

Ethical concerns in clinical trials in India: an investigation



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Executive summary

This report is the product of a journalistic investigation on clinical trials. It set out to identify ethical concerns in clinical trials that were conducted in India and used for approval of new drugs in the European Union (EU). It was initiated after discussions with the health advocacy organisation Wemos and the research organisation Centre for Research on Multinational Corporations (SOMO), both based in Amsterdam. Wemos has been campaigning with EU regulatory authorities to prevent the use of unethically conducted clinical trials towards marketing approval in the EU. The plan was to document available information on up to three trials and the ethical concerns that they raised.

This work is set within the larger agenda of looking at the ethical conduct of biomedical research in India. Such research includes clinical trials in humans that are used for drug development and approval purposes, trials conducted for marketing purposes alone, research that is conducted in the garb of clinical practice, and other unscientific and unethical research practices that may collect information to be used towards drug development.

This investigation followed a trial of lapatinib, a drug for breast cancer, one trial of risperidone, a psychiatric drug, and two trials of quetiapine, another psychiatric drug.

Findings

These trials exploited the fact that most Indians do not have access to good quality and affordable care and therefore may accept offers that might provide better quality and free treatment. They were conducted on people who were vulnerable because they could not afford good quality treatment or the most effective drugs. The patients were also vulnerable because they were seriously ill. In the case of psychiatric patients, they may not have been able to provide informed consent.

Lapatinib, GlaxoSmithKline

1. This Phase 2b trial of lapatinib monotherapy for chemotherapy naïve patients with advanced HER2 positive breast cancer had three sites in India.
2. The majority of breast cancer patients in India cannot afford proper treatment. This trial required seriously ill patients who had not received treatment for their condition. Their economic vulnerability forces patients in India to take part in trials in order to get access to treatment and to disregard the potential risks that participating in clinical trials entails. By carrying out this clinical trial in India GlaxoSmithKline (GSK) took advantage of the vulnerable position of breast cancer patients.
3. The statement by a representative of GSK suggests that patients, who stopped responding to lapatinib, were not assured treatment once the trial was completed.
4. As a concurrent phase multi-country trial conducted before January 2005, the trial contravened an Indian government regulation that was in place when it was conducted. The company's statement does not indicate that the trial was permitted as an exception to this regulation.
5. The approved drug is not affordable to the vast majority of Indians who could benefit from it.

Risperidone, Johnson&Johnson

1. This placebo-controlled trial of risperidone for acute mania was conducted in seven sites in India.
2. It used a trial design that is required by United States (US) regulatory authorities but is viewed by many – including the lead investigator – as methodologically unnecessary.
3. Patients in the risperidone trial were recruited from both government and private hospitals. More than two thirds of patients were recruited from government hospitals where the most severely ill patients are found.
4. Patients in this trial from government hospitals may have viewed trial participation as a way to get improved care as clinical trials require monitoring for efficacy and safety. Patients in this trial from private hospitals may have viewed trial participation as a way to get free care.
5. The patients in this trial were much more severely ill than similar trials of risperidone conducted in the US and other developed countries. The severity of their illness could have affected their ability to consent.
6. Patients in this trial were suffering from an acute attack of a psychiatric condition that would have caused them much distress. They were harmed because they were taken off all treatment before they were put on either the active drug or a placebo. Those on the placebo were also harmed because they were deprived of an effective treatment.

Quetiapine fumarate extended release, AstraZeneca

1. These two placebo-controlled trials of quetiapine were conducted on patients with schizophrenia. An immediate release formulation of the drug had already been approved and these trials were of an extended release version of the drug.
2. The trials examined the drug's impact on patients with acute schizophrenia and for long-term maintenance therapy in schizophrenia.
3. The trial design in these trials was not necessary. Placebo-controlled trials are not required to establish the efficacy of a new formulation of an approved drug. Nor are they required by regulatory authorities in India.
4. Patients in the quetiapine trials in India were recruited from both government and private hospitals. Patients in this trial from government hospitals may have viewed trial participation as a way to get improved care as clinical trials require monitoring for efficacy and safety. Patients in this trial from private hospitals may have viewed trial participation as a way to get free care.
5. Schizophrenia is a serious psychiatric disorder and withholding effective treatment causes patients harm. Patients in the trial of quetiapine for acute schizophrenia were harmed when they were taken off all treatment before being put on either the active drug or a placebo. Patients on placebo – in both trials – were also harmed because they were deprived of an effective treatment until they suffered a relapse.
6. A patient in one of the quetiapine trials committed suicide after 173 days of being on placebo. The authors of the journal article reporting on this trial have stated that this suicide is “not considered treatment related”. Suicide is a known risk for patients with schizophrenia. The investigators do not explain how they concluded that the suicide was unrelated to the treatment. The possibility cannot be ruled out that the patient committed suicide because s/he was deprived of effective treatment.

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7. There were deaths in both the quetiapine trials. No information is available on where these deaths took place. Nor is there information on whether compensation was paid to the families of the patients.

In sum

1. These trials violated the Indian Council of Medical Research's (ICMR) ethical guidelines for biomedical research and the World Medical Association (WMA) Declaration of Helsinki: *Ethical principles for medical research involving human subjects*.
2. The Drugs Controller General of India (DCGI) does not require placebo-controlled trials before granting a drug marketing approval. However, the DCGI does not ban the use of placebo-controlled trials. The ruling on whether a trial design violates ethical principles is left to individual local ethics committees. A trial refused permission by an ethics committee at one trial site may be submitted to another and approved. According to the journal articles reporting these trials, they were conducted after receiving clearance from the local ethics committees. The existing regulatory apparatus therefore permits unethical trials of no benefit to Indians.
3. There is no evidence that government policy permitting such unethical trials will change in the future; on the contrary, the government priority is, apparently, to ensure that clinical research in India produces good quality data according to Good Clinical Practice standards. Ethical guidelines – including its own ethical guidelines – seem to be of secondary importance.

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1. Summary of the investigation

This report is the product of a journalistic investigation of four clinical trials chosen from a list of 12 trials sent by SOMO.

The 12 trials were: four placebo-controlled phase 3 trials of quetiapine, a psychiatric drug marketed by AstraZeneca; three phase 2 trials of lapatinib, a drug for breast cancer marketed by GlaxoSmithKline (GSK); three phase 3 trials of ciclesonide, an inhaled steroid for asthma marketed by Nycomed Pharma/Altana Pharma; one phase 3 trial of pregabalin for neuropathic pain marketed by Pfizer, one phase 3 trial of exenatide, an injectable drug for diabetes marketed by Eli Lilly, and one phase 3 trial of amlodipine/atorvastatin, a combination drug for hypertension and high cholesterol marketed by Pfizer.

Searches were conducted for the study results of these trials. Experts were consulted for their opinions on whether there were ethical concerns in any of the trials.

The companies were also contacted by telephone. E-mails were sent to the person identified as responsible for corporate communications. The e-mails stated that we (Sandhya Srinivasan and Sachin Nikarge) were researchers from the Centre for Studies in Ethics and Rights and wished to obtain more information on these trials. Representatives of two of the companies replied that they would not provide any information. The other three did not reply to e-mails and could not be contacted on the telephone.

