

Clinical trials in India: ethical concerns

Transnational drug companies are moving their clinical trials business to India, giving a new urgency to clinical trials registry reform there. Patralekha Chatterjee reports.

According to the Associated Chambers of Commerce and Industry, an influential national industry association, India is set to grab clinical trials business valued at approximately US\$ 1 billion by 2010, up from US\$ 200 million last year, making the subcontinent one of the world's preferred destinations for clinical trials.

Drug companies are drawn to India for several reasons, including a technically competent workforce, patient availability, low costs and a friendly drug-control system. While good news for India's economy, the booming clinical trial industry is raising concerns because of a lack of regulation of private trials and the uneven application of requirements for informed consent and proper ethics review.

Dr Ambujam Nair Kapoor, a senior scientist of the Indian Council of Medical Research (ICMR), states the problem bluntly: "Unless we put in place systems that ensure safety of patients and good quality of trials, people will get away with whatever they can get away with." ICMR, a national body responsible for the formulation, coordination and promotion of biomedical research, is striving to do just that with the Clinical Trials Registry of India, which it launched in July 2007.

The Clinical Trials Registry encourages the registration of all clinical trials conducted in India before the enrolment of the first participant. "The registry is meant to bring transparency to clinical trials conducted in India," explains Kapoor, who is all too aware of the shortcomings of current trial publication practices, including a tendency to publish trial results only when they are positive. "Trials done earlier where the drug has not been found to be effective are sometimes not publicized," she says, adding that information about failures should also be put in a publicly searchable database.

Working together with the Indian Journal of Medical Research, the Clinical Trial Registry also brought together the editors of 12 Indian biomedical

journals at the beginning of the year to develop policy covering the publication of clinical trials. The editors issued a statement in April urging all those conducting and/or planning to conduct clinical trials involving human subjects to register their trials in the Clinical Trials Registry or any other primary clinical trial register. From January 2010 these journals will consider publication of a trial started in or after June 2008 only if it has been previously registered.

"We are wearing down the resistance [to registration]," says Dr Prathap Tharyan, professor of psychiatry at the Christian Medical College, Vellore, India. Tharyan is the coordinator of the South Asian Cochrane Network, and a member of the Scientific Advisory Group of the WHO International Clinical Trials Registry Platform (ICTRP) and of the steering group of the Clinical Trials Registry. "Investigators who want to publish in good journals have to register. In other words, if I want my research to be internationally known, I have to go to good journals who will increasingly insist on registration of the trials."

The latest developments in India reflect a concerted effort on the part of the global public health community to push clinical trials issues to the fore in the wake of several high-profile cases in which pharmaceutical companies were shown to be withholding information from regulators. In September 2004, for example, the members of the influential International Committee of Medical Journal Editors (ICMJE) published a joint editorial promoting registration of all clinical trials. The ICMJE stated that, beginning 1 July 2005, only registered trials would be eligible for journal publication. In 2007 the ICMJE stated that it would consider a trial for publication if it had been registered in any WHO Primary Registry.

The World Health Organization (WHO) has played a catalytic role in pushing this process forward. WHO's involvement in clinical trial registration began in October 2003 with consultations with different stakeholders to identify a potential basis for collaboration to address complex issues related to trial registration and reporting. This culminated in the establishment of the ICTRP Secretariat.



Men pray before dinner at Sahara Centre for Residential Care and Rehabilitation for drug users in New Delhi, India, in 2004, before participating in a clinical trial of a vaccine to prevent HIV/AIDS.

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Hosted by WHO, the ICTRP started operations on 1 August 2005. It is committed to harmonizing standards within which trial registers and databases worldwide can operate in a coordinated fashion, providing a global trial identification and search capability, and promoting compliance. WHO has also established a network of clinical trials registries, participation in which is voluntary.

According to Dr Davina Ghersi, coordinator of WHO's Registry Platform, the Indian registry is active in this network, but she points out that there is no legal requirement to register a trial there. Ghersi goes on to say that there is such a requirement if researchers want to publish the trial in journals affiliated with either the ICMJE or the Indian journal editors initiative.

Ghersi believes that one of the things that can be achieved through registration is stronger regulation, but also thinks there will be other benefits, notably greater transparency about what sort of research is being done, "For example," Ghersi says, "if every piece of research conducted in India were available on a publicly searchable database somewhere, one would know what issues are being addressed, and if they are relevant to the population in which the research is being conducted."

India's Clinical Trials Registry has all the 20 items of the WHO Clinical Trials Registry Platform. In addition, there are items such as: declaration of



WHO/ P Viot

Street scene in India, one of the world's preferred destinations for clinical trials.

principal investigator's name and address; name of the ethics committee and approval status; regulatory clearance obtained from the Drugs Controller General of India; estimated duration of trial; site(s) of study; phase of trial; brief summary; method of generating randomization sequence; method of allocation concealment; and finally method of blinding and masking.

