from falling barricades, they also prevent medications from penetrating underneath. So, several companies are developing new tricks to get the antifungals where they're needed.

For example, both California-based Apricus Biosciences and Bermuda-based Celtic Pharma have topical versions of the oral stalwart terbinafine now in phase 3 development. MycoVa, from Apricus, takes advantage of a technology called NexACT, which loosens the tight junctions between cells and helps the drug pass through cell membranes, allowing more of the medicine to penetrate the nail, while Celtic's TDT 067 employs lipid vesicles to carry terbinafine through the nail. "That's a very interesting concept," says Bárður Sigurgeirsson, a dermatologist at the University of Iceland in Reykjavík, who is involved in the TDT 067 trial. "You are building a ferry."

Like most topical drugs for onychomycosis, though, even these products with advanced delivery systems must be applied daily. Most studies ask participants to apply the medications for 48 weeks. "That is the pain-in-the-butt factor," says Boni Elewski, a dermatologist at the University of Alabama at Birmingham who was involved in the phase 3 trial of efinaconazole.

To ease the burden, some companies are now developing lasers that use near- or mid-infrared light to kill fungi. With such 'phototherapy', researchers hope to treat onychomycosis with just a few applications, although published evidence of this effect is sparse.

One laser that has shown promise in a clinical trial is Noveon from Nomir Medical Technologies of Long Island, New York. The FDA has cleared Noveon for the general treatment of podiatric and dermatological conditions, but the device isn't yet specifically indicated for onychomychosis. In a trial that looked at infected toes two months after the last of four laser treatments, physicians at the Harvard Medical School in Boston found that 20 of 26 people treated experienced at least some improvement in the appearance of their toenails, with 17 showing at least 3 millimeters of clear toenail growth (*J. Am. Podiatr. Med. Assoc.* **100**, 166–177, 2010). A follow-up study published last year demonstrated that, five months out from final laser treatment, 3 out of 40 people achieved complete cures, and an additional 12 were free of the fungus (*J. Am. Podiatr. Med. Assoc.* **102**, 169–171, 2012).

My father isn't likely to shell out hundreds of dollars for laser treatments, and he still worries about the possible side effects of the oral medications. For him, the infection is mainly an annoyance. What bothers him most is how quickly his jagged nails wear holes in his socks. However, if the FDA approved a topical medicine that was effective enough to give him a reasonable guarantee of a cure, he might try it. For now he'll do what millions of other people with nail infections do: grin and bear it.

***Cassandra Willyard***

# Publication checklist proposed to boost rigor of pilot trials

BOSTON — "Pilot studies are still poorly reported." So concluded a 2010 analysis of 54 papers across seven medical journals that looked at whether clinicians were providing suitable detail when describing their pilot studies—a phrase used to describe small studies in humans that assess the methods intended for larger and more expensive clinical trials (*BMC Med. Res. Methodol.* **10**, 67, 2010). Given the sorry state of the publication record, the authors worried that important information at the feasibility stage was getting lost, with potentially disastrous consequences for the entire clinical research effort. If researchers detailed their exploratory studies more accurately, late-stage trials would be better planned and executed. Perhaps then, fewer phase 3 studies—only around half of which come to a statistically significant result today—would end in failure.

To encourage better publication practices, a group of leading medical statisticians, research methodologists and applied clinical researchers in Canada and the UK is now championing a checklist of minimum reporting requirements for small-scale studies. "It's important to avoid duplication of efforts and wastage of resources for people doing things that others have already tried and have shown perhaps don't work," says Lehana Thabane, a clinical research methodologist at McMaster University in Hamilton, Ontario, and one of the organizers of the new guidelines. A preliminary version of the guidance was presented here at the Society for Clinical Trials annual meeting on 21 May.

