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CLINICAL RESEARCH

Conducting a trial

Beginners hoping to initiate and complete a clinical trial must understand the complexities of the process.

BY KELLY RAE CHI

Before Edward Chu entered his fourth year at Icahn School of Medicine at Mount Sinai in New York, he took a 12-month sabbatical to launch his first clinical trial. He wanted to evaluate whether patients using an anti-blood-clotting drug, usually to prevent heart attacks, should stop before general surgery. He thought that if he dedicated himself to the project for 12 months, he could wrap up any loose ends before he graduated in 2013. That was optimistic, to say the least.

Chu admits that his goal — to recruit 200 patients, half of whom would continue taking the drug before surgery while the other half discontinued it — was ambitious for a year-long project. His adviser offered guidance throughout, but the day-to-day logistics were up to Chu.

Even with an encouraging adviser, financial support from a Doris Duke Clinical Research Fellowship and access to hundreds of potential participants, planning the trial was far more time-consuming than Chu had expected. All investigators need help from specialists and other partners to embark on a clinical trial, but especially first-timers. Although leading a trial often falls to senior researchers, junior investigators training as physicians or undertaking PhDs can have a major role — especially if they are hoping to make clinical studies a big part of their career. Chu needed assistance at almost every step — from his adviser, support staff such as nurses and research coordinators, biostatisticians, members of regulatory review boards, surgeons and cardiologists. In the end, he had to scale the work back into a pilot study, but the experience taught him a great deal about what it takes to make a trial happen.

FIRST STEPS

Initiating and sponsoring a clinical trial to generate safety and efficacy data for a drug, diagnostic test, device or therapy protocol is an all-consuming team project. The planning stages, which involve transforming an idea into a detailed protocol, assessing and procuring resources and getting approval to do the study, are almost always more complicated and time consuming than a junior investigator expects. They involve multiple reviews from regulatory agencies, and a sometimes gruelling effort to motivate busy clinicians — who often have little stake in the outcome — and their staff, key collaborators who help to provide access to a pool of patients. All these moving parts require careful orchestration. For a new ▶

investigator, each step of a clinical trial represents an important learning experience, says Karen Zier, associate dean for medical-student research at Mount Sinai, who helped to pair Chu with his adviser. These are not lessons that trainees can learn solely from a textbook.

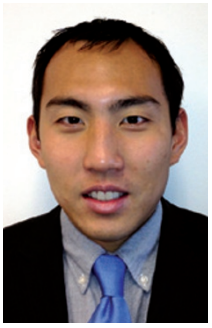
A clinical trial starts with a scientific question. But before designing the trial, researchers must have an idea of whether it is feasible: they must transform the idea into a testable hypothesis; consider the target patient population; and determine the appropriate time frame in which to get results, says Edward Kim, chair of solid-tumour oncology and investigational therapeutics at Levine Cancer Institute in Charlotte, North Carolina. Feasibility analysis is often handled by clinical-research coordinators or other experts at the investigator's home institution, who can help the investigator to decide, from a financial and operational standpoint, whether the study goal is realistic. "There are many cases when you can have a great scientific idea, but it's not practical [to do a clinical trial]," says Kim. Failure is likely, he says, if a trial has too many rigid requirements for patient inclusion, or is too complex to attract or treat enough patients. Junior investigators should talk to mentors and experienced clinical researchers in their field to help them to decide whether an idea is realistic.

Just calculating the appropriate number of participants can be a challenge, says Norma Terrin, director of the Research Design Center and the Biostatistics Research Center at Tufts Medical Center in Boston, Massachusetts. A biostatistician or epidemiologist can help. Other concerns include whether to do a blinded study (in which the participants, researchers or both are unaware of which treatment is being administered), a randomized one (in which participants are assigned to a treatment group by chance) or both; whether there are any potential sources of bias; how researchers will analyse the data; why data might be missing (reasons include patients dropping out of the study or not complying with protocols); and how researchers will deal with missing data points. With due consideration, the study can be designed to minimize data loss, says Terrin.

FINANCIAL STRUGGLE

Trials can be expensive: they range from tens of thousands of dollars for small studies to several hundred million for large, multicentre trials, according to a 2010 report from the Institute of Medicine in Washington DC (Forum on Drug Discovery, Development, and Translation *Transforming Clinical Research in the United States* National Academies Press, 2010). Costs vary from nation to nation owing in part to differing regulatory standards and patient-recruitment practices. Even within a single country, institutions bill in different ways for insurance, lab tests and supplies, staffing and other study costs. This combination of factors makes financing a major hurdle.

