News

Demand for male circumcision rises in a bid to prevent HIV

Demand for male circumcision as a method of combating HIV/AIDS is likely to increase dramatically if the results from two studies, in Kenya and Uganda, are positive. Public health experts are warning men, however, that circumcision may reduce the risk of HIV infection but it does not provide full protection.

The results of two studies, in Kenya and Uganda, are eagerly anticipated following last year's study carried out in Orange Farm, South Africa, which was stopped early because it showed a significant protective effect of circumcision. It is not known whether the current Kenya and Uganda studies that are due for completion in 2007 will confirm the results of the Orange Farm study, but there are signs that the demand for safe and affordable circumcision services is growing fast, particularly in Botswana, Lesotho, Swaziland, the United Republic of Tanzania and Zambia, and in South Africa too.

Public health experts say that countries in southern Africa with very high HIV prevalence and low circumcision rates and where the spread of HIV is predominantly via heterosexual sex may want to consider doing acceptability, feasibility and costing studies for making male circumcision widely available.

The results of the Orange Farm study in South Africa have been widely publicised in the region and discussed by leaders, members of parliaments (MP), health workers, the press and general public. As a result, there are already indications of increasing demand for male circumcision in traditionally non-circumcising societies in southern Africa. At the University Teaching Hospital in Zambia, demand has grown from 1 to 15 a month with a three-month waiting list. Demand at one Swaziland hospital is reported to have risen from less than one per month to 40 a month. Marwick Khumalo, a Member of Parliament (MP) for Lobamba in Swaziland was quoted in the local press: "All male children should be circumcised. To show my seriousness, I have taken all my sons for circumcision." Kenyan MP Jimmy Angwenui said: "In order to stop the spread of HIV/AIDS male circumcision should be made mandatory by the government."

In Swaziland, the health ministry backed a workshop in January to train 60 doctors and nurses in circumcision, responding to what it called a surge in demand. There were so many volunteers to be demonstration-and-practice patients during the training session that a hundred men had to be turned away. Daniel Halperin, Prevention and Behavior Change Advisor for the South Africa Regional HIV/AIDS Programme says: "There is already high demand for male circumcision in Swaziland following a lot of publicity in the local press and radio. Public health facilities are already overwhelmed and men are being turned away and put on a waiting list which is currently around eight months long".

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There would be many advantages to male circumcision, were it to be confirmed as a means of preventing HIV: it is relatively inexpensive, it can be carried out over a wide age range and it is a one-off intervention conferring lifelong reduced biological risk. François Venter, Clinical Director of Reproductive Health and HIV-Research at the University of Witwatersrand, Johannesburg advocates male circumcision as one of the best protective measures. "Male circumcision is the most powerful intervention we have at this point in time. It is phenomenally effective," he told the *Bulletin*. "One of the beauties of circumcision is that it is a one-off operation which takes 16–20 minutes but then has a profound effect on the rest of a man's life. Whereas to promote condom use or microbicides, repeated long-term promotion is needed."

Data from cross-sectional observational studies conducted since the mid-1980s have shown that circumcised men have a lower prevalence of HIV infection than uncircumcised men. But the Orange Farm study backed by Agence National de Recherches sur le Sida (ANRS) was the first randomized controlled trial to show such an effect. The trial randomized 3274 men to either circumcision or to a control group (PLoS Med 2005; 2:e298). A panel of experts stopped the trial after an average of 18 months follow up. There were 20 HIV infections in the intervention group and 49 in the control group, corresponding to a 60–75% protection rate. The study authors state: "Male circumcision provides a degree of protection against acquiring HIV infection equivalent to what a vaccine of high efficacy would have achieved. Consequently male circumcision should

Keystone/AP Photo: Sasa Kralj

A young Xhosa man covers his head with a blanket after undergoing circumcision in Qweqwe in Transkei, in 1997. According to tribal tradition young men are circumcised without anaesthetic, as a rite of manhood.

Circumcision: current practice and acceptability

Cultural acceptance of circumcision will be vital, if this practice is to be an important complementary intervention for prevention of HIV infection.

Around 20% of men globally and 35% in developing countries are circumcised for religious, cultural, medical and other reasons. Male circumcision practices vary throughout Africa. Countries in West Africa, where male circumcision is common, have HIV prevalence levels well below those of countries in eastern and southern Africa despite the presence of other risk factors. In countries of southern and eastern Africa with the highest HIV prevalence, male circumcision rates are generally under 20%.

