A trial of strength

Can industry resist the growing demands for greater transparency?

Peter McIntyre

Patients, doctors, academic researchers and the World Health Organization all want industry to be a lot more open about the drugs they are trialling. The industry is pleading commercial confidentiality. The two sides are locked in an argument over the requirements of a proposed WHO clinical trials registry. The question is: who will blink first?

Patients and doctors hope to gain unprecedented access to information about clinical trials through a one-stop global search engine. A World Health Organization initiative, now under discussion, would allow patients with cancer and other critical conditions to search for trials about promising lines of treatment. It would also bring a more comprehensive and faster approach to making the outcomes of clinical trials public.

WHO looks set to win broad agreement for a 20-item registration data set about trials, including details of products or procedures, the exact aims of the trial and the outcome (see pp. 64,65). Later this year, WHO plans to give every trial a Universal Trial Reference Number (UTRN) and to launch a search engine that will trawl more than 50 clinical trials registries worldwide.

The European Cancer Patient Coalition (ECPC) has welcomed the WHO International Clinical Trials Registry Platform, saying that innovative trials are the last hope for some patients, but that information is often shrouded in a veil of secrecy.

However, the scheme will fall short of full disclosure and may exclude phase I/II 'exploratory' trials. The pharmaceutical industry is also insisting on an option to delay disclosing information about what it deems to be commercially sensitive, including the name of some drugs or even the aim of a trial.

There is a stand-off between the WHO and the industry as to the extent of any exclusions, the length of any delay and who would have access to the information on a confidential basis.

Campaigners say that the commercial case for secrecy is weak, since information can already be found on the Internet by those who know where to look.

A 20-year campaign for more information was given teeth after a series of high-profile scandals. In 2003, the New York Attorney General started civil action against GlaxoSmithKline over reports of suicidal feelings in children and adults taking the anti-depressant Seroxat (paroxetine). In 2004, Merck & Co. (USA) withdrew the anti-inflammatory drug Vioxx (rofecoxib) due to concerns about the raised risk of heart attacks and other cardiovascular events.

MARY GODLESKI / STAR LEDGER / 1009

In January 2005, four pharmaceutical associations and federations covering Europe, America and Japan* issued a joint statement saying: "We recognize that there are important public health benefits associated with making clinical trial information more widely available to healthcare practitioners, patients and others. Such disclosure, however, must maintain protections for individual privacy, intellectual property and contract rights, as well as conform to the regulations in relevant countries."

Exploratory trials

The statement committed the industry to register all clinical trials *other than exploratory trials* (our emphasis) within 21 days of starting patient enrolments. Information would include that "sufficient to inform interested subjects (and their healthcare practitioners) how to enrol". The industry proposed putting other information into a secure database accessible by medical journals on a confidential basis.

Under their plans, trial results would be disclosed only when a drug is commercially available in at least one country. Exploratory trials would be disclosed, "if they are deemed to have significant medical importance and may have an impact on a marketed product's labelling." In the case of failed trials, "study sponsors are encouraged to post the results if possible," but only if results have "significant medical importance".

Although the joint statement represented a shift on the part of the industry, in the eyes of many outsiders it did not go nearly far enough, and it left all the critical judgements about what to release in the hands of the trial sponsors.

The International Committee of Medical Journal Editors (ICMJE) got tough. The editors declared that, from 13 September 2005, they would not publish results from trials unless

* The four pharmaceutical bodies are the European Federation of Pharmaceutical Industries and Associations (EFPIA), the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), the Japanese Pharmaceutical Manufacturers Association (JPMA), and the Pharmaceutical Research and Manufacturers of America (PhRMA)

they were registered before any patients were recruited.

The ICMJE policy embraces the *New England Journal of Medicine*, the *Lancet* and other leading medical journals, and the effect was seismic. As researchers rushed to beat the deadline, there was a 73% increase in the number of clinical trials registered on ClinicalTrials.gov, compiled by the US National Institutes of Health and the US National Library of Medicine. However, ClinicalTrials.gov holds few European phase I/II cancer treatment trials among its 33,000 records.

The International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), which represents research-based pharmaceutical, biotechnology and vaccine companies, launched its own clinical trials portal in September 2005, to link online information from the pharmaceutical industry worldwide.

IFPMA chairman, Daniel Vasella, also chairman and CEO of Novartis, said the portal showed the industry's "commitment to full transparency in the interest of patients and healthcare professionals." However, IFPMA argued that they should be able to delay publication of five "sensitive items", including the scientific title of the study, the intervention itself (such as the name of the drug), the target sample size and the key primary and secondary outcomes.

