Cancer Clinical Trials Exclude Too Many Patients: That's Changing

Calls for equity, inclusion and better access boost pre-pandemic efforts to open up eligibility, streamline trials.

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The good news? Enrollment in new cancer therapy clinical trials has returned to normal, at least within one large trial network, a year after the pandemic began.

The bad news? Normal trial enrollment isn't that great.

Many close for lack of patients. Others slow to a crawl as scientists scramble to find additional volunteers, leading to longer trials, higher costs, delayed results and less reliable data. Size matters in science. The more people in a trial, the more reliable the data scientists collect. And the more people who qualify, the higher the likelihood the study will reflect the real-world population that will eventually use a new drug or therapy.

But far too many cancer patients can't participate due to overly restrictive trial criteria, say leading cancer organizations and scientists like Dr. Joseph Unger of Fred Hutchinson Cancer Research Center, whose new study in JAMA Network Open showed there was little evidence of enrollment reductions to treatment trials during the entire first year of the pandemic.

Forget COVID-19, it's the eligibility criteria that keeps most cancer patients out of trials, limiting both access and representation by routinely rejecting older patients; patients with additional health conditions like diabetes, heart disease, hepatitis, HIV or other cancers; or those who have poor "performance scores," a measure of physical functionality.

Patients with brain metastasis — stage 4 cancer that's spread to the brain from its original location — still can't enroll in most trials. Ditto for those without "measurable disease": Researchers need to be able to see and measure the cancer so they can tell if a treatment is working or not. Tumor too small or not capable of being imaged? You're out. Too many lines of treatment? Sorry, you don't qualify either.

Patient safety is at the heart of most exclusions, but too-tight criteria end up keeping out the patients most in need and exacerbating existing cancer health disparities. Comorbidities, or additional diseases, like heart disease and diabetes are more prevalent in Black, Hispanic/Latino

and Indigenous populations.

“The whole system is ripe for an overhaul,” said Unger, a biostatistician and health services investigator whose research, often in collaboration with the SWOG Cancer Research Network, focuses on barriers to trial participation. “We need to make trials more accessible to patients. It’s not the patients who are the issue, it’s the system.”

Now that system is finally starting to change. Some shifts were prompted by the pandemic; others were long in the works and just now coming to fruition.

Here’s the lowdown on how Hutch researchers are helping to make clinical trials more inclusive for all.

Cancer ‘Olympians’ vs. real-world patients

Cancer trials have largely been driven by drug development and the pharmaceutical industry. But pharma, which conducts many of its trials outside the U.S., doesn’t conduct all cancer trials. Some can be small, run by a sole investigator at an academic center; many are sprawling multicenter trials funded by National Cancer Institute and run through its National Clinical Trials Network, which encompasses SWOG, the ECOG-ACRIN Research Group and other large trial groups.

Through his research, Unger has found cancer patients will join a clinical trial 50% of the time if there’s one available and they qualify for it; all clinicians need do is ask.

But there’s the rub. The criteria often exclude the willing — and even the top cancer expert in the country acknowledges it.

“We don’t need needless eligibility criteria,” said NCI Director Dr. Ned Sharpless during a recent virtual conference on modernizing cancer trials. “Even the pharmaceutical industry is starting to accept it’s bad for everybody — for patients and for progress. The eligibility has to make sense for the trial. [Eligibility criteria] are important to include, but you can’t just copy and paste them from your last trial.”

But many researchers do reuse trial criteria again and again, continually creating studies that only accept the healthiest participants, or as one advocate calls them, “cancer Olympians.”

Dr. Gary Lyman, an oncologist and public health researcher with the Hutchinson Institute for Cancer Outcomes Research, said patient participants who are extremely healthy despite a cancer diagnosis produce the best trial results. Not surprisingly, pharma prefers these patients.

“They want to put their best foot forward by only using low-risk patients in trials,” said Lyman, whose research focuses on health care quality and policy. “If they have their choice, they want Olympians on their studies.”

But super-healthy cancer patients don't reflect the real world, where patients can be overweight or have diabetes or a cancer that's metastasized to their brain. Or all of the above.