Men in Muslim countries are circumcised, as in North Africa and a large part of West Africa. But elsewhere it depends on other cultural factors, including changes that occurred under colonization. For example in Cameroon and the Democratic Republic of the Congo, which are predominantly non-Muslim, most men are circumcised. In Kenya, around 85% of adult men are circumcised, mainly as a rite of passage to manhood.

Only one major ethnic group in Kenya, the Luo, who make up around 13% of the Kenyan population, do not traditionally practice male circumcision. It is among this group that the current trial in Kenya is taking place. Study leader, Robert Bailey, told the *Bulletin* that acceptability studies have shown that approximately 60% of Luo men would prefer to be circumcised if it could be done safely and at minimal cost.

Circumcision rates tend to be low in South Africa, apart from the Eastern Cape where as many as 80–90% of men are circumcised. The Xhosa men in this region undergo circumcision as part of a traditional right of passage, between 18 and 20 years of age (see photo on p. 509. Dr Adrian Puren, co-author of the Orange Farm study and deputy director of the National Institute for Communicable Disease in Johannesburg, says: "Culture is not necessarily a barrier to circumcision. In our trial we found that even Zulus, who traditionally have a low rate of circumcision, they were willing to be circumcised."

Acceptability studies in Kenya, Uganda, South Africa, Swaziland, the United Republic of Tanzania and Zimbabwe have shown that around 60% of men would like to be circumcised. A large Harvard AIDS Institute survey in Botswana found that over 80% of uncircumcised men said they would like to be circumcised if it were performed safely and affordably (*Sex Transm Infect* 2003;79:214-19). Several of the countries that are most severely affected by HIV — Swaziland, Botswana, Lesotho and South Africa — practised male circumcision widely in the past, but the practice waned with urbanization and Westernisation. Promoting it now would be returning to traditional culture, not introducing an unfamiliar practice.

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The two further randomized controlled trials, currently ongoing in the Rakai region of Uganda and the Kisumu region of Kenya, are supported by the National Institutes of Health of the United States. The Uganda trial is in a rural setting and involves 5000 participants aged between 15 and 49 years. The Kenya trial involves 2784 men aged 18–24 in an urban setting. The two trials are due to be completed in 2007, and an interim review of the data was due to be conducted by the Data and Safety Monitoring Board in late June 2006. A further randomized trial assessing the impact of male circumcision on the risk of HIV infection in female partners is currently under way in Uganda with results not expected until late 2007.

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> *François Venter, Clinical Director of Reproductive Health and HIV-Research at the University of Witwatersrand, Johannesburg.*

Circumcision can be risky if it is performed in unsterile conditions. It can lead to infection, bleeding and permanent injury, or HIV infection from non-sterilized "instruments", and possible death if appropriate treatment is not provided. Every year the authorities in the Eastern Cape of South Africa report deaths and serious complications from botched circumcisions of young boys carried out by traditional healers.

Robert Bailey, who is the leader for the current Kenyan trial, did a recent study of complication rates from traditional and circumcisions performed in medical settings in Bungoma District of Kenya. Bailey and his colleagues found that traditional circumcision resulted in a complication rate of 35% while the latter produced a complication rate of 18%. "In our current trial the complication rate is 1.7%. This demonstrates that it is possible to keep complications to a minimum in an African setting." A major problem is lack of sterile equipment and facilities. "We have carried out surveys of health facilities in Kenya and found that all but the major district hospitals are lacking proper instruments, such as sterilizing equipment, working surgical instruments and supplies, to perform safe circumcisions."

There are other concerns about circumcision. During the healing period, sexually active men are likely to be at higher risk of HIV infection. During this time — approximately three to four weeks — men should be instructed to refrain from sexual activity. There are opponents of male circumcision who see it as a violation of human rights, particularly if carried out on children or adolescents. But perhaps the largest potential problem with circumcision is the false perception of security. Male circumcision is not a magic bullet and does not provide full protection. If men perceive they are fully protected then it could lead to a decrease in condom use or an increase in risky sexual behaviour. This was seen in the Orange Farm study when the intervention groups had significantly more sexual contacts. Dr Venter says: "There is a danger that men will see circumcision as an invisible condom and take part in more risky sexual behaviour. However, it would be the same with an HIV vaccine. The message has just got to be put across carefully that circumcision is part of the jigsaw puzzle of prevention." Male circumcision needs to be promoted as part of the range of methods to reduce the risk of HIV, including avoidance of unprotected penetrative sex, reduction in the number of sexual partners and consistent condom use.

