

Giving patients better access to trial information

Patients and many other members of the public have much to gain from a global clinical trials registry initiative launched by WHO. On 19 May, WHO unveiled the rules under which pharmaceutical companies and others doing research must disclose 20 sets of data when they register clinical trials they are planning to do (see boxes on pp. 430–431).

Paul Gelsinger, vice president of Citizens for Responsible Care and Research (CIRCARE), a US patients' advocacy group, knows about the shortcomings of clinical trials. Seven years ago his son Jesse participated in a trial of a gene therapy treatment for ornithine transcarbamylase (OTC) deficiency — a condition which kills one in two newborns affected in the first month of life. Jesse, 18 years old at the time of the trial, wanted to give something back to the doctors who had helped him through his first difficult weeks of life. The doctors injected a normal OTC gene spliced with a virus into his liver. His liver hemorrhaged. On 17 September 1999 he died.

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Nikos Dedes of the European AIDS Treatment Group.

“It never occurred to me that the doctors might withhold information,” says Gelsinger, who later learned that two monkeys had died in tests involving a gene delivery system like the one used on Jesse, and that four humans had suffered liver damage earlier in the same trial. Gelsinger is convinced that if the database set up by the National Institutes of Health (NIH) and Food and Drug Administration (FDA) had been working as it should, the University of Pennsylvania trial would have been shut down long before Jesse's fatal participation.

It is partly to prevent such violations of patients' rights, that WHO launched a global network of clinical trials registers last month — the first step to establishing a web-based search platform available to the general public.

A primary objective of the network, known as the International Clinical Trials Registry Platform, is increased transparency by requiring any company or institution conducting clinical trials to register the details of how these are going to be done.

Companies or other institutions doing clinical trials will be obliged to disclose 20 items that describe the trial's protocol in the form of a standardized summary. Not everyone is happy about this obligation.

“There is a great deal of reluctance on the part of the pharmaceutical industry regarding full disclosure,” says Albert van der Zeijden, chair of the International Alliance of Patients' Organizations in the Netherlands and a keen supporter of the WHO initiative. “But the industry is well aware of the negative image it has at present, and this gives us an opportunity to demand a high level of compliance,” said van der Zeijden, referring to recent cases of companies withholding negative research findings that sparked public outrage.

Nikos Dedes, of the European AIDS Treatment Group, is similarly optimistic: “This is a unique opportunity,” he

says, “and no other organization in the world matches WHO's reputation and credibility.”

Indeed, there are reasons for optimism. Since September 2005, the International Committee of Medical Journal Editors (ICMJE), a body comprising editors from some of the world's most influential journals, has refused to publish trials not entered on a trials register. Publication of the results of trials in these journals is an important step towards getting regulatory approval for new drugs and other products from the FDA. That said, few in the advocacy community, van der Zeijden included, believe that the drug companies will register all the trials they are planning — as they should under the WHO initiative — without the threat of some kind of sanctions.

“It helps that medical journals withhold results of anyone not registered, but that has more of an effect on academic players than pharmaceutical companies,” says Kathy Redmond, Editor of *Cancer World* based in Milan, Italy.

This is a view echoed by Karen Carey Hazell, Consumer Representative



All new medicines — such as the essential drugs pictured here — as well as diagnostics and vaccines need to be tested in clinical trials with human participants for safety and efficacy.

WHO

from the Consumers' Health Forum in Australia, who believes that, over time, registration will have to be made compulsory. "Either that, or other regulatory and funding mechanisms will have to penalize manufacturers that do not register," she says.

Medical and public health editors argue that the ability to publish results on clinical trials and, in future, secure FDA approval, provides some incentive for companies and other institutions to register ongoing any trials they are planning. "A degree of enforcement has been achieved by the requirement from the International Committee of Medical Journal Editors (ICMJE) for trials to be registered at inception if the results are to be considered for publication," Fiona Godlee, Editor of the *BMJ*, wrote in a *BMJ* editorial in May.