What this means in practice was demonstrated when Deborah Zarin, Director of ClincialTrials.gov, investigated what was actually filled in by companies on her register. She reported in the *New England Journal of Medicine* in December 2005, that in May 2005, 10% of entries gave no information about the drug being tested. Three industry giants, Merck (USA), GlaxoSmithKline and Pfizer, used a non-specific term such as "investigational drug" between 29% and 91% of the time.

Zarin concluded that an optional register would not work. "When trial sponsors have the option of providing information of marginal clinical value in a particular data field, our findings show that some companies provide useful information and others do not."

Pressure from the editors substantially improved the quality of information. In May 2005, Merck used a non-specific entry such as "investigational drug" for 120 out of 132 trials registered. In October 2005, it provided the name of the drug for all 52 new trials and retrospectively added the name for all but one existing trial. However, GlaxoSmithKline still registered 20% of its trials with a non-specific entry, while Pfizer withheld the drug name for 10% of its trials.

A similar story was revealed for "primary outcome measure" which was commonly left blank by industry before 20 May 2005. Since then, three-quarters (76%) of industry records include an entry.

In September 2005, the four industry groups broadly adopted the WHO registration data set, but continued to argue that information about the five "sensitive" items could be delayed until the drug won approval. Other important areas of disagreement include the timing of when trials should be registered, the role of ethics committees, and the proposal for a WHO unique trial number, which the IFPMA says is unnecessary and bureaucratic. WHO says that the existing system has led to trials being reported twice and double-counted during meta-analysis.

Full disclosure

WHO is challenging critics to spell out exactly what they have to lose by full disclosure, and asks how delayed disclosure is compatible with maintaining public trust. It has launched an open forum on its website, asking for precise examples of how commercial confidentiality or

As researchers rushed to beat the deadline, there was a 73% increase in clinical trials registered

WHO is challenging critics to spell out exactly what they have to lose by full disclosure

intellectual property rights could be damaged (www.who.int/ictrp/comments4/en/). WHO says that the registration of all trials – including early- and late-phase trials – is "a scientific, ethical, and moral responsibility".

It adds, "The Registry Platform also considers it critical on scientific grounds, and in the public interest, that all 20 items in the Registration Data Set be fully disclosed at the time of registration."

WHO will also organise a public forum on delayed disclosure when the Scientific Advisory Group meets in Geneva on 26–28 April.

However, WHO does concede that academic and commercial concerns might justify delaying disclosure, saying, "the issue currently open for discussion is the timing of disclosure, not whether to disclose." It seems that WHO may go along with delaying disclosure of some information for six months or a year.

Ida Sim, WHO project co-ordinator, said: "Many people in the pharmaceutical industry say that disclosure is the right thing to do. It is not just better for patients, it is also better for the industry. If information is available then their products are more useful.

"We might not get complete openness at first, but we can always extend and review the policy. But our first policy statement has to have scientific and ethical integrity or we have lost the game, because this is about restoring public trust."

Beat Widler, global head of clinical quality assurance for Roche, said that the company will include all 20 WHO elements by March 2006. "We have always given the name of the investigational product. We agreed with some of the critics that it does not make sense to write 'investigation drug', because that hides the purpose of the whole exercise."

However, he criticised lack of clear aims for registration and what he saw as the exclusion of the industry from day-to-day discussions within WHO.

"We need to have absolute clarity about the intentions and the goals of these registries. There is a lot of confusion in the public domain, and also amongst the journal editors to be quite frank. The original intention was to provide early access to novel therapies for patients in life-threatening conditions. It has evolved into a much more general discussion about transparency and it is not clear what kind of transparency we mean.

"I am personally involved in the IFPMA working group that is very actively involved with the development of the [IFPMA] search portal, but nobody from this group has been officially invited to participate in the WHO working group, although we have asked many times. It is a pity that people in the industry who have the knowledge and developed a genuine interest in promoting transparency have been sidelined. We need to bring all the people who want to find solutions around the table, and not limit it to groups who frankly have their own political agenda."

Iain Chalmers, a member of the WHO Advisory Board for the International Clinical Trials Registry Platform, and editor of the James Lind Library, believes that complete openness is the only way to regain public trust. "The reputation of the industry is lousy at the moment. People regard it as behaving as disgracefully as the tobacco industry. But there are people in the industry pushing for unlimited openness right from phase I. This is the only way to restore public confidence. Change is inevitable, but it will only happen fully if the journals and the research ethics committees insist on it. The WHO can try to persuade, but it has not got the muscle to ensure it happens."