Early-career investigators might be able to get their own institutions or foundations to provide small start-up grants — typically ranging from US$20,000 to $50,000 — to fund collection of preliminary data. At the MD Anderson Cancer Center in Houston, Texas, for example, the Duncan Family Institute Seed Funding Research Program awards $50,000 per year for two years to support preliminary research on cancer prevention and risk, with the goal of improving the success of proposals submitted for larger grants. And some of the 60 institutions supported by US National Institutes of Health Clinical and Translational Science Awards (CTSAs) provide money for pilot studies. For example, the Institute for Clinical and Translational Science at the University of Iowa in Iowa City offers up to $50,000 for a preliminary study lasting no longer than one year. There is a wide range of CTSA start-up grants, from a small amount to screen an assay to larger amounts to get projects off the ground, says Bobbi Gardner, a spokeswoman for the National Center for Advancing Translational Sciences in Bethesda, Maryland, which administers the CTSAs.



E. CHU

"A study can fall by the wayside unless someone is there to push the protocol and research agenda."
Edward Chu

The figures are similar in other countries. Cancer Research UK, for example, offers feasibility-study grants of around £25,000 (US$40,000) a year for two years. In rare cases, it might provide as much as £80,000.

Many institutions, including those with CTSAs, fund shared clinical-trial resources in the form of, for example, a biostatistics department, a study facilitator or coordinator, or specific programmes. Foundations run by patient advocates — who are often impatient with the slow pace of clinical research — not only fund clinical trials but also support them by, for example, helping to recruit participants. If a trainee's institution has no track record in clinical research, there is the possibility of collaborating with a researcher at one that does.

Then there are industry partnerships: companies will often fund clinical trials of their own drugs or devices. Junior investigators should keep in mind, however, that involving industry can mean that it takes longer to sort out reimbursement, data sharing, intellectual-property issues and any extra reviews required legally or by the company itself.

Before putting together a team or enrolling patients, clinical-trial investigators must secure regulatory approval for their study plan. The specifics of the approval process vary by country and even within countries, but the basic goal is the same: to protect the safety of research participants. Protocols should be written according to the local version of Good Clinical Practice, an international standard for designing and carrying out clinical trials, provided by International Conference on Harmonisation in Geneva, Switzerland.

In some countries, including the United States, Australia, Japan, New Zealand and South Africa, the protocol is usually examined by an institutional review board (IRB) affiliated with the investigator's hospital or medical centre. IRBs uphold federal, state and local regulations and university policies. Each board interprets regulations differently, so multisite studies involving more than one board are often complicated. As a general rule, researchers should make their protocols extremely easy to understand — members of review-board panels will not necessarily be familiar with the subject area.

Researchers must be prepared to justify every aspect of a protocol; for example, if it calls for four biopsies, the investigator must be able to explain the reason for each. If the IRB thinks that the risks of any of the steps outweigh the potential benefits, it will ask for changes. This back-and-forth can take months, and it doesn't end there: IRBs often ask for update reports at regular intervals during the trial.

Researchers in the United States may also need to allow an extra one or two months to file an application for an investigational new drug or investigational new device to the Food and Drug Administration (FDA), which will do a safety review. This step doesn't just apply to new pharmaceutical compounds: it may also be necessary if, for example, an investigator is using a nutritional supplement to treat a disease; in that case, the supplement is technically a new drug and requires an FDA review, notes Harvey Arbit, a regulatory-affairs consultant who lectures at the University of Minnesota in Minneapolis. Complicating matters, the wording of the protocol may influence whether filing is necessary: if the filer states that the supplement is "normalizing physiological functions" rather than "treating", the decision becomes more difficult. There is no foolproof way to decide, says Arbit — when in doubt, it is safer to file. Even if the investigator does this but ends up receiving a letter from the FDA stating that filing was unnecessary, it is good to have the documentation.

THE RIGHT PEOPLE

Chu's goal of enrolling at least 200 patients in his study meant that he had to work with multiple clinical specialists. But he found it daunting, especially as a newcomer, to approach cardiologists and surgeons individually to sell his study. Specialists tend to be sceptical of studies and protective of their patients — and Chu's study had associated risks. But after

approaching many physicians, he was eventually able to get about a dozen on his team.

Clinicians help to identify patients eligible for the study. Crucially, they can boost recruitment by mentioning that they are excited about the project, says Jeff Burns, director of the Clinical and Translational Science Unit at the University of Kansas Medical Center in Kansas City. But the next steps of enrolment — pre-screening the patients by reviewing medical histories, approaching them to gauge interest, discussing protocols and informed consent, and setting up in-person screening visits — require a huge amount of work. A common mistake is for novice investigators to rely too much on the clinician's office to sign up patients. Clinicians and their staff focus on treating patients, not research; as a result, a study can fall by the wayside "unless someone is there to push the protocol and research agenda", says Chu. Enrolment should be monitored at each step by a team member fully invested in the study — perhaps the principal investigator, a trainee physician doing a medical residency or a medical student. Researchers with sufficient funds can hire a dedicated recruitment coordinator to screen prospective participants for any reasons they should be disqualified from the study, as well as to explain the study and its risks and send out consent forms.

