outcomes from subsets in the trial. “The best measure is the primary endpoint,” he says. “You don’t want to make it easier to go fishing.”

It’s not that patients and sponsors shouldn’t be allowed to see how the clinical sausage

is made, Nissen says, but rather “there are so many intangible factors that vary from study to study. If a center doesn’t perform well on recruiting for one study, it may be because [the study] was not a good fit for the facility or its patients.” Nissen cautions that if individual centers did begin publicly reporting recruitment figures, people might extrapolate too quickly and blacklist centers or physicians on the basis of poor recruitment in a given trial.

Rebecca Hersher

Fifth time’s the charm?

Perseverance is a virtue. After seeing its experimental drug rejected four times over five years by the US Food and Drug Administration (FDA), Discovery Labs, a small Pennsylvania biotech, is once again seeking regulatory approval for Surfaxin (lucinactant), a liquid medication for the treatment of respiratory distress syndrome in premature infants. The FDA repeatedly raised concerns about Surfaxin’s manufacturing procedure, issues that Rusty Clayton, Discovery Labs’ head of research and development, says the company has finally resolved ahead of its fifth review date, set for early next month. “We’re working with the FDA,” Clayton says. “Sometimes it takes six months, and sometimes it takes six years.”

Discovery Labs is hopeful this time around—and history could be on its side. According to Kenneth Kaitin, director of the Tufts Center for the Study of Drug Development in Boston, nearly all drugs

that have come before the FDA three times or more eventually win the approval they seek. Typically, FDA rejection letters contain a hint as to whether it sees a fundamental flaw in the experimental agent or whether the underlying issues can be addressed with new data. Thus, most companies figure out pretty quickly whether they can mend their applications; if there’s no fix, they usually abandon their products.

That has made prolonged battles with the FDA fairly unusual. In fact, the last drug to require five reviews to gain approval was New York-based Forest Laboratories’ inhaled asthma steroid Aerospan (flunisolide) in 2006. Here we survey the new molecular entities approved between 2008 and 2010 and detail how many rounds they endured before receiving a green light from the FDA.

Rebecca Hersher

Source: FDA PDUFA Reports FY2008-FY2010