Chalmers also called for a reduction in the number of repetitive and unnecessary trials.

"I want to see systematic reviews of data to show that existing trials are still necessary. There is an awful lot of indefensible redundancy in clinical research, driven by marketing and because people are too lazy to check what has already been done."

Final option

The European Cancer Patient Coalition points out that exploratory trials for cancer treatment are on patients who have run out of options, not on healthy volunteers. In its submission to the WHO debate, ECPC says, "For many patients, participation in a phase I trial might be their last option to stay alive. This is why access to information about early clinical trials is of critical importance to cancer patients, in stark contrast to patients with other chronic diseases.

"Patients face considerable barriers when

Proposed data set for the WHO clinical trials registry

1. **Primary Register and Trial ID #.** Select name of Member Register in which this trial was first registered (the trial's "Primary Register"), and that register's register-specific unique ID assigned to this trial
2. **Date of Registration in Primary Register.** Date when trial was officially registered in the Primary Register DD/MM/YYYY
3. **Secondary ID#s.** Other identifying numbers and issuing authorities besides the Primary Register, if any. Include the sponsor name and sponsor-issued trial number (e.g., protocol number) if available. Also include other member and non-member trial registers that have issued a number to this trial. There is no limit on the number of Secondary ID numbers that can be provided
4. **Source(s) of Monetary or Material Support.** Major source(s) of monetary or material support for the trial (e.g., funding agency, foundation, company)
5. **Primary Sponsor.** The individual, organisation, group or other legal person taking on responsibility for securing the arrangements to initiate and/or manage a study (including arrangements to ensure that the design of the study meets appropriate standards and to ensure appropriate conduct and reporting). The Primary Sponsor is normally the main applicant for regulatory authorisation to begin the study. It may or may not be the main funder
6. **Secondary Sponsor(s).** Additional individuals, organisations or other legal persons, if any, that have agreed with the Primary Sponsor to take on responsibilities of sponsorship.
   A Secondary Sponsor may have agreed:
   - to take on all the responsibilities of sponsorship jointly with the Primary Sponsor; or
   - to form a group with the Primary Sponsor in which the responsibilities of sponsorship are allocated among the members of the group; or
   - to act as the Sponsor's legal representative in relation to some or all of the trial sites; or
   - to take responsibility for the accuracy of trial registration information submitted
7. **Contact for Public Queries.** e-mail address, telephone number, or address of the contact who will respond to general queries, including information about current recruitment status
8. **Contact for Scientific Queries.** e-mail address, telephone number, or address, and affiliation of the person to contact for scientific inquiries about the trial (e.g., principal investigator, medical director for the study at the sponsor). For a multi-centre study, enter the contact information for the lead Principal Investigator or overall medical director
9. **Public Title.** Title of the study intended for the lay public in easily understood language
10. **Scientific Title.** Scientific title of the study as it appears in the protocol submitted for funding and ethical review. Include trial acronym if available
11. **Countries of Recruitment.** The countries from which participants will be, are planned to be, or have been recruited
12. **Health Condition(s) or Problem(s) Studied.** Primary health condition(s) or problem(s) studied (e.g., depression, breast cancer, medication error)
13. **Intervention(s).** Enter the specific name of the intervention(s) and the comparator/control(s) being studied. Be sure

attempting to find out about clinical trials in progress. Some doctors will not tell their patients about clinical trials … because they are convinced that the treatment they prescribe is superior to trials, or because they are not well informed about ongoing trials themselves."

ECPC is calling for easy-to-understand information about phase 1 trials on patients, even if this was limited to title, rationale, condition, intervention, brief description of study and expected outcomes.

Jan, who runs Leukämie-online (www.leukaemie-online.de) for leukaemia patients in German-speaking countries, found out at the age of 28, that he had chronic myeloid leukaemia (CML).

He believes his life was saved by an "investigatory" trial.

to describe the intervention(s) for every arm of the study in separate entries. Use the International Non-Proprietary Name if possible (not brand/trade names). For an unregistered drug, the generic name, chemical name, or company serial number is acceptable. If the intervention consists of several separate treatments, list them all in one line separated by commas (e.g., "low-fat diet, exercise")

The comparator/control intervention is/are the intervention(s) against which the study intervention is evaluated (e.g., placebo, no treatment, active control). If an active control is used, enter the name(s) of that intervention, or enter "placebo" or "no treatment" as applicable.

For each intervention, describe other intervention details as applicable (e.g., dose, duration, mode of administration, etc.)