WHO and its partners also hope that theirs is a formula for success. The WHO initiative aims to bring together participating registers of clinical trials around the world in one global network. This will provide a single point of access to the information stored in them and a web-based search platform where members of the public can obtain basic information about ongoing and completed clinical trials, including contact details for the study.

The goal is to increase transparency and accountability on the part of companies and institutions that do clinical research, and, in turn, boost public trust and confidence in that research. WHO experts say that even once the platform is up and running at the end of this year, it will be important to continue the discussion on how to improve the system.

"The debate on trials registration will no doubt continue for many years to come. But now is the time for progress and action while continuing to allow for robust debate and reasonable disagreements," said Dr Tikki Pang, Director of WHO's Research Policy and Cooperation department.

Whatever the difficulties involved in dragging the pharmaceutical compa-

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No delayed disclosure for registration of clinical trials

In a major step towards making clinical trials more transparent and publicly accountable, WHO unveiled the disclosure rules for pharmaceutical companies and others when they register trials they are planning with human participants under the International Clinical Trials Registry Platform initiative.

WHO said on 19 May that there would be no delayed disclosure of any of the 20 key details that companies or other research institutions need to submit when they register clinical trials. WHO called on these research institutions to register all clinical trials prior to enrolment, regardless of the type of study, as participation for these institutions is voluntary.

WHO has already announced the 20-item data set (see box on opposite page), which must be provided when a trial is registered under the initiative.

The decision on disclosure rules comes after two years of consultations, culminating in a 26 April meeting with representatives from the pharmaceutical, biotechnology and device industries; patient and consumer groups; governments; medical journal editors; ethics committees; and academia.

During those consultations some groups raised concerns that academic or commercial competitive advantage could be jeopardized by the immediate disclosure when a trial is registered of five of the 20 items: the name of the intervention(s) tested; the primary outcome; key secondary outcomes; the target sample size; and the scientific title for registered trials.

But in the end, WHO concluded that registration and immediate disclosure of registered data prior to recruiting participants for all clinical trials — including early trials involving patients or healthy volunteers — were the only way to ensure transparency and fulfil ethical responsibilities to patients and study participants.

Commenting on the decision, Dr An-Wen Chan, who is helping coordinate the project at WHO, said: "This is a major step forward. We hope it will contribute significantly to making clinical trials more transparent and to enhancing public trust in science".

The clinical trials initiative comes in response to a growing chorus of scientists, academic leaders and editors of top medical journals calling for new standards and rules for the registration of all clinical trials, i.e. studies in which treatments are tested on humans.

Currently, there are several hundred registers of clinical trials around the world but little coordination among them. The WHO International Clinical Trials Registry Platform is a major initiative to bring participating registers together in a global network to provide a single point of access to the information stored in them.

For more information please see: <http://www.who.int/ictpr/en/> and for the link to a web site inviting public comments please see: <http://www.who.int/ictpr/comments4/en/index.html>

Fiona Fleck, *Bulletin*

nies to the registration table, few doubt the value of the exercise. Ironically, it is precisely the information drug companies are most sensitive about — the results of phase I and II trials — which patients facing regimen failures or resistance problems are most in need of.

"There are a huge number of novel targeted therapies in pre-clinical and early clinical trials," says Jan Geissler, vice president of the European Cancer Patient Coalition, and a cancer survivor himself. "Patients with resistant cancers often seek out these trials on the net as their last and only chance." Nor is this just

a matter of blind desperation. Geissler cites a recent study showing that on average the response rate to phase I clinical trials in cancer patients is over 10%. "In my personal case," Geissler adds, "I joined a phase I/II trial after I was diagnosed with a cancer which, five years later, 98% of patients are surviving. The standard treatment offered at the time would have given me a 40–60% chance of survival."

It's not everyone who can bounce back from a devastating diagnosis to go searching on the internet, and Geissler believes that such courage deserves better than it currently gets.