The cost of male circumcision varies depending on where the operation takes

place and who performs it. However, data from Nyanza, Kenya suggesç that circumcision can be done in medical facilities for about US$ 25 per procedure. This includes US$ 8 for medical expendables such as sutures and needle, bandaging and analgesics, US$ 7 for surgical preparation (preparing the room, cleaning linens, sterilizing instruments, and US$ 10 in overheads (physician's fee, maintenance of room and equipment). Professor Tom Quinn from Johns Hopkins University told the 2006 Conference on Retroviruses and Opportunistic Infections that he calculated that 16 operations would prevent one incident HIV infection over 10 years. The cost per HIV infection averted could be as low as US$ 1052, if protection occurs in both sexes, making circumcision extremely cost effective.

The current position of WHO is that safe circumcision should be provided where people want it but that a policy decision on whether to promote it should wait until the results of the Kenya and Uganda trials are available. In the meantime a UN Work Plan on Male Circumcision is being implemented to help countries improve the safety of their circumcision practices. WHO has produced a technical manual, *Male circumcision under local anaesthesia*, which addresses the provision of safe male circumcision services for newborns, adolescents and adults and gives detailed technical information on the different surgical approaches.

How could male circumcision protect against HIV?

Male circumcision is the surgical removal of all or part of the foreskin of the penis. There are several biological explanations at to why this operation may reduce the risk of HIV infection. Removal of the foreskin reduces the ability of HIV to penetrate the skin of the penis. In addition, on the underside of the foreskin are located many special immunological cells such as Langerhans cells which are prime targets for HIV. Another possible explanation is that small tears in the delicate skin of the inner surface of the foreskin during sexual intercourse could allow a portal of entry for HIV. Men with a foreskin are more prone to have some infections, including sexually transmitted infections, which can enhance HIV transmission. Male circumcision is associated with a much lower risk of penile cancer. Several studies now suggest that female partners of circumcised men have a lower risk of cancer of the cervix. Other benefits include prevention of inflammation of the glans and foreskin (balanitis) and prevention of scar tissue causing an inability to retract the foreskin (phimosis).

If the two ongoing trials are positive then governments in sub-Saharan Africa may want to decide whether to commit funds to train medical staff and provide appropriate equipment and facilities. Dr Puren says: "It will put further stress on a health-care system already straining to roll out an ARV (antiretroviral) programme."

Bailey warns: "People want the services. If they are not provided with the services they will seek unqualified practitioners who will exploit the situation. We have to build the capacity to provide safe and affordable services." Venter adds: "There are already long queues for circumcision in South Africa so there will need to be careful planning. We need to train more people to carry out the operations safely. There is no need for doctors to do it. It is a simple procedure that trained technicians could carry out."

When should circumcision take place? One option would be to promote routine circumcision of infants, possibly as part of the antenatal care package. Botswana, in fact, took a policy decision to offer this some years ago but it has not been implemented. Circumcising at this age would reduce the complications that result from traditional circumcision rites in adolescence. But the major benefits of preventing HIV infections would take more than 20 years to be realised.

The other alternative is to offer circumcision through health facilities, and possibly schools and youth centres to young men before they become sexually active. Dr Venter believes a proactive recruitment programme should be carried out. "We need to incentivize circumcision. For example every man who comes forward should be given 100 rand (US$ 14.50)." ■

Jacqui Wise, *Cape Town*

WHO coordinates health provision for quake survivors

Days after a devastating earthquake hit two Indonesian provinces, 6000 health workers from across the country were dispatched to the disaster zone. To help Indonesian Government efforts to provide emergency health care, WHO has been coordinating dozens of international organizations and charities to aid survivors.

Within hours of a 6.2 magnitude earthquake that hit the Indonesian provinces of Yogyakarta and Central Java on May 27, a massive relief effort, comprising both Indonesian and overseas organizations, got under way. A fortnight after the quake, approximately 75 international nongovernmental organizations (NGOs), and more than 10 government teams and UN agencies had sent personnel and supplies to the stricken region to support the Indonesian Government's own relief efforts.

WHO's role was as the lead agency of the Health Cluster, set up in June 2005 as one of the key components of wider humanitarian reforms within the UN. At the country level the Health Cluster's role is to coordinate the health response. The Cluster system proved successful in the South Asia earthquake in 2005. In Indonesia, this approach helped to involve most of the NGOs engaged in relief efforts in efforts to assist the two provincial health authorities, as they grappled with the aftermath of the quake: over 5700 dead, nearly 38 000 injured, 470 000 dwellings damaged or destroyed and 1.5 million people affected.