After the searches and consultations with experts, four trials were chosen for investigation (the process of identifying these trials is described in Appendix II):

1. A phase 2b trial of the cancer drug lapatinib marketed by GlaxoSmithKline. The participants were patients with advanced breast cancer who had not had any treatment. An oncologist shown a list of three cancer drug trials commented that this trial had denied patients effective treatment.
2. Two placebo-controlled trials of the anti-psychotic drug quetiapine fumarate extended release (XR) for schizophrenia. The drug is marketed by AstraZeneca. In a report¹ published in 2007, experts stated that the immediate-release version (IR) of this drug had already been approved for marketing and the XR formulation should have been tested against the IR version.
3. A placebo-controlled trial of the antipsychotic drug risperidone for acute mania. The drug is marketed by Johnson & Johnson. This trial was not in the list provided by SOMO but was chosen for follow-up because the trial has been criticised in a commentary² as unethical. The commentary writer stated that the drug should have been tested against an established drug instead of against a placebo.

¹ Schipper Irene, Weyzig Francis. *Ethics for drug testing in low and middle income countries: considerations for European market authorisation*. Amsterdam: Centre for Research on Multinational Corporations; 2008 Feb.

² Patel V. Ethics of a placebo-controlled trial in severe mania. *Indian J Med Ethics* 2006; 2: 11-2.

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These trials were chosen because the trial designs raised ethical questions; they were conducted on vulnerable groups, and they were conducted primarily or exclusively in countries where concerns have been raised about the quality of regulation of such trials. In addition, in the case of lapatinib, the drug is very expensive and therefore unaffordable for most people who would need it.

Method of investigation

Once the trials were chosen for further investigation, information was collected on the trial sites and contact details of the investigators in these trials, the institutions where the trials took place, and the drug companies.

At this stage of the investigation of the four trials, I (Sandhya Srinivasan) approached everyone as a freelance journalist writing on clinical trials in India. I introduced Sachin Nikarge as my colleague. My visiting card containing my address and telephone number was provided to those with whom we conducted face-to-face interviews. All written correspondence to investigators, institutions, company representatives and key informants carried information on my affiliations (Infochange News and Features, *Indian Journal of Medical Ethics* and the Centre for Studies in Ethics and Rights) with the websites of the organisations.

Contacting investigators

An attempt was made to contact all the investigators for an interview. Face-to-face interviews were conducted with Shona Nag and Dinesh Doval, investigators in the lapatinib trial, Sumant Khanna, lead investigator in the risperidone trial, and Jitendra Trivedi, investigator in all three psychiatric drug trials. Telephonic interviews were conducted with R Sathianathan, Kurien Kuruvilla and Vijay Debsikdar, investigators in the risperidone trial, and Prasad Rao, investigator in one of the quetiapine trials.

Podila Sharma, an investigator in all three psychiatric drug trials, was contacted for a telephonic interview and was sent a list of questions by e-mail. The e-mail was acknowledged but no further information was provided. Shiv Gautam, an investigator in one of the quetiapine trials, was contacted by telephone. He asked to be phoned later but then did not take any calls.

Contacting institutions

Shelley Awasthi, member of the institutional ethics committee of the King George Medical College in Lucknow, a site for all three psychiatric drug trials, was interviewed in person at the institute premises. Hari Gautam, the former vice chancellor of the KGMC, was interviewed on the telephone.

The office of the director of the National Institute of Mental Health and Neuro Sciences, a site for the risperidone trial, was contacted by telephone for an interview on clinical trials. A request was also sent to the office by e-mail. This e-mail was not acknowledged.

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Letters were sent by courier to the head of the institutions where the trials had taken place, asking for details on the trials conducted on their premises. Responses were received from three institutions.

A request for an interview on clinical trials was faxed to the office of the Drugs Controller General of India. The DCGI's office acknowledged receipt of this request but did not reply to the request or to follow-up telephone calls.

Contacting companies

A second attempt was made to contact the spokesperson of the companies manufacturing the three drugs. A list of questions on the trials was sent by e-mail and courier to the director (corporate communications) of Johnson & Johnson and AstraZeneca and the medical director of GSK. Telephone calls were also made to Quintiles, the contract research organisation that ran the psychiatric drug trials, but the calls were not returned. Johnson & Johnson and GSK sent e-mailed responses.

Interviews with experts

Information was gathered from experts including medical specialists, clinical pharmacologists, government officials familiar with the regulatory process, and those working in non-governmental organisations and the contract research industry. They were interviewed on the clinical trial scenario in India, regulatory and ethical issues, and a technical analysis of the clinical trials under consideration. Information was also gathered from presentations, interviews and informal discussions at meetings on clinical research³.

Further details on the contact and correspondence with researchers, institutions and companies are provided in Appendices I and II.

³ Second International Conference of the South Asian Chapter of American College of Clinical Pharmacology on "Drug discovery and development: south Asian perspective" on October 4-5, 2008 (SS attended as a journalist associated with CSER, SN as a registered participant associated with CSER); Fifth Global Conference on Clinical Research and Development, Institute of Clinical Research [India], October 10-11, 2008 (SS and SN attended as registered participants associated with CSER); Conference of the Clinical Research Education and Management Academy on "Global issues in patient recruitment and retention: challenges and solutions", November 3-4, 2008 (SS attended as an invited speaker and journalist and listed all affiliations: Infochange News and Features, *Indian Journal of Medical Ethics* and Centre for Studies in Ethics and Rights).

Interviews

The interviews were unstructured. A list of questions on each trial was used as guide. Interviews with researchers began with general questions on the outsourcing of clinical trials to India, and concerns that trial participants would be exploited in these trials. They eventually led up to questions about the type of trials being discussed (psychiatric trials or cancer trials), the conditions in which such trials were carried out, whether informed consent was possible and why patients would participate in these trials. This was followed by questions about the trial(s) of interest to this investigation. Consent was sought to tape face-to-face interviews and for one telephonic interview (it was given in all but one case). All those who are quoted in this report were contacted by telephone for their e-mail addresses and sent their quotes by e-mail for their approval. Kurien Kuruvilla, an investigator in the risperidone trial, did not provide his e-mail address. R Sathianathan provided his e-mail address but did not reply to the e-mail. Vijay Debsikar's e-mail address was provided by his wife but he did not reply to the e-mail. All others who are quoted here have given their approval to the quotes attributed to them.

Discussion on ethical issues in the investigation

Possible ethical concerns in this journalistic investigation were discussed during its progress. The work involved reading regulatory documents, journal articles and other reports, along with contacting company representatives, researchers and institutional heads of the research sites. The information sought was of the type that was – or should be – in the public domain. No attempt was made to contact patients. It was felt that in this investigative process the accepted ethical principles of media practice should be followed: it would be made clear at the very start that the purpose of gathering information was to make it publicly available, and anonymity would be provided when it was requested, or offered when it was felt necessary to obtain information.

This report was finalised after comments from Annelies den Boer, project coordinator Medicines, Wemos Foundation, Amsterdam, The Netherlands; Francis Weyzig, Centre for Research on Multinational Corporations (SOMO), Amsterdam, The Netherlands; Amar Jesani, Anusandhan Trust and Centre for Studies in Ethics and Rights, Mumbai; Bebe Loff, department of human rights and bioethics, school of public health and preventive medicine, Monash University, Melbourne, Australia; and S Srinivasan, managing trustee, LOCOST Standard Therapeutics, Vadodara, Gujarat, India. Ruth Macklin, department of epidemiology and population health, Albert Einstein College of Medicine, New York, USA, commented on the issues raised in the lapatinib trial. CM Gulhati, editor Monthly Index of Medical Specialities (MIMS) India, commented on the section on regulation of clinical trials in India.

Amar Jesani and Neha Madhiwalla, Centre for Studies in Ethics and Rights, gave regular inputs into the investigation and also provided ethics consultation for this purpose.