RECRUITMENT DRIVE

It took Chu six months to design his study, get IRB approval and assemble a research team. Only then could he begin recruiting patients and collecting data. A few months into data collection, he ran a preliminary analysis that revealed that he would in fact need several hundred participants in each study group to provide a significant result. By the end of his fellowship year, he had enrolled only 50.

One problem was that a potential participant's cardiologist and surgeon often disagreed about whether they should discontinue or continue the anti-platelet medication, so Chu could not invite that person to participate in the study. Furthermore, potential participants' medical histories were often more complex than anticipated, making it difficult to determine who was suitable for the trial.

Enrolment challenges are not unusual. A 2011 study found that nearly one-third of clinical studies terminated at Oregon Health and Science University (OHSU) in Portland between 2006 and 2009 were under-enrolled for various reasons; such terminations cost OHSU at least $1 million in 2009 alone (D R. Kitterman *et al. Acad. Med.* **86**, 1360–1366; 2011). Low recruitment is a big problem in the United States and elsewhere, says William Balke, a programme director of clinical-research services at the University of California, San Francisco (UCSF). "If we don't do a better job [at recruitment], we're wasting the public's money and we're not advancing science," he adds. One reason for the problem is a lack of thorough feasibility analysis to determine, for example, whether there are enough patients to do the desired study.

Some institutions run formal recruitment programmes; for example, UCSF has a Recruitment and Implementation Core, which serves the university and affiliated investigators. Investigators can also turn to online participant registries and tools such as ResearchMatch.org — a free online service that connects volunteers with researchers — or even use less conventional communication routes, such as social media. "We have been extraordinarily, surprisingly successful recruiting patients through Craigslist and keeping in touch with them through e-mail, text messages and Twitter," says Balke.

But researchers need to exercise caution when reaching out to patients through social media. Rahlyn Gossen, founder of Rebar Interactive, a digital-marketing company based in New Orleans, Louisiana, which recruits and retains study subjects, says that researchers' messages to potential participants need to be approved by the local IRB, regardless of whether they are online. Regulations on patient recruitment were not written with social media in mind, so Gossen recommends that investigators check with the board before they submit their official protocol for approval. "Some boards might allow you some variation, but I've also run into some that won't let you post on social media at all," she says.

"If we don't do a better job at recruitment, we're wasting the public's money."
William Balke

At the end of Chu's clinical-trial year, he and his supervisor decided to turn the trial into a feasibility study, to be completed while Chu finishes medical school. Still, he feels that he accomplished a lot in one year — and he learned a lot about the complexities of the clinical-trial process. Now in his fourth year of medical school, Chu is still enrolling patients and collecting data, and is looking forward to launching a new clinical trial in the future. "It's a learning experience," he says. With the understanding he has gained, Chu expects his next trial to be "easier to manage". ■

Kelly Rae Chi *is a freelance writer based in Cary, North Carolina.*

FUNDING

NSF grant changes

The US National Science Foundation (NSF) has changed some of its grant-submission requirements, effective from 14 January. The project-summary section of the submission now asks applicants to use separate text boxes for their proposal overview, their description of the project's intellectual merit and their explanation of its broader impacts. Submitting these sections as one document will cause the application to be rejected. NSF spokeswoman Maria Zacharias says that reviewers were spending too long teasing out the merits and impacts of proposals. Applicants may also now list research products such as patents, data sets or software in addition to publications — a boon for junior investigators, says Zacharias. The changes stem from a review by the NSF's oversight board, and a federal directive that the agency recognize the broader impact of research it supports.

TENURE

Respect for librarians

Many more US university librarians should be tenured faculty members, argue groups representing universities and colleges, academic libraries and professors. A statement released on 10 January and spearheaded by the American Association of University Professors in Washington DC notes that librarians support research needs, contribute to intellectual and academic freedom, perform outreach and should have a right to contribute to university policy. "There's a lack of recognition as to what librarians actually do," says Deanna Wood, an associate professor and reference librarian at the University of New Hampshire in Durham and part of the Joint Committee on College Library Problems, which drafted the statement.

SALARIES

Academic pay lagging

Early-career scientists with full-time jobs in US academia earn an average of US$58,000 annually, less than those in industry, non-profit or government, says a report from the US National Science Foundation (NSF). Industry pays the most: $100,000 per year in early career, and $130,000 for those 10 years past their PhDs. Academics who got a doctorate a decade ago or more earn $93,000 a year on average. Daniel Foley, a statistician for the NSF in Arlington, Virginia, says that the data underscore the need to train researchers for work outside academia.