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>
> *Dr Arturo Pesigan, Head of the Health Cluster in Yogyakarta.*

"WHO's main role is supporting the Indonesian Government in its work responding to the emergency situation, particularly on human health-related concerns, and WHO has been in close relationship in supporting the work of the Ministry of Health (MoH)," says Dr Arturo Pesigan, Head of the Health Cluster in Yogyakarta.

Unlike the December 2004 tsunami which devastated the province of Aceh, the area affected by the 27 May earthquake was far more localized. It has been easier to obtain accurate numbers related to its effect on the population and therefore an easier task for government agencies and NGOs to get aid to where it is needed. The rapid government response is also, arguably, related to the region's importance, whereas Aceh is on the periphery, the island of Java represents the heart of Indonesia and Yogyakarta is the spiritual and cultural centre of the island.

"Yogyakarta and Central Java provinces have not been overwhelmed. At the national level the earthquake was not even declared a national disaster. Indonesia didn't call for international assistance, but welcomes it," says Charlie Higgins, the UN's Area Coordinator in Yogyakarta. "The government rapidly moved in 6000 health workers from within Indonesia to reinforce local structures," he adds.

The experience of responding to the aftermath of the tsunami — although on a much larger scale to the disaster caused by the May earthquake — stood WHO in good stead to respond to the current emergency, says Pesigan, who is also the Regional Advisor for Emergency and Humanitarian Action from WHO's Office for the Western Pacific Region.

"Like we did in the tsunami, WHO supported the immediate establishment of the crisis centre for the provincial level health response. It was crucial to establish good coordination mechanisms with the government and all the players in the health sector. WHO mobilized its team within a few hours. Vehicles and essential supplies were immediately dispatched. Preparedness strengthened from the tsunami experience facilitated the establishment of a logistics system that readily provided personnel, transport, equipment, medicines and supplies and support was immediately provided from the country office, the regional office and headquarters," Pesigan explains.

The WHO-coordinated health response is split into several main areas: hospital and medical services; communicable disease surveillance and response; immunization; logistics and health supplies; medical emergency supplies management; mental health, water/sanitation and reproductive health; and maternal and child health. Two weeks after the earthquake struck, the emphasis had already shifted from providing emergency medical care to addressing secondary health problems.

WHO/SEARO: Mr Gunawan

The local deputy mayor in the village of Banyusocha launches a campaign for vaccination. The village is in the district of Gunungki dul, one of the hilly areas of Yogyakarta struck by the earthquake.

The large number of orthopaedic injuries and the risk of disease are the main medical issues. There has been an increase in the number of tetanus cases reported. "Surveillance for communicable diseases is one of the priority concerns of the WHO, the MoH and the Health Cluster," says Pesigan.

A few days after the earthquake struck, WHO urged donors to make sure their donations were appropriate before shipping them, as sending the wrong items could hamper rather than help the relief effort. Still, donated drugs which are unfamiliar to the country's medical staff, flooded into the area, presenting a logistical challenge to local health officials.

This has led to a request for donations of only locally procured drugs from now on, and the Indonesian Government has also announced that the only shortfall in terms of personnel is orthopaedic specialists, it is also short of orthopedic medical supplies and equipment.

As the effort to clear rubble and begin the process of housing reconstruction gets under way, the risk of exposure to tetanus increases. In coordination with the Ministry of Health and UNICEF, WHO is implementing a plan to immunize the entire over-15 population in the affected area — some 1.3 million people — with a booster dose of tetanus-diphtheria.

Children aged six months to five years will be vaccinated against measles. Vitamin A is also being distributed.

Although water supplies and sanitation were affected by the earthquake, there have been no major health problems associated with the lack of water. UNICEF is coordinating efforts to distribute over 320 000 litres of water and set up the estimated 31 000 latrines that are required.

"It's not a desperate situation. There are some problems with sanitation and water supply but people are not crowded into camps and most sanitary facilities remain intact or can be repaired," says Higgins. UNICEF is also responsible for education and temporary tent-based schools have been set up in order to maintain some semblance of continuity in education, pending the government's reconstruction of the 400 schools affected.

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However, with hundreds of thousands of people made homeless, reconstruction of housing will be a mammoth task, as is the provision of temporary shelter in the meantime. According to the UN Office for the Coordination of Humanitarian Affairs (OCHA), there are estimates of emergency shelter coverage for only 12 of the approximately 80 sub-districts in the two affected provinces and even where coverage is known, it is only 65% on average.