2. Background of clinical trials in India

The larger context of clinical trials in India is poverty and the absence of affordable health care.

For more than a decade, government policy has been to reduce public support for health care services, and these services are under-resourced. Health economists have pointed out that only 15 per cent of the Rs 1,500 billion spent in the health sector in India comes from the government. Four per cent comes from social insurance and one per cent from private insurance companies. The remaining 80 per cent is spent by individuals using private services and without insurance. Two-thirds of health care users bear 100 per cent of their health care expenses. Seventy per cent of these health care users are poor. More than half of the poorest 20 per cent of Indians sold assets or borrowed to pay for health care⁴.

Patients in both government hospitals and private hospitals are desperate for better quality and affordable care. Patients choose public hospitals because they cannot afford treatment in private hospitals but even here they pay for some drugs, tests and procedures, and this constitutes a burden that many cannot afford. The vast majority of Indians must pay for medical treatment from their own resources. Patients in private hospitals are more able to afford treatment but catastrophic medical expenses can force them to sell assets, go into debt, or stop essential treatment. Various surveys have found that medical expenses are a major factor forcing many Indians below the poverty line⁵.

In this situation, government moves to encourage clinical trials in India must be viewed with concern. Changes have been made in the law to permit international trials. Staff and infrastructure improvements and regulatory changes are meant to speed up processing of applications. Public hospitals are being promoted as clinical trial sites. Monitoring systems are being set up to ensure high data quality and meet the requirements of drug regulatory authorities abroad. Training institutes are being encouraged to provide the manpower to run clinical trials.

The government has not expressed a stand on the manner in which the clinical research industry is growing in India. Clinical trials are conducted by contract research organisations (CROs) which are developing the infrastructure for trials by making inroads into small towns, identifying trial sites in small private hospitals and developing databases of potential trial participants. Medical professionals are given substantial incentives to recruit their own patients into clinical trials. This situation creates a major conflict of interest that threatens the well-being of patients.

India is viewed as a favoured global site for international clinical trials of drugs. According to the Drugs Controller General of India (DCGI), India will be a preferred site for clinical trials because, in addition to its medical infrastructure and trained, English speaking manpower,

⁴ Duggal R. The out-of-pocket burden of healthcare. *Agenda: Access to public health*. Pune, India: Centre for Communication and Development Studies, 2005. pp 20-25.

⁵ Iyer A. Ill and impoverished: The medical poverty trap. *Agenda: Access to public health*. Pune, India: Centre for Communication and Development Studies, 2005. pp 16-18.

it has a “large, diverse and treatment-naïve [untreated] population with six out of the seven genetic varieties of the human race”; a pool of patients with both acute and chronic diseases, an increase in the number of patients with lifestyle disorders and the highest recruitment rates for such trials internationally⁶. The Indian government has seized upon this opportunity and is taking steps to change the regulatory climate here to accommodate the needs of international clinical trials.

2.1 Regulation of clinical trials

Clinical trials in India are regulated by Schedule Y of the Drugs and Cosmetics Rules. The Rules are enforced by the office of the DCGI who is also responsible for monitoring all clinical trials submitted to that office for approval. For new drugs being developed in India clinical trials have to be conducted in India from phase 1.⁷ For marketing approval of drugs already approved in other countries, a phase 3 clinical trial is required on about 100 patients in three or more centres, in order to establish the drug’s impact on the Indian ethnic population. An application for a new indication of an already approved drug is treated as an application for a new drug’s approval. New formulations of approved drugs may be subjected to bioequivalence studies.

Till January 2005, clinical trials of new drugs being developed outside India were permitted only with a “phase lag”: a phase 2 trial could be conducted in India only after phase 3 trials were completed elsewhere⁸. Phase 1 trials of foreign drugs were not permitted, except for drugs of special relevance to India. This clause enabled, for example, phase 1 trials of HIV vaccines in India. In fact, international multicentre trials have been conducted in India since the mid-1990s⁹.

As of January 2005, an amendment of Schedule Y of the Drugs and Cosmetics Rules¹⁰ did away with the phase lag in international clinical trials conducted by foreign sponsors. There are no longer any restrictions on “concurrent phase” clinical trials in India. Phase 2 and phase 3 trials of drugs discovered abroad may now be conducted in India in the same phase and at the same time as they are conducted in other parts of the world. The trial sponsor must obtain approval from the DCGI before starting a trial. For this approval, the sponsor must submit data from pharmacokinetic and animal studies and previous phase trials; information on the regulatory status of the drug in other countries, the trial protocol, investigator’s brochures and informed consent documents. Trials cannot be started without clearance from the local ethics review committee (EC) at each site.

⁶ Presentation by Surinder Singh, Drugs Controller General of India, at the meeting of the Institute of Clinical Research (India), Mumbai, October 10-11, 2008.

⁷ Phase I trials collect information on the drug, including its safety and adverse reactions. They are usually conducted on a small number of healthy volunteers. Phase II trials evaluate the effectiveness and safety of a drug on patients. Phase III trials are conducted on larger numbers of people to confirm the evidence from earlier phase trials towards obtaining marketing approval of the drug. Phase IV trials are conducted after a drug obtains marketing approval. They are conducted for various purposes including monitoring for drug interactions and testing for new uses of the drug.

⁸ CM Gulhati, editor, *MIMS India*, interviewed by e-mail, November 15, 2008.

⁹ Sumant Khanna, advisor, CliniRx Research, Delhi, interviewed in Delhi, October 1, 2008.

¹⁰ Government of India. Ministry of health and family welfare. The Drugs and Cosmetics Act and Rules. As amended up to the 30th of June 2005. <http://cdsco.nic.in/html/Drugs&CosmeticAct.pdf>

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Before 2005, the Drugs and Cosmetics Rules suggested, but did not require, that clinical trial documents be reviewed by an ethics review committee. The Rules as amended in January 2005 require that the clinical study report include a statement that the trial was conducted according to the principles of the Declaration of Helsinki, Indian Good Clinical Practice guidelines, and the Indian Council of Medical Research's ethical guidelines for biomedical research on humans.

The Indian Council of Medical Research (ICMR) first published detailed guidelines for biomedical research¹¹ in 2000. These include guidelines for ethical review. Revised guidelines published in 2006¹² state that the ethics review committee is also responsible for monitoring trials. A draft bill to make the guidelines legally binding is pending with the ministry of health¹³. Once passed, the law will require that all ECs register with a Biomedical Research Authority. This authority will also evaluate the functioning of ECs.

However, ethics review is far from adequate. Not all ECs are established as per legal provisions; members are not sufficiently trained for this work, and support is not given to them to conduct thorough reviews. An ICMR survey found that only 40 of 179 institutional ethical committees follow the prescribed legal provisions and function as per various ethical guidelines¹⁴. There is no central register of EC decisions and if a protocol is rejected by one local EC it may be submitted elsewhere. The sponsor is not obliged to inform an EC – or the DCGI – if the protocol being submitted to it has been rejected elsewhere.

Further, the DCGI is not equipped to monitor existing clinical trials in India. The DCGI's office currently has a staff of four or five professionally qualified people and at present does not inspect clinical trial sites though the government has announced that it is recruiting new staff for this purpose. Audits of clinical trial data are at present only conducted by contract research organisations and sponsors. The United States Food and Drug Administration (USFDA) has recently started auditing trial sites¹⁵.