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Dr Chandra Gulhati

Though the launch of the Clinical Trials Registry marks a new chapter in the clinical trial registration process in India, there are daunting challenges ahead. Since its launch in 2007, 64 clinical trials have been registered, but there is still no legal obligation to register. Steps are being taken to encourage voluntary registration, including the Clinical Trials Registry workshops to which people likely to be conduct-

ing clinical trials – medical colleges, research institutions, state drug controllers, and nongovernmental organizations – are invited, but for some, such steps are inadequate.

Dr Chandra Gulhati, editor of the *Monthly Index of Medical Specialities*, for example, would like to see more teeth in the clinical registration process in the country. "The first step should be the Drugs Controller General of India making it obligatory for all trials to be registered on the Clinical Trials Registry site before permission is granted to conduct them," Gulhati says. "The failure to do so should carry a penalty. In addition, while registering trials, the composition of hospital ethics committees, which approved the trial, should be disclosed."

Gulhati is particularly concerned about ethics committees lacking independence. "Fewer than 40 Ethics Committees in India are properly constituted and functioning, which means that the safety of the subjects of clinical trials is on the back burner," he says, adding that it is also worrying that there is no legal requirement for investigators or members of the Ethics Committees to declare a conflict of interest. He considers this a particularly serious problem given the increasing number of hospitals now owned by drug companies. "Clinical trials at such hospitals should carry a statement of disclosure about the relationship," Gulhati says. ■



WHO/ K Selleck

Dr Davina Ghersi

Overcoming migrants' barriers to health

With increasing numbers of people on the move, migrant health has become a key global public-health issue. Alice Ghent reports.

Climate change, global conflict and economic necessity are driving the highest levels of migration in history. According to the International Organization for Migration (IOM) some 192 million people are living outside their place of birth, representing about 3% of the world's population.

The sheer scale of human displacement has turned migrant health into a priority global public-health issue, an issue rendered more complex by the diversity of the populations involved – from people in search of work or education to more vulnerable groups like asylum seekers and refugees.

Apart from the increased potential for the spread of infectious disease brings, there is also rising concern that migrants' health needs are not always adequately met. Many countries restrict access to health care for certain migrant groups – including irregular migrants and asylum seekers. For example, until a recent court ruling, the United Kingdom restricted access to free health care to some migrants – including irregular migrants – to counter any possibility that they were entering the country primarily for free medical treatment.

Dr Daniel López-Acuña, director of WHO's Health Action in Crises

Recovery and Transition Programmes, says migrant health issues are “now coming to a head in some countries, which is why they have been raised at the highest levels within the public-health agenda at national and international health levels”.

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For López-Acuña, the threat of communicable diseases spreading is only one aspect of the issue: “With ever-increasing migrant populations in many countries, more strain is being put on government systems that provide health services to the public,” he says. This strain is even greater

when the flow of humanity is between lower-income countries, says Dr Eric Laroche, assistant director-general of the Health Action in Crises cluster of departments at the World Health Organization (WHO). “Providing health care for new flows of migrants can place extra burdens on the receiving country,” he says, and cites poverty, marginality and the stress of displacement among the factors affecting the health of populations on the move.

At the World Health Assembly in May, WHO agreed on four strategies to address the vulnerabilities and health-care needs of migrants.

“Advocacy and policy development is crucial to ensure migrants have equitable access to health services,” says López-Acuña. “There is also a need to assess trends in migrants' health by improving country health information systems, which can help identify and fill gaps in service delivery.” López-Acuña also believes it is essential to train policy-makers and health stakeholders on migrant health issues, and to improve service delivery to reinforce migrant-friendly public-health services and establish minimum health-care standards for all vulnerable migrant groups.

Between 1960 and 2005 the number of international migrants in the world more than doubled, from an estimated 75 million in 1960 to almost 191 million in 2005, according to a United Nations report, *Trends in total migrant stock, 2005 revision*. Migration is now running at about 3% annually, according to the IOM. Undocumented migration is harder to track but the International Labour Organization estimates that there are 15–30 million irregular immigrants internationally.

Refugees represent 9.7% of global migrants, according to the *World refugee survey* in 2005, which estimated that there were 17 million global refugees, most of whom were hosted by African countries.

Family reunification and the allure of a better life, including enhanced prospects for work or education are driving migration to countries belonging to the Organisation for Economic Co-operation and Development (OECD). From 2004 to 2005 immigration to OECD countries increased by four million people. This labour-driven trend is expected to continue as high-



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Migrant community health worker provides health assistance in Thailand, in 2006.

income countries with low fertility see their populations decline and age.