Basic food assistance is being provided by the Indonesian Government in the form of rice rations, supplemented with World Food Programme fortified noodles and biscuits. The quake affected an area of rich farmland that produces a surplus of food, but caused only limited damage to irrigation, says Higgins.

In the medium term, food supplies are expected to recover, but, in the short term, there have been inevitable bottlenecks: "There have been reports in the media about problems of delivery of food. Some gaps in sanitation have been identified. There were also complaints of waiting lists in hospitals," says Pesigan. "Though there may be problems, the concerted efforts of the national and international agencies have been working hard to address the deficiencies." ■

Jane Parry, *Hong Kong SAR*

Clinical trials initiative: patients or patents?

The pharmaceutical industry fears that WHO's clinical trials initiative may limit companies' ability to compete and dent profitability, as compliance — which is voluntary — will mean having to apply for patents earlier than they currently do. Some companies have pledged to adhere to the recommendations, nonetheless. Others may resist.

WHO's newly proposed rules on the disclosure of data when researchers register clinical trials they are planning has drawn a mixed reaction from corporations, academic and other institutions funding pharmaceutical R&D.

The pharmaceutical industry fears that companies may refrain from doing R&D in certain fields, firstly, because they would not want to make sensitive information public too early — as required under the initiative — as it would become available to their competitors, and secondly, if they are unable to protect their innovations with patents.

The International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) stated clearly it does not agree with the final vision WHO presented on 19 May of how the International Clinical Trials Registry Platform (ICTRP) initiative will work (see *Bulletin* Vol. 84, No. 6, June 2006) but that it was prepared to work with WHO to develop a new concept that addresses these industry concerns.

"Whilst the industry shares other stakeholders' concerns about ensuring adequate transparency," IFPMA Director Harvey Bale tells the *Bulletin*, "it believes that the WHO position is a reflection of the views of some stakeholders, but it is not a consensus".

"The IFPMA, in conjunction with its member associations and companies, will work with the WHO, national drug regulatory authorities and other stakeholders to reach a final consensus position on the ICTRP," Bale says, noting that the Geneva-based industry association had launched its own "transparency platform", the IFPMA Clinical Trials Portal, in 2005, which it would continue to develop in the meantime.

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For Dr David Korn, Senior Vice President in the Biomedical and Health Science Research division of the Association of American Medical Colleges, the reaction to what he called a "bold" and "frankly unexpected" move to include early phase trials, comes as no surprise. "In all of my interactions with industry leaders, they have always argued that disclosure of early phase research, often dubbed 'hypothesis-generating', as contrasted with 'hypothesis-testing', would be unacceptable to them," he says.

Guy Willis, IFPMA Director of Communications, cites as daily preoccupations of industry players: fierce competition, shareholder expectations, and, above all, the crucial issue of patentability — a weakening of which could dent profits.

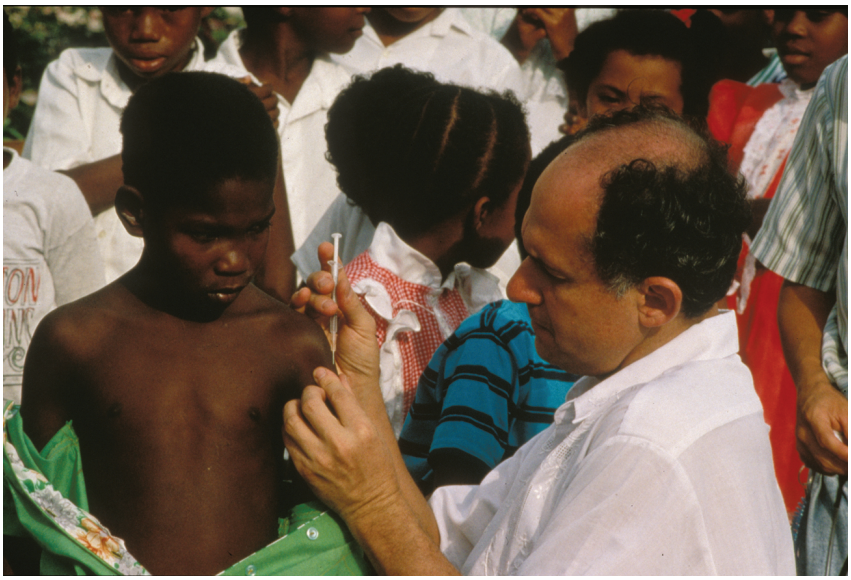
Patents are the life blood of the R&D-driven segment of the industry and a company's ability to stake a claim with a new product, a key