¹¹ Indian Council of Medical Research. *Ethical guidelines for biomedical research on human subjects*. New Delhi: ICMR; 2000. <http://icmr.nic.in/ethical.pdf>

¹² Indian Council of Medical Research. *Ethical guidelines for biomedical research on human participants*. New Delhi: ICMR; 2006. http://icmr.nic.in/ethical_guidelines.pdf

¹³ Bill on Biomedical Research on Human Participants (Promotion and Regulation). Mentioned in Indian Council of Medical Research. *Ethical guidelines for biomedical research on human participants*. New Delhi: ICMR; 2006. http://icmr.nic.in/ethical_guidelines.pdf

¹⁴ Mudur G. India plans to audit clinical trials. *BMJ* 2005; 331: 1044.

¹⁵ Sumant Khanna, interviewed in Delhi, October 1, 2008. Arun Bhatt, president of Clininvent Research Pvt Ltd, interviewed in Mumbai, November 13, 2008.

2.2 Government steps to promote clinical trials

At a meeting of the Institute of Clinical Research [India] (ICRI) in Mumbai, Surinder Singh, Drugs Controller General of India, described a number of other steps that the government plans to undertake towards encouraging international clinical trials in India¹⁶.

In addition to changes in the law (that have already taken effect), single window clearance for applications is planned in order to reduce the approval procedure to between two and six weeks. A two-tier approval process is already in place. Category A protocols consist of protocols from the US, United Kingdom (UK), EU and Japan. Category A trials will get fast-track approval of six to eight weeks. Category B trials from other countries will get approval in eight to 12 weeks. The government will grant a license to import supplies within two weeks of the application being made. The DCGI has also promised that local EC review will be completed in six to eight weeks. By 2009, he said, timelines will be in harmony with international clinical trials.

The DCGI announced plans to recruit subject experts and has also got approval for 60 new drug inspectors. 20 of these inspectors will be responsible exclusively for auditing clinical trials.

The DCGI has announced various short-term, medium-term and long-term goals towards encouraging international clinical trials in India. The short-term goals (2008) include developing guidelines for registering CROs, training clinical trial site inspectors, a “robust” review process, and meeting timelines. Mid-term goals to be achieved in 2009 are registration of CROs, inspection of sites, guidelines for registering ECs, and mandatory registration of clinical trials. Import duty has been lifted on clinical trial supplies and permission for export of clinical trial specimens will be granted at the same time as the protocol is approved by the DCGI. Clinical trials have been exempted from sales tax. The DCGI also stated that fingerprinting of trial participants is planned to prevent them from entering more than one trial.

The government’s long term goals (2010 to 2015) as stated by the DCGI include changing the law to permit phase 0 (microdosing) and phase 1 trials. As of now, the Drugs and Cosmetics Act does not permit phase 1 trials of foreign drugs in India unless the drug is of local relevance. However, discussions are currently on to introduce phase 0 and phase 1 trials for which consultations have been held with industry, researchers, lawyers, social organisations and Non-Governmental Organisations (NGOs). At the ICRI meeting in October 2008, the DCGI stated: “We will *have* to have phase 0 and 1 trials in India.” Other long-term goals include a central drug authority, and penal provision for CRO fraud. He also stated that a “clinical trials export promotion council” is under consideration.

¹⁶ Information in this section on “Government steps to promote clinical trials” is drawn from the inaugural address of Surinder Singh, Drugs Controller General of India, at a conference of the Institute of Clinical Research (India), Mumbai, October 10-11, 2008.

2.3 Trends in international clinical research in India

International clinical trials have been conducted in India starting in the mid 1990s though it was only in 2005 that regulations were changed to routinely enable concurrent phase trials.

The DCGI has stated that there are 582 (registered) clinical trials being conducted in India, of which 72 per cent are conducted by the pharmaceutical industry¹⁷. (A search in October 2008 of www.clinicaltrials.gov for trials with a site in India lists 789 studies, planned, recruiting terminated and completed.)

2.4 Contract research organisations

Drug companies conduct clinical trials through contract research organisations (CROs), commercial entities whose job it is to get the research done and to meet regulatory requirements. Since the early 2000s, there seems to have been a sharp rise in the number of contract research organisations functioning in India; the DCGI has stated that the estimated number of contract research organisations in India registered with the USFDA has gone from 60 to 150.

CROs may handle some or all aspects of a sponsor's project including: regulatory approvals for trials, identifying recruiting sites and investigators, monitoring sites, data entry and management, submitting data for marketing approval and drafting study reports for submission to journals. These activities may also be split up and handled by different organisations. Some organisations focus exclusively on providing data management and statistical analysis. Trial sites that do not have institutional review boards may approach "stand alone" ethics committees not affiliated to any institution. Site maintenance organisations (SMOs) are focused exclusively on recruiting patients and coordinating the work of investigators conducting clinical trials¹⁸.

Some CROs commit to drafting journal articles and getting them published. One organisation, IRL Research, focuses on patient recruitment. IRL Research's staff members at each site develop a database of potential trial participants taken from the hospital database. "Independent databases" are also developed through physician referrals, health camps, patient education programmes and community outreach through social workers and NGOs, and advertisements in the media¹⁹.

2.5 Why do people participate in clinical trials?

A CRO-conducted survey of the informed consent process in clinical trials provides some interesting information on the patient recruitment procedure and the quality of informed consent in clinical trials in India²⁰. This survey was of patients participating in trials run by the

¹⁷ Surinder Singh, Drugs Controller General of India, at a conference of the Institute of Clinical Research (India), Mumbai, October 10-11, 2008.

¹⁸ Arun Bhatt, interviewed in Mumbai, November 15, 2008.

¹⁹ www.irlresearch.com .

²⁰ Presentation by Dan McDonald, vice president, business development, Excel Life Sciences, at a meeting of the Institute of Clinical Research (India), Mumbai, October 10-11, 2008.

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CRO Excel Life Sciences and began in July 2008. As of October 2008, 525 patients from 40 sites had been interviewed. Most were treatment naïve (untreated for the condition for which the drug was being tested) when they entered the trial.

Seventy six per cent of patients said the trial's principal investigator was their primary physician. A further 21 per cent said they were referred by their primary care physician. In other words, 97 per cent of patients entered the trial *because* of their primary care physician. It is well known that the doctor-patient relationship in India is unequal. Patients may not question their doctors' judgement. They may be easily influenced by the doctor's advice. They may also believe that refusal to follow the doctor's advice to enter a trial would affect their access to care.

When the trial's principal investigator is also the person's primary physician, there is scope for a direct conflict of interest, especially if physicians are paid recruitment fees to recruit their patients into trials.

The survey's findings on why people entered a clinical trial were enlightening:

15 per cent stated that they entered the trial because they were looking for a cure.

13 per cent were looking for "observed benefits".

15 per cent were looking for a better treatment.

16 per cent were looking for higher quality care.

10 per cent were looking for free medication and medical care.

15 per cent said the doctor advised them to enter the trial.

5 per cent said they entered the trial to receive money for participation.

11 per cent said they entered the trial to help advance scientific knowledge.

Some of the categories – such as "observed benefits" – are not clearly described. However, it is a matter of concern that 26 per cent of participants stated that they entered the trial to obtain free care or higher quality care. It is quite possible that such patients overlook risks to participate in trials. Another 15 per cent stated that they were following their doctor's advice – a possible concern if their doctor received fees to recruit them into the trial. The five per cent who entered the trial to receive money for participation are very likely to have overlooked the risks of participation.

According to the ICMR's guidelines, "... payments should not be so large or the medical services so extensive as to make prospective participants consent readily to enroll in research against their better judgment, which would then be treated as undue inducement." However, patients in bioequivalence trials (used to check that generic versions of approved drugs or for new formulations of approved drugs work as well as the approved drug) may have paid up to Rs 20,000 to participate in the trial.