"Brain metastasis has been an historical exclusion," said Lianne Kraemer, 44, a former pediatric speech therapist from Chicago who has metastatic breast cancer, or MBC, but only in her brain. "In the five years that I've had brain mets, I've seen only a slight change. Now they allow people with what they call 'stable brain mets.'"

That's not enough, she said. Too many drug companies regularly exclude these patients from trials, choosing to run separate trials to see how a drug will perform first in the body and then the brain.

"It's appalling that this has been going on so long," said Kraemer, who admits she's running out of options. "Think of all the people who are so desperate and they can't participate in trials. It's not a small thing when you exclude that many patients. Excuse the pun, but it's a no brainer."

A member of the MBC Alliance and its effort to improve outcomes for those with brain metastasis, Kraemer points to patients with triple negative breast cancer who face a 50% risk of mets in the brain.

"Metastatic disease is a systemic disease and that means the brain," she said. "We should be looking at drugs in the body as a whole. And pharma companies could have separate cohorts at Phase 1, so if these patients do poorly, it's not going to affect the whole trial."

Revamping trial criteria

In 2016, the American Society of Clinical Oncology, Friends of Cancer Research and the U.S. Food and Drug Administration addressed some of these issues, producing new FDA recommendations for trials enrolling patients with brain mets, HIV, organ dysfunction and prior cancers.

But Lyman, who is part of the ASCO/Friends' collaboration, said it's up to whoever runs a trial to use these recommendations — or not.

"They've been adopted in certain cases but not in others," he said. "There's much more awareness that we need to open up criteria, but the uptake has been very spotty. You still won't find many regulatory [pharma] trials for the FDA including patients with brain mets."

Recently, the group worked with research sites, patient advocacy groups, the NCI's trial network and industry to identify additional areas to revamp. These included washout periods (a so-called "holiday" from any other drugs pre-trial), concurrent medications, prior therapies and performance status.

They published recommendations for each category followed by a summary published in the May issue of the journal Clinical Cancer Research. A companion modeling study illustrated how

profound these changes could be. Of 10,500 patients with late-stage non-small cell lung cancer, the broadened criteria would allow 98% to participate in a trial, while the traditional rules would allow just 48%.

Opening trials up to sicker patients

Lyman, who is part of the performance status working group, said he believes the new recommendations will make a huge difference in enrollment, particularly the decision to open cancer trials to patients with a performance status score of PS2.

The performance status scale measures a patient's functionality, ranging from 0 — fully active and healthy — to 5, dead. PS2 patients are "ambulatory and capable of all self-care" but are unable to work. These patients are also traditionally excluded from trials. But that's now changing.

"Some PS2 patients won't be good candidates for experimental therapies but some may be successfully treated," Lyman said. "The idea is to not use PS2 by itself to exclude a patient. We're advising they completely evaluate the patient and make the best clinical judgment."

The group has also endorsed alternative trial designs that would include lower-functioning patients but exclude them from the primary analysis of results. The side effects may be higher in these patients, Lyman said, so there could be less-encouraging results.

"I'm not sure how the pharmaceutical industry will embrace this," he said. "The FDA may have to nudge them. But once drugs are approved and on the market, there won't be restrictions. Patients with comorbidities and those with poor PS scores will be using them. We need to know how a broader range of patients respond to these treatments."

What about the elderly?

Another population routinely excluded is the elderly, said Hutch hematologist and clinical researcher Dr. Mohamed Sorror, whose research focuses on them.

"In my specialty of blood cancers and stem cell transplant, most of the studies have been done in younger, healthier patients," he said. "Then the results are applied to older and frail patients, ones with multiple comorbidities."

Sorror believes elderly patients should be treated differently, just as pediatric patients are.

"When it comes to adults, we mix everybody in one bag," he said. "From 20 and above up to 70 and 80 years old, thinking it's fair, but that's not fair. Patients 65 and above are different from younger adults. Their health is different. Their goals of therapy are different. Even their cancer is different."

So Sorror is creating trials just for this population. He even recently put a trial together that

purposefully left out younger, healthier patients.