competitive factor. The timing of that claim — broadly speaking: the later, the better — is critical, though more so in Europe than in the United States where patent law enshrines the principle of 'first to invent' as opposed to 'first to file'. Late application for a patent gives a trial sponsor time to realize the full potential of what he has developed, and, as Willis puts it: "The later you patent, the later your patent expires." Late application for a patent implies, in turn, the late release of results because, Willis argues, once the results have become public, acquiring the patent becomes problematic. Andrew Freeman, Director of R&D Policy at GlaxoSmithKline shares Willis's concerns: "Early disclosure of drug names and trial outcome could, in rare circumstances, prevent patentability or give away novel ways of assessing the effects of investigational medicines," he says.

Outside of the pharmaceutical industry, such arguments find few supporters. "The trial sponsors have no reason to refuse to register their protocols, which is the only way to make sure that the interest of patients is protected," says Professor Silvio Garattini, Director of the Mario Negri Institute in Milan, while Davina Ghersi, a senior research fellow at the University of Sydney, points at out that after extensive consultation with the pharmaceutical industry regarding the minimum data set, none of the parties who objected to the public release of data were able to provide concrete examples demonstrating how full disclosure at the time of registration had given rise to negative outcomes for the trial or its sponsor. "The WHO Platform Secretariat reporting in the *Lancet* stated that the arguments for delayed disclosure were neither convincing nor compelling," she says — a position, which, when presented to IFPMA's Willis, drew a terse: "That's one point of view."

The debate is further clouded by the fact that there are already wide variations in the disclosure of clinical trials data. Exploratory trial information is, in some instances, available for a fee. So why not formalize disclosure as per the WHO's minimum data set?

For Dr Gerd Antes, Director of the Cochrane Center in Freiburg, Germany, the question is deeply puzzling. "It is hard to understand [the pharmaceutical industry's] argument on early phase trials results without thinking in terms of hidden agendas," he says. Antes suspects that clinical trials sponsors' reluctance to embrace the WHO initiative may have to do with murkier arguments than those generally put forward, something trial sponsors vehemently deny.



WHO/TDR: O. Martel

A field trial of a malaria vaccine in Santa Maria village, in Tumaco, Colombia in 1994. Millions of people participate in clinical trials every year.

Antes' view is shared by others in the research community who say that pharmaceutical companies have become used to doing clinical trials outside the public spotlight. What little pressure there is to conduct human trials on an ethical basis comes from the ethics boards. But in developed countries these are often peopled by 'retired university professors' with little appetite for controversy, while in developing countries they often lack people with the relevant expertise. Add to this, a significant number of small-to-medium-size companies in some countries with perhaps only one or two drugs in their portfolio — drugs which may have been developed and tested in less than optimal conditions — and you have a recipe for inertia, some in the research community say.

Professor Jacques Demotes, Coordinator of the European Clinical Research Infrastructures Network (ECRIN) and a clinical researcher in Bordeaux, paints a similar picture of relatively unregulated clinical trials in France. It is a landscape he doesn't think all bad. "A lot of good research and good drugs have come out of academic institutions that did not necessarily observe the strictest clinical trials protocols," he says. "It would be a shame if a too-sweeping regulatory framework [of the kind WHO envisages] discouraged research in the future." That said, Demotes believes changes should be made. "I understand the position of the pharmaceutical companies who operate in a capitalist system, after all," he says. "But there has to be some recognition of the fact that drugs and health products generally are not the same as shoes or televisions."

It remains to be seen if the lead taken by WHO, or whether the International Committee of Medical Journals' refusal to publish results of unregistered trials will help to enforce the International Clinical Trials Registry Platform and, in turn, change the way clinical trials are carried out, registered and made public.

According to Freeman, GlaxoSmithKline will be registering all its phase 1 healthy volunteer trials, "in the interests of transparency and openness". So perhaps there is hope that other companies will adhere to the WHO initiative recommendations, in which participation is voluntary.

Korn, from the Association of American Medical Colleges, believes that, broadly speaking, there will be a digging in of heels on the part of pharmaceutical manufacturers.

"If the purpose of early phase clinical trial registration is primarily to deal with safety issues, then it may be that an array of data fields somewhat different from the "minimal data set" would be sufficient to fit the purpose," Korn says. "But if the expert consensus is that the full "minimal data set" should be required for early phase clinical trial registration, then I do think industry will resist strongly." ■

Gary Humphreys, *Los Angeles*