2.6 Incentives for clinical trial investigators

When the government declared its plans to use government hospitals as clinical trial sites²¹, government institutions were already the sites for many clinical trials. Public hospitals are resource-starved (the per capita expenditure on health was \$100 in 2005, of which less than 20 per cent was by the government²². In 2002, public expenditure on health was less than one per cent of the Gross Domestic Product²³ and this percentage has not changed since then). Patients at public hospitals are often forced to go to private centres and pay for basic tests, drugs and supplies.

Government doctors running trial sites do not officially receive fees for recruiting patients into clinical trials. A CRO with a trial site in a government institution will pay about 15 per cent of the budgeted expenses for that site directly to the institution. The hospital department running a trial site gains some equipment and the salaries of junior/additional investigators are paid by the trial sponsor for the duration of the trial. Administrators and senior staff at government hospitals may view clinical trials as helping the work of an under-resourced hospital.

Principal investigators also get invited to all-expenses paid conferences abroad. For government doctors, such trips may be enough incentive to conduct trials, even without recruitment fees.

The incentives to investigators in private hospitals are more upfront; the investigator is paid according to the number of patients recruited (additional benefits include all-expenses paid trips abroad to attend conferences).

Investigators in private hospitals get paid recruitment fees of between \$1,500 and \$3,000 (Rs 60,000 to Rs 120,000) per patient, depending on the drug and the type of trial. Oncology trials get higher payments because the trial takes a comparatively longer time and there are fewer patients available for recruitment.

The following example illustrates the economic incentives of a clinical trial in a private institution. Psychiatrist Prasad Rao agreed to be interviewed²⁴ for the investigation. Dr Rao is with the Asha Hospital, a private hospital in Hyderabad, Andhra Pradesh and runs a busy practice, with 70-80 patients in the out patient department (OPD) every day. Asha Hospital has three independent investigators, each with 6-7 ongoing trials. Each investigator recruits 10-15 patients per trial. Recruitment rates are about 4-8 per investigator per month.

According to Dr Rao, payments to the principal investigator at a trial site are meant to cover various research-related expenses. "For example, I have two doctors and a nurse working under me for each trial and they will be on the trial for about a year. I also have

²¹ Kashyap SD. Haffkines short-listed for clinical trials training. *Times News Network*. March 15, 2005: <http://timesofindia.indiatimes.com/articleshow/1052189.cms> accessed October 31, 2008

²² World Health Statistics 2008 <http://www.who.int/countries/ind/en/>

²³ National Health Policy, 2002 (India) http://mohfw.nic.in/NRHM/Documents/National_Health_policy_2002.pdf

²⁴ Dr Rao was interviewed because he was an investigator in one of the trials discussed in this report.

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communication costs and then there is the cost of the hospitalisation of the patient. We also have to maintain a research pharmacy with 24-hour air conditioning and a minimum space for each trial. Then there should be facilities to store blood samples at minus 20 degrees. And once we start a research centre we should also be able to store the records for 15 years. For all this we must buy space in the hospital.”

The principal investigator will be given a monthly sum for investigators’ salaries – Rs 12,000 per month per investigator for the course of the trial and for data processing. Variable expenses such as communication costs and the patients’ hospitalisation charges are reimbursed. Other than this, the payment is per patient recruited and the number of visits completed per patient, at each stage. For example, in a six week trial there will be eight visits. “Now, if there are too few patients per visit, there is hardly any savings.” This comment suggests that the more patients an investigator recruits, the smaller the incremental cost and the more money she or he makes. Just as it is more economical to do a blood test in batches, it is more economical to have just a few sites recruiting large numbers of patients each. Certain costs such as the investigator’s salary, communication, equipment and laboratory facilities do not vary much. This arrangement is also more profitable to the investigator if he/she has a stake in the institution where the trial is being conducted.

Recruitment fees are paid in stages. The investigator receives the first payment at the time of screening, for each patient screened, and this payment is Rs 10,000 to Rs 15,000 per patient. Further payments are based on the patients actually recruited into, and maintained in, the trial. “We are paid Rs 5,000- Rs 7,500 for each following visit. This fee varies depending on the work to be done. In dementia trials requiring a four-hour visit, the payment could go to Rs 7,500 to Rs 10,000. A three-week trial will require six to seven visits.”

“Foreign sponsors have not increased their budgets; on the contrary, they have been cutting costs and my payments have not increased in more in six years. Now they are very tight, earlier there was more flexibility. We keep hearing that clinical trials are increasing in number, but the actual budget for the investigator has not increased. Previously for investigator meetings, they used to take us abroad depending on the countries involved in the sites. Now India sites have meetings only in India. We are not getting increments for our work, there is some “decrement”. We are trying to negotiate lots of things.”

For a psychiatric drug trial, at a single site that plans to recruit 10 patients, the site would recruit two to three patients a month and recruitment would take place over three to five months. The patients would come in for 10 visits over the course of the trial. “The principal investigator would put in six to nine hours per month, or 72-108 hours of work over a year from recruitment to analysing trial data and giving it to the sponsor,” said Arun Bhatt, president of Clininvent Research Pvt Ltd, a contract research organisation. Ideally, principal investigators should not be running more than three trials at a time.

“I will budget \$20,000 to \$25,000 for the site if 10 patients are recruited and all 10 complete the trial,” said Dr Bhatt. This money includes recruitment fees, staff salaries, equipment and communication. Drugs and other materials are provided by the company. Expenses for patients are reimbursed separately. The payment is made in instalments and is made directly to the principal investigator. If the money is paid directly to an institution or site management

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organisation, the investigator still will get a recruitment fee per patient. “We estimate that at least 50 per cent of this money goes directly to the investigator,” said Dr Bhatt. “This additional income is an attractive incentive for a small-town specialist compared to a consultant in a corporate hospital in Mumbai.”

Such large payments create a conflict of interest for the investigator.

3. Ethical guidelines for biomedical research

As of January 2005, biomedical research in India must comply with the ethical principles laid out in the World Medical Association Declaration of Helsinki. It must also follow the the Indian Council of Medical Research's ethical guidelines for biomedical research on humans.

3.1 World Medical Association Declaration of Helsinki

The Declaration of Helsinki is accepted as an international standard for biomedical research. The Declaration has been revised a number of times since it was first adopted by the World Medical Association's General Assembly in June 1964. The Declaration of Helsinki was last revised on October 22, 2008²⁵ and is the relevant document for ongoing and future research.

The trials described in this report took place between 2002 and 2006. The 2000 version of the Declaration – with notes of clarification inserted in 2004 – is referred to in this report as it would have been applicable during this period. The following paragraphs, on research among vulnerable groups, the informed consent process, the use of placebo controls and the benefits of research are particularly relevant in these trials.

The economically and medically disadvantaged need special protection:

Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care. (Paragraph 8)

Investigator/physicians recruiting their patients into a clinical trial must be careful not to exercise undue influence:

When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship. (Paragraph 23)

Placebos or sugar pills should not be used when testing new drugs if an effective treatment for that condition already exists:

The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists. (Paragraph 29)

²⁵ World Medical Association Declaration of Helsinki. Ethical principles for medical research involving human subjects. Adopted by the WMA General Assembly, Helsinki, Finland, June 1964 and last amended at the 59th WMA Assembly, Seoul, October 2008. Available from: <http://www.wma.net/e/policy/pdf/17c.pdf>

In 2004, a clarification was added to paragraph 29:

“The WMA hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:

*- Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or
- Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.*

All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.”