According to Sally Hargreaves, an expert in migrant health at Imperial College, London, the implications of rising rates of immigration for health services are poorly understood. She says health-care provision for the many different migrant groups varies widely from country to country.

Other commentators too have noted that in the Netherlands, for example, migrant health has been the subject of sustained and systematic attention since 2000, while Italy has been setting migrant-related health policy targets since the 1990s. Spain on the other hand has only recently started to include migrant health and health-care issues in national and regional plans for the integration of immigrants.

In some countries migrants find themselves completely excluded from routine health services. “What is increasingly being documented too is that vulnerable migrants – whether entitled to free health care or not – face numerous barriers to accessing an appropriate level of health care, and this has implications for both individual and public health, as well as for health-care providers,” Hargreaves says.

Hargreaves believes there is a “real need to explore and document models of best practice in the developed-world context for delivering services to various migrant groups, and their impact on health outcomes.” She also considers defining a new research and policy agenda for migrant health to be “an urgent priority”. As an example of policy under strain, Hargreaves cites criticism of the United Kingdom screening new migrants arriving through its airports for tuberculosis. Critics have said resources could be used more effectively by improving community-based tuberculosis screening programmes that encompass a wider range of health-care issues.

Perhaps, not surprisingly, among the governments that have worked hard to address health care for migrants are those most familiar with the challenges. Australia, for example, with nearly a quarter of its population (5.3 million) born overseas, has a long experience in the delivery of specialized health-care services for migrants.



Migrants on a medical barge displaced by conflict in the Sudan, in 2006.

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Responsibility for health is split between the states and the federal government. The states have their own variations of migrant care but the system recognizes that not all migrants are the same. In the state of Victoria, for example, migrants can access a range of health services through Community Health Centres or general practice surgeries, while there is also a specialized service for refugees who may have special needs due to torture or hardship brought about by war and dislocation.

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Australia admits 13 500 refugees a year. On arrival refugees are entitled to a free medical assessment. However, asylum seekers face greater barriers to accessing medical care. Many are not eligible for free medical treatment

under the national insurance scheme called Medicare and have to seek services offered for free. This situation has been remedied at least partly in the state of Victoria, through access to hospital-based care and several other state-funded services.

Demos Krousos is the director of the Melbourne-based Centre for Culture, Ethnicity and Health, which Victoria set up in 1993 to advise health-care institutions on how to improve access to health services for culturally diverse communities. “There was recognition that migrant-health services needed to become socially and culturally inclusive,” he says.

“In order to achieve this, institutions have to be reformed on a philosophy of social inclusion – that it is a human right to have equal access to health-care services. Health-care institutions are the last great institutions to be unreconstructed in this area,” he says, adding: “You can have discrimination simply by failing to include people.”

Instead of focusing on the needs of specific migrants, the emphasis is on making health care accessible to everyone. Staff should not make assumptions, he says. “The woman from Iraq may not be Muslim. We urge people to learn about the individual in their office. They must reflect on their values and ask are they treating people fairly?” ■

Iranian health houses open the door to primary care

Working in pairs out of modest, village-based facilities, the Islamic Republic of Iran's trained community health workers, the *behvarzan*, provide basic health care to most of the country's rural population. Mojgan Tavassoli reports.

They have been described as an "incredible masterpiece". The Iranian health houses, conceived and introduced during the 1980–1988 war with Iraq, have been at the centre of a so-called master plan to bring health care to every district.

Devised in 1981, the plan was informed by a health-care development programme from the Western Azerbaijan province that had focused strongly on what we now recognize to be primary health care. It emphasized community participation and intersectoral cooperation to serve the needs of the thinly distributed and rapidly swelling population.

Locally sourced health workers or *behvarzan* from the Farsi words *beh* (good) and *varz* (skill) were originally trained to meet the basic health-care needs of people living in rural areas. A female *behvarz* was responsible for, among other things, child and maternal health; a male *behvarz* for sanitation and environmental projects. Both worked out of the health house, a rural medical post and the most basic unit of service delivery in the country's health-care plan.

The health houses refer patients to rural health centres, which cover about 6000 to 10 000 people, and have up to two physicians and several health technicians. These centres are responsible for elective and emergency case management, supporting the health houses, and supervising both the health technicians and the *behvarzan* or community health workers.

Dr Sirous Pileroudi, a retired former senior official with the Ministry of Health and one of the founders of the Iranian health-care system, describes the health houses as an "incredible masterpiece". "At the beginning, we could never imagine such a breakthrough," he says. "We were at war and the country was in a miserable condition."