"The registers for ongoing clinical trials are frequently inaccurate, incomplete and out-of-date," he says. Meg Gaines, who once faced "salvage chemotherapy" as her only hope to survive ovarian cancer, and who now runs the Center for Patient Partnerships in Wisconsin, is similarly dismayed

How will the platform work?

The planned International Clinical Trials Registry Platform will not be a register itself, but rather will provide a set of standards for registers to follow to be internationally acceptable.

The project has set down 20 aspects about a planned trial that should be reported prior to recruiting participants in order to register that trial. These 20 items must all be publicly disclosed upon registration.

The platform is also developing a global trial identification system that will assign to every qualified trial a unique reference number to cross-reference duplicate records across registers and information systems worldwide.

The platform will create an internet search portal where scientists, patients, doctors, donors and anyone else who is interested can search among participating registers for information about clinical trials taking place throughout the world.

Visitors will not be able to enrol in a trial directly through the site, but they will find contact information for the person who can assist them with enrolment or any other queries.

The 20 items to be submitted when registering a clinical trial are as follows:

1. Name of primary register, and unique ID number assigned by the primary register to this trial.
2. Date of registration in primary register.
3. Secondary ID: other identifying numbers and issuing authorities.
4. Source(s) of monetary or material support.
5. Primary sponsor: individual, organization, group or other legal person responsible for the trial.
6. Secondary sponsor(s).
7. Contact for public queries.
8. Contact for scientific queries.
9. Public title: intended for lay public in easily understood language.
10. Scientific title of the study, as it appears in the protocol.
11. Countries of recruitment.
12. Health condition(s) or problem(s) studied.
13. Intervention(s).
14. Key inclusion and exclusion criteria for participant selection, including age and sex.
15. Study type: for example, single arm or randomized trial.
16. Date of enrolment of first participant, anticipated or actual.
17. Target sample size: number of participants that trial plans to enrol.
18. Recruitment status of this trial. Pending: participants are not yet being recruited or enrolled at any site. Active: participants are currently being recruited and enrolled. Temporary halt: there is a temporary halt in recruitment and enrolment. Closed: participants are no longer being recruited or enrolled.
19. Primary outcome(s).
20. Key secondary outcomes.

For full details please see: http://www.who.int/ictrp/data_set/en/index.html

by the state of available registries. "It's very hard for people in these circumstances, dealing with the terror of a fatal diagnosis, to trawl through the different sites and struggle with the scientific jargon only to find that the trial that seems to offer hope is no longer active," she says.

The internet is very good at bringing people and goods, or people and services together. Deborah Collyar, a two-times breast cancer survivor, now president of Patient Advocates in Research, believes that web services such as EmergingMed.com, have a great deal to offer. "You can

put your profile into the system and the search engine seeks to match you with trials currently going forward," she says. "It's very simple and very effective."

Such a system would certainly have helped the Italian man Kathy Redmond tells a story about. "He was a leukaemia patient who began to develop resistance to the drug Gleevec," she says. "The prognosis was bad so he went on line and surfed his way into Clinicaltrials.gov, the registry run by the US National Library of Medicine." It was there that he discovered that a trial looking at precisely the problem

he was experiencing was taking place in Toronto.

"He got on the plane and flew to Canada. When he arrived in Toronto he was told by one of the research staff that an identical trial was going forward in his home town, Rome. Italy has no clinical trial register. The man had no way of knowing what was happening on his doorstep."

If WHO's plan to bring together the world's clinical trials registries works, that brave traveller's doorstep is about to get a little closer to home. ■

Gary Humphreys, *Los Angeles*

In search of a sustainable philanthropy

Philanthropists are important funders of health care in developing countries, but their funding can be unreliable and misdirected. One philanthropist found that the best way to establish a health-care project of lasting benefit was to address unmet needs in the local health system, listen to the experts and work closely with local partners.