Finally, the findings of research in a community should benefit that community:

Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research. (Paragraph 19)

This last principle is stated more strongly in the 2008 revision of the Declaration of Helsinki: *Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research. (Paragraph 17)*

3.2 The Indian Council of Medical Research’s ethical guidelines on biomedical research on humans

As of January 2005, it is mandatory for clinical trials in India to conform to the ICMR’s guidelines and to the guidelines in the Declaration of Helsinki.

The Indian Council of Medical Research’s guidelines were first published in 2000²⁶ and this version of the guidelines would have been applicable for the trials described in this report. The revised guidelines were published in 2006²⁷ and are the relevant guidelines for ongoing and future research.

The guidelines state that: “persons who are economically or socially disadvantaged should not be used to benefit those who are better off than them.” (Section III iii b in ICMR, 2000; Section IV iii b in ICMR, 2006)

The 2000 guidelines state that trial subjects should be fully informed of the research before they consent:

²⁶ Indian Council of Medical Research. *Ethical guidelines for biomedical research on human subjects*. New Delhi: ICMR; 2000.

²⁷ Indian Council of Medical Research. *Ethical guidelines for biomedical research on human participants*. New Delhi: ICMR; 2006. Available from: http://icmr.nic.in/ethical_guidelines.pdf

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'Any research using the [sic] human beings should be selected so that burdens and benefits of the research are distributed without arbitrariness, discrimination or caprice.' Research should abide by the principles of "maximisation of the public interest and of distributive justice whereby, the research or experiment and its subsequent applicative use are conducted and used to benefit all humankind and not just those who are socially better off but also the least advantaged; and in particular the research subject themselves. (Principle VIII)

This is restated more forcefully in the 2006 guidelines:

Principles of the maximisation of the public interest and of distributive justice whereby the research or experiment and its subsequent applicative use are conducted and used to benefit all human kind and not just those who are socially better off but also the least advantaged; and in particular, the research participants themselves and or the community from which they are drawn." (Principle VIII)

The ICMR guidelines also state that the use of placebo is unethical when an effective treatment exists:

RCT < reduces considerable bias but can also creates ethical problems when the comparative arm has placebo. Hence a proper justification should be provided for using the placebo. In keeping with the Declaration of Helsinki as far as possible standard therapy should be used in the control arm. In the following situations placebo can be used:

- i. self limited disease;*
- ii. where no proven prophylactic, diagnostic or therapeutic method exists (p 42)*

4. Lapatinib for advanced HER2 positive breast cancer

There are one million new cases of breast cancer worldwide²⁸, with 548,000 deaths annually²⁹. Some 400,000 women in India are currently living with breast cancer and about 120,000-150,000 new cases are added every year. According to data from the National Cancer Registry, given in a 2001 report of the Indian Council of Medical Research³⁰, breast cancer is the second most common cancer among women, after cervical cancer.

4.1 Treatment options for breast cancer

The treatment options for breast cancer depend on the stage at which it is detected and whether it is confined to one area or metastasised to other parts of the body. They can include a combination of surgery, chemotherapy and radiation. The choice of drugs for a particular patient depends on the stage of the disease as well on the drugs that she has already taken and to which she has stopped responding. Chemotherapy can cost between Rs 30,000 and Rs 3 lakh (€ 470 – 4,700) for a six-month course of treatment. Hormonal therapy (given for 5 years) can cost between Rs 25,000 to Rs 1.8 lakh (€390 – 2,800), depending on whether branded or generic drugs are used³¹. Consequently the majority of women go untreated.

New drugs for breast cancer

In the last decade, a new class of drugs is believed to have revolutionised the treatment of certain cancers. Targeted therapies are tailored to different types of cancers and are meant to counteract the tumour growth process without affecting normal tissue. Targeted therapies are given after the woman undergoes tests to identify the type of process involved in her cancer.

The first such targeted therapy in breast cancer was trastuzumab (brand name Herceptin, marketed by Genentech in the US and by Roche internationally), approved in 1998 for treatment of patients with metastatic breast cancer whose tumour growth is fuelled by excessive production of the HER2 protein³², also described as HER2 positive breast cancer. Since then it has been approved for use in earlier stages of this cancer. In 2005, it was approved for adjuvant (post-surgery) use as well. Today, trastuzumab is the international standard of care for this particular breast cancer. This type of cancer is responsible for 25-30% of all breast cancers³³. In India, YK Sapru of the Cancer Patients Aid Association says that about 100,000 women would benefit from this drug if it were available to them.

²⁸ World Health Organisation 2008 <http://www.who.int/mediacentre/factsheets/fs297/en/index.html>

²⁹ World Health Organisation 2003 <http://www.who.int/mediacentre/news/releases/2003/pr27/en/>

³⁰ <http://mohfw.nic.in/pg22to34.pdf>

³¹ Shona Nag. Interview at JCDC in Pune September 25, 2008.

³² <http://www.fda.gov/Cder/foi/appletter/1998/trasgen092598l.pdf>

³³ <http://womenshealth.about.com/library/weekly/aa092598.htm>

The price of new drugs for the poor and uninsured

However trastuzumab, available in India for 10 years, costs Rs 120,000 a month. In a country where less than five per cent of the population has any insurance and the per capita income was \$950 in 2007³⁴, and 456 million people or 42 per cent of the population is below the poverty line³⁵, the price of trastuzumab puts it out of the reach of the vast majority of women in India who need it.

In India, Roche holds the patent for trastuzumab. In April 2008, the Cancer Patients Aid Association launched a campaign calling on the government to get drug companies to lower their prices for cancer drugs.

For the majority of Indian women with breast cancer, treatment options depend on what they can afford. All drugs for cancer are outside price control in India³⁶.

“Response rates vary according to the kind of chemotherapy used,” said Dinesh Doval, one of the investigators in the lapatinib trial discussed here. “CMF chemotherapy is oldest (also cheapest and least effective) and costs Rs 2,000 to Rs 3,000 per cycle. Anthracycline-based is better and costs Rs 8,000-10,000 per cycle. Taxanes (paclitaxel or docetaxel) are even better and cost Rs 50,000-60,000 per cycle. (Herceptin, another type of drug, is the standard of care internationally.) The number of cycles depends on the response. For stage 4 cancer we don’t talk about a fixed number of cycles.”³⁷

About 10 per cent of those who require treatment obtain it. In cases of advanced disease for which trastuzumab is the international standard of treatment, it should be taken for as long as it has effect – that is, as long as the cancer does not progress and there are no serious adverse effects. However not even 0.5 per cent of those who need trastuzumab can get it, according to one oncologist.

4.2 Lapatinib – the latest targeted therapy for breast cancer

In 2006, the drug company Glaxo Smith Kline (GSK) announced the development of a new targeted therapy, lapatinib (brand name Tykerb or Tyverb). The drug was approved in various countries over 2007 and 2008.

Like trastuzumab, lapatinib is used for HER 2 positive breast cancer.

Lapatinib has been approved only for patients who have received – and stopped responding to – trastuzumab and other cancer drugs, anthracyclines and taxane. It is approved for use only in combination with the drug capecitabine. Lapatinib is taken by mouth, unlike trastuzumab which must be taken in monthly injections.

³⁴ <http://siteresources.worldbank.org/DATASTATISTICS/Resources/GNIPC.pdf>

³⁵ Chen S, Ravallion M. *The developing world is poorer than we thought but no less successful in the fight against poverty*. Policy research working paper 4703. Washington, DC: The World Bank Research Development Group; 2008 Aug.