There was strong opposition at the time of its inception from health experts who thought the infrastructure too ambitious and the scheme a regres-

sion in health care owing to the limited education of the *behvarzan*. Despite this opposition and the debilitating eight-year war with its neighbouring country, Iraq, the master plan to bring health to every district has been largely successful. According to Dr Mohammad Esmael Motlaq, the director of the Centre for Healthcare Promotion affiliated with the Ministry of Health, more than 90% of the Islamic Republic of Iran's 23 million rural population enjoys health-care services through the health houses staffed by these community health workers.

"People enjoy primary health care services free of charge," Motlaq says. "The health workers are well familiar with the culture and traditions and that is a big advantage."

There are now about 17 000 health houses in the Islamic Republic of Iran, according to the most recent Ministry of Health statistics. Almost 30 000 community health workers are working in these health houses, more than 16 000 of them women. On average, each health house serves 1500 people in its village and surrounding settlements.

Community health workers are often from the village they serve, their appointment confirmed by the local rural council. Their efforts have not gone unnoticed. In a speech made in September 2007 at a ceremony to pay tribute to their work, the health minister, Dr Kamran Baqeri Lankarani, said that these community workers had made a significant contribution to the sharp decline in mortality rates in the past three decades, helping to reduce deaths among infants and pregnant women, and curbing contagious diseases.

Motlaq concurs, saying the *behvarzan* are the axis of the village. "A community health worker is from the people and has their approval. These workers regularly supervise people's health."



Some primary health care efforts started in the 1970s. In 1975, latrine building helped to create healthy surroundings. Male primary health care workers were involved in environmental sanitation activities and in communicable disease control.

Indeed, community health workers often have an impressive knowledge of their patients' case histories. Log books on each household are kept at the health house. These contain the name, gender and age of all family members, sanitation conditions of the household, history of pregnancies, details of care for those aged under-five and dental-care records.

Among their duties, female community health workers are responsible for vaccinations, registrations and administering medicines. A male community health worker is charged with activities mainly outside the health house, such as making follow-up visits to patients and identifying them in surrounding villages. The minimum age for male and female health workers is 20 and 16 respectively. They are required to have had 11 years of regular education, plus two years of theoretical and practical training before being awarded a certificate to be allowed to practice. "Even after their graduation, the *behtarzan* are subject to regular monitoring and distance-learning," Motlaq says.

Dr Kamel Shadpour, another of the Iranian health-care pioneers, says the practice of keeping the "vital horoscope" – a circular chart resembling a horoscope and displaying extensive details of births, deaths and family-planning activities – is central to the health houses' functions and provides crucial data to higher levels of the network and the Ministry of Health about the health houses' activities.

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Moigan Tavassoli

Dr Sirous Pileroudi, a retired former senior official with the Ministry of Health and one of the founders of the Iranian health-care system.



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Weekly theoretical course for village health workers at the district health centre of Rezaiyeh.

They did well when the main issue in the country was to contain contagious diseases. They are doing the same now vis-à-vis chronic diseases like diabetes and hypertension, and also in improving nutrition, the control of iodine disorders, iron-deficiency anaemia and fluoride treatment."

“Health houses serve as the powerful arm of rural health-care centres.”

Dr Kamel Shadpour

Motlaq says the strengths of the Iranian primary health care system are that health houses are highly efficient compared to other health-care service-providing units (such as ambulatory and hospital services), that the primary health care system provides an effective education system for community health workers, it standardizes services and is effective also because of the community health workers' close links with the villages in which they work.

Despite the progress made in primary health care over the past three decades, Motlaq says rapid societal changes present further challenges – epidemiologic, demographic and socioeconomic – requiring the Islamic Republic of Iran to introduce several changes. These include improving cooperation between scientific and executive bodies and decentralizing decision-making to address local needs. He says that

the Islamic Republic of Iran needs to improve health information systems to acquire critical data for such decentralized decision-making. He also says that the health-care system should be more flexible and sensitive to environmental changes, that communities should play a more active role in primary health care and that chronic diseases should be better integrated into primary health care.

Maryam Alaini, 25, has been working in the health house in the village of Afjeh in the suburbs of the capital, Tehran, for two years. "I'm a high-school graduate. I'm the sole female community health worker and I am working with a male health worker," she says. "Besides my natal village Afjeh, we cover satellite villages, namely Sink, Henzak and Anbaj. We are responsible for 50% of the health-care services in the village and the rest is up to a physician who visits the village every Saturday. Fifteen people visit the health house each day and the figure more than doubles when the physician is available." She says the clients come to the health house for general consultations, to have their blood pressure checked, to be treated for diabetes, or for minor ailments such as the common cold.

Alaini's health house covers 1215 Iranian and 67 Afghan-born villagers. She knows many of them and is fond of her job. "We visit our schools once a week and tell the schoolchildren how to keep their hair, nails, mouths and teeth clean. If we observe any problem, we will refer the case to the relevant doctor," Alaini says. ■