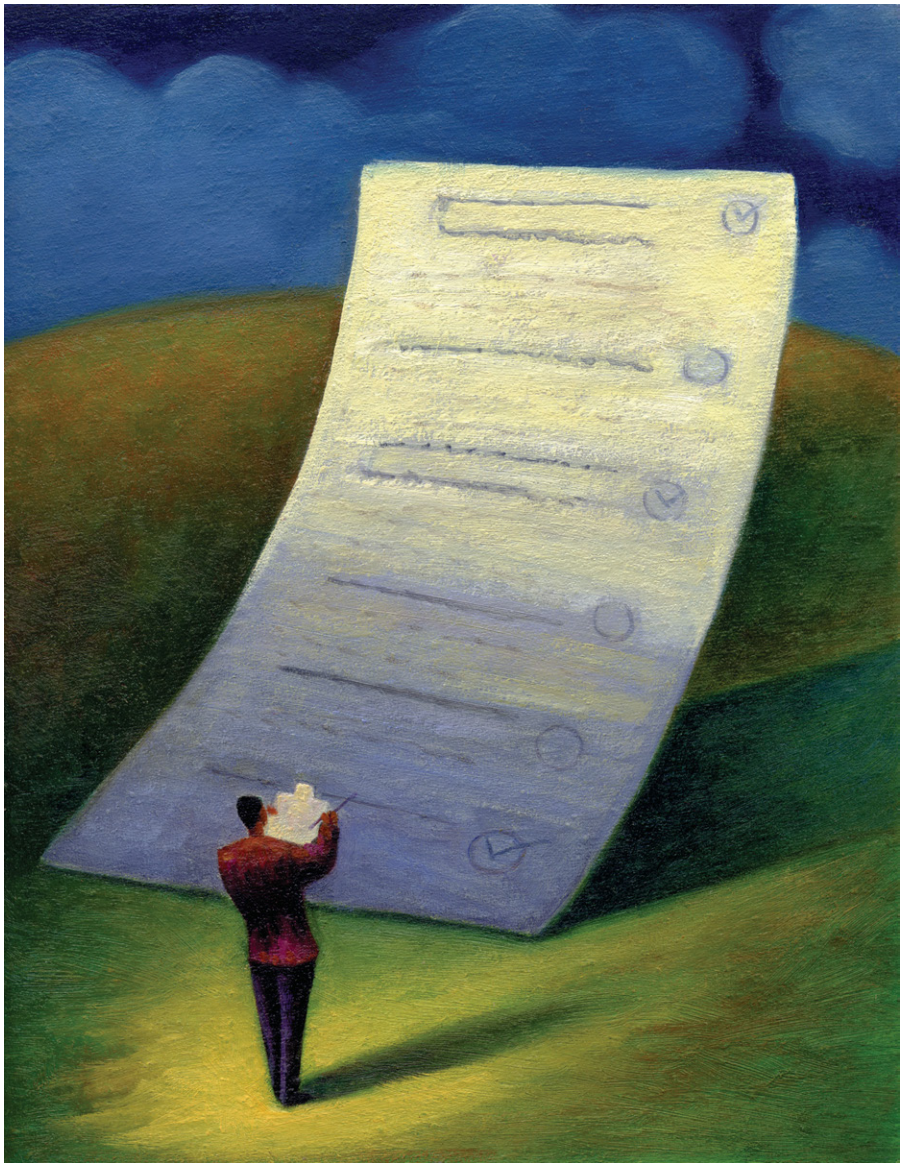
Thabane and his colleagues modeled the effort after the CONSORT Statement, a 25-item checklist and flow diagram to help scientists better summarize parallel-group randomized control trials. CONSORT, short for CONsolidated Standards of Reporting Trials, offers a standard way for authors to describe how trials are designed, analyzed and interpreted. The checklist includes, among other items, a point emphasizing the need to describe the eligibility criteria used to select participants for a study and several items surrounding the reporting of how investigators apply randomization and blinding protocols. The document, first published in 1996 and revised twice since, is widely thought to limit the influence of bias, aid in interpretation and improve the quality of research used in healthcare decisions. It is now endorsed by several leading editorial groups and more than 600 medical journals, including *The Lancet*, *BMJ*, *JAMA* and the *New England Journal of Medicine*. (*Nature* journals, including *Nature Medicine*, don't officially endorse CONSORT, but authors are encouraged to use the statement as a guideline.)