³⁶ Srinivasan S. Work two years and maybe you can afford to get treated for TB. *Access denied*. Infochange Agenda. Pune: Centre for Communication and Development Studies; 2005 Ap. Pp. 35-39.

³⁷ Dinesh Doval, telephone interview November 10, 2008.

Like trastuzumab, lapatinib (with capecitabine) must be taken as long as the drug works: to be stopped only if the cancer progresses or complications develop. A month's treatment with lapatinib costs about Rs 60,000 (plus capecitabine which costs Rs 25,000 per month).

The approval history of lapatinib

The trial pivotal to the approval of lapatinib was a randomised clinical trial³⁸ conducted on women with metastatic HER-2 positive breast cancer who had already received trastuzumab until it stopped working. One group of women got the anti-cancer drug capecitabine. Another group got a combination of capecitabine plus lapatinib.

The researchers found that the two-drug combination delayed the growth of tumours by about six weeks compared to the single drug.

This trial was conducted from March 2004 to November 15, 2005. It did not have a site in India. The results of this trial were published in the *New England Journal of Medicine* (NEJM) in 2006³⁹.

In 2006, GlaxoSmithKline submitted a new drug application to the US Food and Drug Administration for approval to market lapatinib in combination with capecitabine. It obtained USFDA approval on March 13, 2007⁴⁰. GSK obtained marketing approvals from Switzerland⁴¹ on May 23, 2007 and the Drugs Controller General of India⁴² in July 2007. At present the drug is approved only in combination with capecitabine, and only for the treatment of patients with advanced HER-2 positive breast cancer who have stopped responding to therapy with trastuzumab.

Debate before lapatinib was approved in the EU

In the EU, GSK applied to the European Medicines Agency (EMA) in October 2006. The EMA first granted provisional approval in December 2007 but then withdrew it in March 2008 when new data became available that the drug was toxic to the liver. (The European Medicines Agency's Assessment Report (EPAR)⁴³ does not give details on these data.)

The Assessment Report referred to the pivotal phase 3 trial published in the *NEJM*. The EMA's Scientific Advisory Group (SAG) stated that the six-week delay in tumour growth was not considered clinically meaningful in the context of "advanced breast cancer in late lines of treatment". It was "concerned that there were no statistically significant overall survival data for patients treated with this drug."⁴⁴ It asked for additional evidence that the drug was effective enough to justify its use.

³⁸ NCT00078572 on www.clinicaltrials.gov

³⁹ Geyer Charles E et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. *N Engl J Med* 2006; 355: 2733-43.

⁴⁰ <http://www.fda.gov/bbs/topics/NEWS/2007/NEW01586.html>

⁴¹ http://us.gsk.com/html/media-news/pressreleases/2007/2007_06_03_GSK1085.htm

⁴² <http://cdsco.nic.in/New%20Drugs%20Approved%202007.htm> accessed 2008 Aug 28

⁴³ European Medicines Agency. Assessment report for Tyverb. 2008 April.

<http://www.emea.europa.eu/humandocs/PDFs/EPAR/tyverb/H-795-en6.pdf>

⁴⁴ A clinical pharmacologist confirmed this judgement.

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In response, GSK proposed revisions to the summary of product characteristics, the package leaflet and a “risk management plan”. The company also presented an “updated overall survival analysis showing a trend to improved survival in the combination arm”, and a secondary analysis showing a reduced incidence of cancer metastasis in the brain.

“In summary, the applicant argued that there are no approved ErbB2- directed therapy after trastuzumab, that treatment with lapatinib plus capecitabine was associated with a number of important clinical benefits in terms of TTP [time to progression], response rate, overall survival, incidence of brain metastasis as 1st site of recurrence, time without symptoms as measured by QTWiST [trade-off between clinical benefit and toxicity], and that it has a number of favourable characteristics in that it is an oral treatment, that does not prolong hospitalisations or impair health-related quality of life. Furthermore, treatment with lapatinib plus capecitabine was associated with minimal severe or life-threatening toxicity, low cardiotoxicity, and minimal lung toxicity. The applicant concluded that the observed benefits of the combination largely exceeded the risk for the patients in the target indication, and that unmet needs will be met.” (EPAR; page 56)

Based on this, the EMEA granted conditional approval for use of lapatinib with capecitabine after trastuzumab failure. “Conditional approval” means that more evidence is awaited on the drug’s impact on survival and on slowing down the spread of breast cancer. The company is expected to update this information and also conduct a study on the impact of the drug along with a trastuzumab combination on the spread of cancer to the brain.

(These details of the approval process in the EU are presented in this report because they indicate that there was a disagreement within the EMEA on the clinical benefits of lapatinib and the company convinced the EMEA that the benefits of the drug were greater than its risks.)

Expanding use of lapatinib

Among the countries where lapatinib has been approved are the United States, the European Union and India. It is marketed under the brand names Tyverb and Tykerb. It is poised to compete with trastuzumab, which was described as “the most successful cancer product launch ever in the USA”⁴⁵ within a couple of years of its launch in 1998. The market for both drugs is expanding as the indications for their use grow, and the drugs receive approval for use in early stage cancer. There are a number of trials (planned, ongoing or completed) testing lapatinib with various drug combinations for early breast cancer as well as for various types of cancers. The US trial registry www.clinicaltrials.gov lists 134 (planned, recruiting, ongoing and completed) trials of lapatinib⁴⁶. The registry lists 14 trials of lapatinib in India.

⁴⁵ http://www.ims-global.com/insight/news_story/0011/news_story_001103.htm

⁴⁶ As of October 26, 2008

4.3 Two-dose monotherapy on “chemotherapy naïve” participants

One of the trials of lapatinib mentioned in the EPAR⁴⁷ had three sites in India. This is a phase 2b⁴⁸ trial of lapatinib monotherapy (as opposed to in combination with other drugs) as the first option of drugs for women with locally advanced (the cancer has spread but is confined to the breast) or metastatic HER2 positive breast cancer. The study’s results are reported in the *Journal of Clinical Oncology*.⁴⁹ and also summarised in the company’s website (trial identification number EGF 20009)⁵⁰. The details given below are taken from the journal article.

Trial details

Purpose of the trial

The purpose of the trial, as stated on the clinical trials registry and in the journal article, was to evaluate the efficacy and tolerability of two doses of lapatinib. The primary endpoint was efficacy as measured by the patients’ response to the drug. The secondary endpoints were clinical benefit, time to response, duration of response, progression-free survival rates at four and six months, and time to treatment failure.

Trial sites

The trial began in July 2004 and concluded in January 2006. It was conducted at 19 sites worldwide. GSK has stated that 10 countries participated in the trial: the US, Chile, Hong Kong, India, Malaysia, Mexico, Pakistan, Peru, Singapore and Taiwan⁵¹.

Inclusion and exclusion criteria

The trial was conducted on women with histologically (through biopsy) confirmed invasive breast cancer (locally advanced or metastatised) with incurable (“stage IIIB, IIIC with T4 lesion or stage IV”) disease at the time of diagnosis, or relapsed after surgery. Participants had to be over 18 years of age and had to have a life expectancy of more than 12 weeks. Women who had previous drug treatment of any kind (“chemotherapy, immunotherapy, biologic therapy or anti-ErbB1/ErbB2 therapy”) other than adjuvant therapy (chemotherapy immediately after surgery to prevent the cancer’s recurrence) were excluded from the trial. Any neo-adjuvant (prior to surgery) or adjuvant therapy should have been done at least 12 months before entering the study.

⁴⁷ European Medicines Agency. Evaluation of medicines for human use. Doc.Ref.: EMEA/302222/2008 Assessment report for Tyverb. International non-proprietary name: Lapatinib. Procedure EMEA/H/C/795.