“This study was for the ones usually excluded — blood cancer patients getting bone marrow transplants,” he said. “We looked at what we could do with additional supportive care to not just prolong survival but improve their quality of life. We’re trying to minimize changes where they lose function or become dependent after treatment and have to go to a nursing home facility. We don’t want to cure the cancer but give them problems for the rest of their life.”

The trial has three different interventions compared to standard of care. One group will receive supportive (also known as palliative) care, with patients seeing a specialist weekly for 10 weeks during treatment. The second group will have the patient work with specialists who will create a personalized program of care with exercise, strength training, diet and breathing exercises patients can do on their own to stay fit and functional during treatment. The third group will receive both interventions.

Trial accrual was impacted by COVID-19, but he said he’s hoping to add additional sites to bring in more participants. He also hopes the study will spawn a more robust geriatric oncology program at the Hutch.

“Fred Hutch has always led research in blood cancer and transplants,” he said. “We should also lead in creating and expanding geriatric oncology. If we build something specific for older and frail patients, we’re doing ourselves a great service for our patients and our investigative community.”

Relationships and recruitment

The Hutch is also taking steps to boost the recruitment of historically marginalized ethnic-minority populations into trials, said Elizabeth Carosso, research project manager with the Fred Hutch / University of Washington Cancer Consortium’s Office of Community Outreach & Engagement.

Carosso manages the OCOE’s new Recruitment and Retention Resource, designed to teach investigators at the Hutch, UW and elsewhere how to better build and maintain relationships with partners in Black, Indigenous and other communities of color so they can better serve their health needs. It’s an objective researchers have discussed for years.

“Everyone just kept saying, ‘Yeah, that’s a big problem,’ and then continued to do what they’d always done,” Carosso said.

The pandemic and a growing awareness of structural racism, even within scientific research, changed everything.

“When I came back to the Hutch after four years at a different organization, I walked into a different world,” she said.

The OCOE now has an online intake form for investigators hoping to increase participation by

people of color in cancer and other clinical trials. They also offer help with trial design and initial planning, with Carosso strongly recommending investigators check in before they even start putting together a proposal. Building in inclusive practices from the get-go is best, she said.

“We get requests once everything has been funded and they’ve failed to enroll the participants they hoped for,” she said. “By then you can’t make suggestions about budgets or subcontracts to integrate a community partner. Doing that late in the game is more difficult.”

The OCOE’s community health educators and program leads are also creating a series of videos with tips on how to work with Indigenous, rural, African American, African-descent and urban communities as well as how to conduct community-based participatory research. The OCOE also invites researchers to present proposals to community advisory boards for feedback.

“They get very honest feedback from the community coalitions,” Carosso said. “They don’t just nod their heads. They say ‘Change this wording’ or ‘Consider providing more of an incentive.’ They bring up childcare, transportation, time off from work, all the day-to-day challenges that a lot of investigators don’t realize participants have to deal with.”

Carosso said change is definitely happening. The Hutch IRB, the Institutional Review Board that determines whether a clinical trial can go forward or not, has also become involved, “referring multiple investigators to complete our intake form.”

For Carosso, it’s past time for crucial changes that will help move the science forward.

“There will never be trust, there will never be change, until you build a relationship,” she said. “These disparities are never going away if we wait for someone else. Every single one of us — the investigators, the IRBs, all of us — have to take action.”

More changes coming?

Additional changes may be coming down the pike, as well, particularly as researchers validate the legitimacy of pandemic workarounds.

“There was guidance put out by FDA and NCI about how to make trials more flexible during the pandemic,” Unger said. “Things like allowing remote consent and remote visits and having local providers do assessments of care instead of having trial participants go to big academic centers.”

Unger calls these “good changes” and believes they’ll be adopted long-term. “If it turns out that we get the same quality data,” he said. “I can easily see a push to make this routine when the pandemic over.”

The ASCO/Friends video session with Sharpless and other national experts mentioned additional aspirations: increased telemedicine; engagement with electronic health records, electronic consent; trial drugs shipped to patients’ homes, simulated or synthetic control arms to cut cost

and speed development, and more.

“We’re really impeded by too much trial bureaucracy and unnecessary repetition of all kinds of things,” said FDA Acting Commissioner Dr. Janet Woodcock in the video. “There are many opportunities to streamline.”

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