14. Key Inclusion and Exclusion Criteria. Key inclusion and exclusion criteria for participant selection, including age and sex

15. Study Type. A single group study is one in which all participants are given the same intervention. Trials in which participants are assigned to receiving one of two or more interventions are NOT single group studies. Crossover trials are NOT single group studies.

For multiple group studies (two or more study groups), a trial is "randomized" if participants are/were assigned to intervention groups by a method based on chance

16. Date of First Enrolment. Anticipated or actual date of enrolment of the first participant (MM/YYYY)

17. Target Sample Size. Number of participants that this trial plans to or had planned to enroll

18. Recruitment Status. 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 enrollment
- Closed: participants are no longer being recruited or enrolled

19. Primary Outcome(s). Outcomes are events or experiences that trial investigators measure because it is believed that they may be influenced by the intervention or exposure. The Primary Outcome should be the outcome used in sample size calculations, or the main outcome(s) used to determine the effect of the intervention(s).

Enter the names of all primary outcomes of the trial. Be as specific as possible (e.g., "Beck depression score" rather than just "depression"). For each outcome, also provide all the timepoints at which it is to be measured. Examples: Outcome name: all cause mortality, Timepoint: one year; or Outcome name: Beck depression score, Timepoint: 6, 12, and 18 weeks

20. Key Secondary Outcomes. Outcomes are events or experiences that trial investigators measure because it is believed that they may be influenced by the intervention or exposure. Secondary outcomes are events or experiences other than the primary outcome(s) that will be used to evaluate the intervention(s), and that are specified in the study protocol.

Enter the name of each secondary outcome of the trial. Also provide all the timepoints at which this outcome is to be measured. Examples: Outcome name: cardiovascular mortality, Timepoint: 6 months; or Outcome name: functional status, Timepoint: 4 and 8 weeks

"I went onto the Internet and there was a US group of patients having a discussion on Yahoo. I went from doctor to doctor to get different opinions and evaluate options." After a doctor from Mannheim spent more than an hour on the phone explaining his options, Jan joined a 20-patient phase I/II trial combining imatinib (Glivec, then known only as STI-571) with pegylated interferon-alpha. Five years later he is in complete remission.

"If phase I is excluded, I would be disappointed. I think the commercial arguments are not very strong. You can find all the information about phase I trials on the Internet if you understand medical terms, are Internet-savvy and speak the right language. I am sure the companies know exactly where to look, because patients seek advice, share knowledge with other patients and have no reason to withhold information."

He points out that a patient-run unofficial Glivec site (www.newcmldrug.com) includes a lively discussion about a new drug for CML being trialled by Bristol-Myers Squibb, BMS-354825/dasatinib. "We pretty well knew about BMS from the day it started in human trials."

But Widler from Roche doubts whether registries would help patients in a phase I setting. "Generally, once you have approval for phase I, the trial starts virtually the next day. By the time a patient finds out through the registry, the trial is already finished."

Roche and IFPMA are discussing the possibility of a separate section of the register, where sponsors could outline the main thrust of a phase I trial and doctors or patients could register an interest in new products.

"If the emphasis is to give access to patients who basically have no hope on the basis of current therapies, then the design of the trial, the 20 fields, the fact that the industry has some reservations because of intellectual property, all become irrelevant. The only thing you need to know is that there is something out there that has a potential to treat my condition, and I would like to be part of it," says Widler.

There are ethical questions about the digital divide and how some patients would get access to trials which others never hear about. But Sim from WHO does not think that registries affect this problem. "There is biased recruitment now and registration does not change that. Patients are being recruited and they are hearing about trials. With delayed disclosure, what would be lost is the sense of transparency and accountability in the short term. You would not be able to search for trials on a website. But patients would still find out about trials and get in."

There are also ethical concerns about patients chasing trials that have little to offer. Widler says patients should understand that when they join a phase 1 trial they are hoping for a miracle. "We are talking more about hope than about a medicine or treatment. We need to be very careful how we deal with this."

However, Jan insists that many patients can only survive with what are seen as exploratory trials. He believes it is important that patients enrolling on trials find out about the background and rationale. "How can patients give informed consent without listening to their doctor and informing themselves about the trial?"

A recent study (NEJM 2005, 352:895–904) showed that the response rate to phase I clinical trials for cancer patients averaged 10.6% with large variations between trials.

It is unlikely that the gap between the hopes of campaigners for open information and the fears of industry and academics about competitive advantage will be bridged before the public debate in Geneva. An era of total openness has not arrived, but a dramatic reduction in the extent of commercial secrecy is under way. How far and fast that will go may depend on who blinks first.

"We pretty well knew about BMS-354825 from the day it started in human trials"