Nairobi, Kenya will soon see a brand new women's hospital offering free treatment to women. It comes courtesy not of the government, nor of the usual international aid agencies, but of an unlikely collaboration between a local obstetrician and the mother of the world's most famous basketball star.

Deloris Jordan, mother of Michael, has long been active in local philanthropy in the United States and her home city, Chicago, working through the James R. Jordan Foundation, named after her late husband. She first went to Kenya 13 years ago, bringing American children on a cultural visit. She

ended up bringing back a young Masai man and putting him through an MBA course. He has since returned to Kenya to build a tourism business in his community. Deloris Jordan has returned many times since, but her visit three years ago, she says, changed her life.

"I went back to Kenya in 2003, at the invitation of the vice-president, for the 40th anniversary of independence. I was invited to visit the Nairobi Women's Hospital with about 40 beds. The line outside was long, but they were all treated whether they had money or not. I met the staff there, and later when the hospital's founder Dr Samuel Thenya came to the United States on a visit, I flew to Washington to meet him, because I wanted to know why a young man would set up a women's hospital. I started working with him to try to get the hospital some equipment, including some of the things our hospitals throw away."

Mrs Jordan says she is determined that her project will be more than a rich person's plaything, or a pathway to recognition. "I found that working in Africa and especially Nairobi, it's vital

to learn about their culture, not trying to take over but learning from them what their needs are."

"I learnt a lot from my visit to London on World Health Day in April," she says, referring to the launch of *The world health report 2006: Working together for health*, which highlights the plight of 57 developing countries with serious shortages of health workers. "I wanted to learn how to really reach out into the villages, to truly make a lasting difference." She describes Mary Robinson, former president of Ireland and former UN High Commissioner for Human Rights, as a fountain of useful advice.

A key message that Mrs Jordan took from the WHO event was the need to retain staff in a continent

where health workers are continually seeping away in search of a better living abroad. "I found that some of Dr Thenya's health-care staff and nurses were looking for work abroad. This is, of course, a big problem in Africa. They need to feel needed there, and that they have a future there. They need decent benefits. It's the only way a project will last." One of the hospital's immediate goals is to set up an exchange programme to train nurses and other staff in the United States.

"For me, it's all about networking and partnership, not just here but also in Kenya. We talked to the mayor of Nairobi and the parliament about a better facility." The city council has donated land for a larger 150-bed hospital. The plan is to move the old hospital's staff to the new facility and replace much of the old equipment. Completion is planned for 2010, at an estimated cost of \$20 million.

"My main role was networking in the United States, to try to get some of this equipment that Pfizer and so on don't need. I later partnered with the Clinton Global Initiative. When (former) President Clinton visited Nairobi, they told him I'd been there, and he called me to find out what I was doing. He then began to help Dr Thenya, providing some medicines for the AIDS patients there."

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Deloris Jordan, philanthropist and mother of US basketball star Michael Jordan.



Mrs Deloris Jordan tours the Nairobi Women's Hospital and stops to chat with a patient, listening to her concerns about the availability of health care.

Doctor Thenya is no mean networker himself. He originally built the hospital as a private venture to cater to Nairobi's well-to-do women, using funds from 16 local doctors and health industry figures who became shareholders. But the charitable — and unprofitable — side of the hospital grew into a magnet for women from villages near the capital who have historically been excluded from gynaecological services.

So he cast his net wider, says Deloris Jordan. "He has partnered with some of the corporations there, including Coca-Cola and Nestle Tea. USAID is supporting him too."

Katherine Marshall, Director of the World Bank's Development Dialogue on Values and Ethics, and formerly responsible for the Bank's Africa programmes, says Mrs Jordan's project meets all the criteria for a sustainable project.

"It needs a long-term commitment, and this is often lacking in private philanthropy. I remember visiting a great AIDS clinic in Ethiopia that did wonderful work. They had a plaque listing all their private donors down the years, but it was striking how donors' names would appear for three or four years and then disappear as they lost interest. This left the clinic constantly scabbling for new donors."

