Current Perspective

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RCTs: The Gold Standard's Future

Randomized clinical trials (RCTs) have long been appropriately the "gold standard" for clinical research. Properly designed and conducted, an RCT provides information that is accepted by stakeholders as statistically and clinically valid. In a randomized trial, participants are distributed by chance to different groups to compare different drugs, devices, or treatment plans. In order to be valid, the different arms of the trial should be comparable, with specific inclusion and exclusion criteria, and be powered (by an appropriate sample size) to address the predetermined study objectives. Ophthalmology has a rich history of RCTs —from Arnall Patz' trial of oxygen in preterm infants at risk for retinopathy of prematurity to clinical trials of new immunomodulating drugs.

Typically, drugs under development will undergo four phases of clinical trials. Phase 1 is a small trial to study purely safety and side effects. It is not powered or designed to study efficacy, and every person receives the drug—but at different doses. Phase 2 trials—true RCTs—are small scale, typically double-masked, and designed to explore effectiveness as well as safety and dosage. Phase 3 RCTs constitute large scale studies of effectiveness, safety, dosage, and comparisons to placebo or treatment alternatives. There are many design variants for phase 3 trials, and they are the largest, longest, and most expensive of the three phases. Phase 4 trials occur after the FDA has approved a drug and are meant to provide "real-world" evidence of safety and to identify rare adverse events not evident in phase 3. They are a form of postmarket surveillance studies.

RCTs have drawbacks, however. These particularly include:

Cost. The typical cost for phases 1-3 varies between $15 million and $60 million with occasional trials exceeding $500 million. Ophthalmology trials are among the most expensive, on average. The cost per patient in a trial can exceed $50,000.

Time. Each RCT phase has two major time sinks—time to enroll and time to follow the patients. Phase 3 trials typically run 2-4 years. Challenging enrollment processes and criteria can prolong the study.

As a result, studies show that 86% of clinical trials don't finish on time, and nearly half of trials don't meet their initial recruitment goals.

This was a subject of some discussion at the 36th annual J.P. Morgan Healthcare Conference in early January. The meeting included about 9,000 attendees representing over 450 companies and included leaders in the life sciences industry, emerging companies, technology innovators, and the investment community.

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While clinical trials are only a small part of the total cost of drugs and devices, they are a critical step in the development and approval pathway. Getting answers quickly and with high-credibility data benefits company, physician, and patient alike.

The Academy's IRIS Registry may have an important role to play. As a vast repository of clinical data, it can identify potential study-eligible patients and help monitor and facilitate patient enrollment in RCT phase 2 and phase 3 trials. It can have a particular utility in phase 4 or postmarket surveillance studies. The IRIS Registry can help monitor and analyze what is happening in the real world of drug and device use to recognize or search for previously unrecognized safety issues and compare outcomes from rigidly conducted RCTs to what is seen in real-world clinical practice. As an example, IRIS Registry studies have demonstrated that clinicians employ anti-VEGF drugs differently in clinical practice than in clinical trials—and the treatment results can be different. This helps inform and modify subsequent recommendations for patient management.

RCTs remain the gold standard. New registry data analytic capabilities should serve to provide a real-world perspective on the application of RCT results and thus benefit all parties engaged in patient care.

EXTRA **MORE ONLINE.** For more about the IRIS Registry, see aao.org/eyenet/article/all-about-trust?november-2018.