## Extended reach

A number of extensions to the CONSORT Statement have been published over the past decade to cover trials that are not large, parallel-arm clinical investigations. These include instructions on how to report other types of trial designs for pivotal studies, as well as guidance on more types of interventions, including acupuncture and other nonpharmacological treatments. An extension is now even in the works for trials involving traditional Chinese medicines. However, none of the CONSORT guidelines covers pilot or feasibility trials.

That's a problem, says Gillian Lancaster, a statistician at Lancaster University in the UK, because the recommendations of the existing CONSORT guidelines are not entirely applicable to most earlier-phase trials, even those that have small placebo control arms or involve some degree of randomization or blinding. "The objective should be different for a pilot study," she says.

Lancaster was one of authors of the 2010 analysis and a co-organizer of the new effort. In the 2010 paper, she and her colleagues found that more than 80% of pilot studies focused on efficacy testing, with most of these same studies finding the results 'inconclusive'



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**Checking it twice:** A final list to guide the reporting of pilot trials is expected next year.

and calling for further research. Those kinds of murky outcomes should not come as a surprise: efficacy testing in medicine requires a larger sample size than is generally included in such preliminary investigations. Lancaster and her fellow checklist creators say most pilot studies should stay focused on getting a sense of the process, resources and management needed for a full-blown trial. According to the proposed guidelines, the analysis of pilot studies should be mainly descriptive, outlining well-defined aims and objectives that highlight methodological rigor and scientific validity. "And most importantly, the lessons learned that could be useful in designing the main study," notes Thabane.

"My worry is that [pilot studies] are often interpreted as negative studies," Thabane says, "which would be inappropriate or even incorrect."

Mary Foulkes, an expert in clinical trial design and analysis at George Washington University's Biostatistics Center in Rockville, Maryland, who is not involved in writing the guidelines, says she would welcome such a checklist. "There can be a lot of ramifications and unintended consequences of this process," she notes. Besides improving scientific communication and transparency, just the existence of such a guidance document could inspire journal editors, who might not otherwise be attuned to the problems associated with pilot trial reporting, to publish more such studies. (Pilot trials often go underreported in addition to being poorly reported.) Plus, funding bodies might be prompted to support more such proof-of-principle trials.

### You say pilot, I say...

For now, one of the largest challenges facing the authors of the new guidelines is one of terminology. Modeled after definitions used by the UK's National Institute for Health Research, the checklist distinguishes between a pilot study—a version of the full-scale study run in miniature to test whether components of the main study can all work together—and a feasibility study, which can evaluate particular aspects of the research in isolation ahead of a main, all-encompassing study. It's a subtle distinction, and one that is often overlooked and many times intentionally ignored.

"There's really a divergence of opinion on whether the distinction between these two types of studies is either workable or useful," says Sandra Eldridge, director of the Pragmatic Clinical Trials Unit at Barts and The London School of Medicine and Dentistry in the UK, who is chairing the committee that is drafting the new checklist. In preliminary thinking-aloud usability testing, "quite a lot of people thought it was a good idea to split the definition, but some people found it very difficult to distinguish between the two." (To complicate matters, the terms 'vanguard' and 'exploratory' are sometimes used interchangeably with 'pilot' and 'feasibility', particularly in North America. The US National Institutes of Health does not formally distinguish between these terms, according to agency spokesperson Renate Myles.)

Between July and November of this year, the draft checklist—with pilot and feasibility studies split up—will be further refined through an online Delphi study, a type of structured survey designed to reach consensus, in a targeted group of around 100 experts in the field. Final guidelines are expected to be presented at the Society for Clinical Trials meeting next year.

Then the real work begins, notes David Moher, a clinical epidemiologist at the Ottawa Hospital Research Institute in Canada and a member of the three-person CONSORT executive committee. "Part of the issue is not simply developing the guideline. There are a whole bunch of issues around implementation," he says. For instance, journal editors will need to get behind the effort, and study authors will need to know how to meet the new requirements. Moher's advice to the organizers of the new checklist: "They ought to have a very worked-out plan of endorsement, adherence and advice to journals."

*Elie Dolgin*