"Also, the project should ideally address unmet needs in the health system. These are best identified by people who

live and work there, so it's vital to work closely with local partners. Normally, the best way to achieve this is to work within the existing health system. But it is possible, though difficult, to set up a hospital on its own that becomes a little jewel, and can serve to elevate the whole health infrastructure around it," Marshall says.

"I recently visited a hospital in Cambodia that fit this bill perfectly. There is an argument that working through health ministries just increases the opportunities for money to disappear," she says, referring to Sihanouk Hospital Center of HOPE in Phnom Penh, which counts among its sponsors Japanese philanthropist Toshu Fukami and rock singer Elton John. Indeed, health workers in Cambodia frequently estimate that 5–10% of the country's health budget disappears before it is even disbursed by the finance ministry.

While western governments have often seen millions disappearing down bureaucratic black holes, Deloris Jordan says her approach of working with local doctors and international companies with a Kenyan presence is the best guarantee against corruption.

As the only hospital in Kenya devoted to women's health, the Nairobi Women's Hospital certainly fills an unmet need. One of its key projects is the Gender Violence Recovery Center. A vital service is the free documentation of sexual assault. Rape victims in Kenya are often unable to lay charges because they cannot afford medical

documentation of the assault, which typically costs 14 000 Kenyan shillings (US\$ 190). The centre also provides free counselling and emergency contraception to rape victims.

"It's a great centre that does amazing work," says Nomi Fuchs-Montgomery, Kenyan Core Team leader at the US State Department's Office of the Global AIDS Coordinator.

Indeed, the success of this private philanthropic initiative is attracting some decidedly public interest. British Robinson, Senior Advisor for public-private partnerships at the State Department's AIDS project, says she would very much like to speak to Mrs Jordan "on how to further leverage her initiative by partnering" with the US President's Emergency Plan for AIDS Relief (PEPFAR). ■

Owen Dyer, *London*

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Global public health sees new crop of leaders

Change is in the air in global health. Many top posts in the world's international public health organizations have changed hands over the past year or two. And, as the *Bulletin* was going to press, the sad news came of the untimely death of WHO's Director-General Dr Lee Jong-wook at the age of 61, prompting the need for a change of leadership at the top of WHO itself.

Among recent, high-profile changes in public health positions: Dr Derek Yach took over as Global Public Health Director of the Rockefeller Foundation in January 2006 and Dr Richard Feachem has announced he will be stepping down as executive director of the Global Fund to Fight AIDS, Tuberculosis and Malaria at the end of his five-year term in July. Dr Tachi Yamada will leave GlaxoSmithKline to take over the global

public health programme at the Bill & Melinda Gates Foundation on 1 June; the John E. Fogarty International Center division of the United States National Institutes of Health recently appointed a new director, Dr Roger Glass and one of the leading international research institutes in Asia, the International Centre for Diarrhoeal Disease Research, Bangladesh, is looking for a new executive director.

Experts say that this flurry of changes is probably due to a mix of circumstances, all feeding into global trends in the field. Some of the movement is due to increasing opportunities in public health worldwide, fed by a proliferation of the organizations that are dedicated to the issue. As research increasingly finds connections between development, public health and globalization, the public health sector has grown larger and more influential than it was a few decades ago.

Few will comment on what the individual leadership changes mean, but everyone agrees that good leadership is vital for the success of an increasingly dynamic and competitive sector. "The opportunities for people in global health have moved dramatically beyond a few positions in academia. It's a very

dynamic sector and becoming increasingly competitive,” says Yach.

Ten years ago intergovernmental organizations such as WHO and UNICEF were the main employers for senior disease experts who wanted to contribute to public health. Today these organizations are employing people earlier in their careers and there is a wide range of other employers for public health professionals, including nongovernmental organizations (NGOs) and public-private partnerships.

Universities have noticed this development: today 20 accredited schools of public health in the United States offer courses in international public health, according to the Association of Schools of Public Health in Washington, DC. These graduates go on to work in disaster-relief organizations, migrant-refugee health organizations, research and academic institutions, international agencies, various other NGOs, lending agencies with projects in developing countries, multilateral agencies such as the WHO and other governmental agencies.

The proliferation in groups has contributed to another trend, according to Yach: “With that dramatic increase in activity and funding has come a wider array of activities in play by many of them,” he says, adding that this may result in a smaller share of resources being devoted to more traditional public health challenges, such as infant mortality and vaccine-preventable diseases.

Dr Andres de Francisco, Deputy Executive Director of the Global Forum for Health Research in Geneva, however, notes that today’s crop of new NGOs and other public health groups is better equipped to address issues that have fallen through the cracks of the mainstream global public health agenda, such as developing new drugs for neglected diseases.

Even as organizations expand and receive more money, awareness is growing that more can be done with less, and that tweaking a programme or providing a simple preventative intervention

can exponentially augment results. Against this backdrop, the amount of funds being poured into or pledged for public health efforts worldwide has never been greater, and a can-do attitude in global public health — that problems can be solved with the right commitment — is growing too.

The new global public health leaders, however, face many challenges. For example, the new leaders urgently need to address inter-agency cooperation. “I think the deeper issue that people are recognizing is that there isn’t a mechanism for these different institutions to talk together to see how they can work more effectively together,” Yach points out.

For instance, with major multi-billion-dollar initiatives to fight HIV/AIDS several questions arise: are they working in the most effective way in terms of policy? How should they interact with the World Bank and other players? And is there interaction in terms of the money that is needed by people on the ground? These are some of the challenges for global health leaders, Yach says.

This situation promises to develop into what Yach calls a “contested future” in global public health, but also a healthy competition that he hopes will result in “some sense of vision emerging” over the next few years.

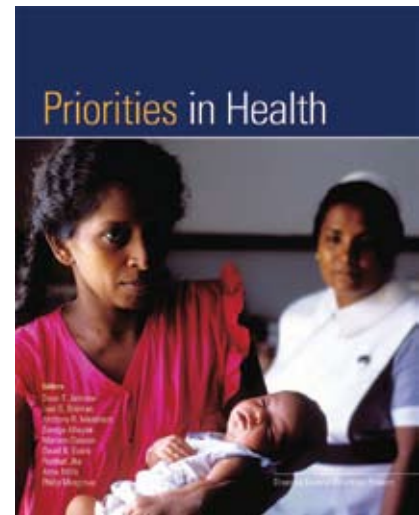
A major challenge for global leaders will be how to reconcile the technical-fix approach with access to innovations, Yach says. Dr Joel Breman, Senior Scientific Advisor at the Fogarty International Center’s Division of International Epidemiology and Population Studies, agrees that, in future, action in the field will be linked closely with modern science and tech-

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Dr Joel Breman, Senior Scientific Advisor, Division of International Epidemiology and Population Studies (EPS) of the Fogarty International Center, US National Institutes of Health.



IBRD/World Bank

Priorities in Health, a recent report which synthesizes the messages of *Disease control priorities in developing countries (DCP2)* into a plain language guide for policy-makers and public health leaders.

nology. Later on, that goes hand-in-hand with implementing findings on molecular medicine and understanding genetic predisposition to disease.

“This is going to be the century of molecular medicine and of un-

derstanding disease pathogenesis, meaning how different people acquire and then manifest disease at the cellular and then at the molecular level, rather than — as in the past century — in the organ and whole-body level,” says Breman, who is a co-author of the second edition of *Disease control priorities in developing countries (DCP2)* (see picture).

“There are ways of designing new interventions based on that understanding. So let’s talk about prediction

and prevention rather than detection and response,” Breman says.

Optimistic, Breman points to increased awareness as a precursor to action. “If the political will is there, then money follows and programmes follow and people get energized down the line,” Breman says. “And those of us in public health are excited about this and want to take advantage of it.” ■

Theresa Braine, *Mexico City*