⁴⁸ According to the US definitions A phase 2a trial is for proof of concept; a phase 2b is to establish the dose. This definition is not used in the Indian law.

⁴⁹ Gomez HL, Doval DC, Chavez MA, Ang PC, Aziz Z, Nag S, Ng C, Franco SX, Chow LW, Arbushites MC, Casey MA, Berger MS, Stein SH, Sledge GW. Efficacy and safety of lapatinib as first-line therapy for ErbB2-amplified locally advanced or metastatic breast cancer. *J Clin Oncol*. 2008 Jun 20;26(18):2999-3005

⁵⁰ <http://www.gsk-clinicalstudyregister.com/files/pdf/20700.pdf> last accessed November 12, 2008

⁵¹ Statement by Sadhna Joglekar, GSK, October 28, 2008. The correspondence with GSK is given in Appendix II.

Conduct of the trial

A total of 138 women were treated with lapatinib (69 in each dosage arm) for a median of 17.6 weeks. One group received 1,500 mg of lapatinib in a single daily dose. The other group received 500 mg of lapatinib twice a day. The drug was given to them for 12 weeks unless the disease progressed or they withdrew from treatment for other reasons. Patients who benefited from the treatment “were permitted to continue lapatinib until disease progression or withdrawal for another reason.”

Post-trial treatment

There is no mention of what treatment the women received if they stopped treatment (either because they stopped responding to lapatinib or they withdrew for other reasons), and whether they paid for this treatment or it was paid for by the trial sponsor.

Ethics approval

In the journal article, the authors state: “Ethical approval was obtained from the relevant local ethics committees and the study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided signed, informed consent before enrolment into the study.”⁵²

Trial rejected by at least one ethics committee

GSK has stated that it knows that the ethics committee of the All India Institute of Medical Sciences, a central government institution, rejected the trial, adding: “It is not unusual for a particular EC to reject research protocols. This can be for a number of reasons, which may be unrelated to the formal content of the study.”

Results

The trial found that lapatinib had a clinical impact when given as first-line therapy. It also found that there was not much difference in effect between the two dosage arms⁵³.

Serious adverse events including deaths

Seven per cent of the patients reported serious adverse events.⁵⁴ related to the drug and seven of the patients withdrew from the trial because of adverse events (four because of serious adverse events). Six women died in the study, and one of these deaths was judged to be related to lapatinib treatment. According to the journal report, “This was a case of hepatic failure (liver failure) and bacterial peritonitis (infection of the inside lining of the abdomen), which began after 223 days of 500-mg twice daily lapatinib in a 73-year-old patient who had presented with extensive measurable and nonmeasurable liver metastases, chronic nonalcoholic hepatopathy (liver disease), and grade 1 elevations in alkaline phosphatase, ALT, and AST levels before the first dose.”

⁵² Gomez *et al.*, *op. cit.*, p 3000.

⁵³ Information on the secondary endpoints is not given here as it is quite detailed.

⁵⁴ A serious adverse event is a medical event during a clinical trial that results in hospitalisation, serious disability, life-threatening illness, or death of the trial participant or congenital anomaly in offspring.

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Two experts were asked if it was appropriate to have included this patient in the trial " as inadequate liver function was one of the exclusion criteria, and this patient had liver disease at the time she entered the trial.

These experts did not express concern about the death. One stated that there may have been medically good reasons to include the patient as the drug was expected to reduce tumour size and improve liver function. The second noted that the death took place after the patient had been on the experimental drug for 223 days.

Some questions about the trial

Were the women deprived of the standard of care?

The international standard of care for this type of cancer is trastuzumab. There is no local "standard of care" in India. A patient has "treatment options" and these depend on what she can afford.

GSK has stated: "At the time of conducting study NCT 00089999 in 2004-2005, the standard of care in India for majority of patients with advanced or metastatic breast cancer was primarily chemotherapy. For those who could afford it, trastuzumab was the standard of care." The company has stated that "the standard of care required by the study design is, as a minimum, consistent with local standards of care."

An oncologist has stated that he had reservations about the phase 2 monotherapy trial. The trial included patients with locally advanced (large tumour but not spread beyond the breast region) breast cancer. There is an established local – in India – standard of care, he said. Women with locally advanced cancer should not have been offered an experimental drug as first-line treatment. They should have been offered chemotherapy to shrink the tumour, surgery with adjuvant chemotherapy, followed by radiation. "Denying this treatment to women with locally advanced breast cancer is a clear denial of the standard of care. In general in metastatic cancer the options do not have very good results," he said. None of the treatments will cure the patient. They have limited impact on the progress of the disease, and can only delay death. "In such cases, there may be a case for deferring other treatment options for a short period. I may, for example, try out the experimental drug for a month and switch to existing treatments if there is no improvement. *But it is absolutely unacceptable to withhold treatment for locally advanced cancer: there is an established standard of care which has good results.*"

Did patients give their informed consent?

According to the journal report, eligible patients gave their written consent to receiving lapatinib before, or rather than, other therapies, after being told of their treatment options – the various treatments available for their condition.

The oncologist states: "In India, patients may give consent very easily, leaving such decision to the doctor. Further, it is very easy to provide the patient with choices in such a way that trial participation seems to be easily acceptable. I can say, 'These are the choices, and these

are the limitations and strengths of each choice, and there is also an experimental drug which is being tried out and these are the possible risks and benefits of participating in a trial.' Or I can say, 'These are the choices, and this is what they cost, and there is an experimental drug which is being tried out and if you join the trial you will get free treatment.'"

Was the information in the trial essential?

CM Gulhati, editor of *Monthly Index of Medical Specialities (India)*, states that the trial was scientifically appropriate. It was necessary to test the drug on chemotherapy-naïve patients. "This is quite normal for a drug which is to be used as 'first line therapy'. There is no prohibition under Indian laws." He also stated that there was no connection between phase 2 trial of monotherapy and the phase 3 trial used for lapatinib's approval "These were different trials with different, independent objectives with different protocols. Hence one cannot connect one trial (lapatinib in two dosage schedules) with the other (lapatinib + capecitabine). Scientifically and clinically there cannot be any objection."

Investigation of the phase 2 monotherapy trial in India

This trial had three sites in India⁵⁵. However, there are only two Indian authors in the journal article reporting the lapatinib monotherapy trial. GSK has stated that a total of 27 patients were recruited from India.

Shona Nag at the Jehangir Hospital, Pune, and Dinesh Doval at the Rajiv Gandhi Cancer Institute and Research Centre, Delhi "provided study material or patients" for the trial. They provided 7 and 16-18 (Dr Doval was not sure of the number) patients respectively for this trial. According to Dr Nag, there was no CRO involved in the trial, and the investigators interacted directly with GSK⁵⁶.

Dr Nag's affiliation is given (in the journal article) as Jehangir Hospital, Pune. She is also a consultant at the Ruby Hall Clinic.⁵⁷, across the road from the Jehangir Hospital. Ruby Hall has recently added a cancer hospital, Kamalnayan Bajaj Centre, which entered into a 10-year collaboration with Siemens for technology and product development that "identifies Ruby Hall Clinic as Siemen's beta site centre; the fifth site in the world and Asia's only beta site"⁵⁸. Dr Nag also treats patients in the government-run Sassoon hospital.

The Jehangir Clinical Development Centre

The Jehangir Hospital, a tertiary care centre in Pune, has recently set up the Jehangir Clinical Development Centre (JCDC), a site maintenance organisation (SMO). An SMO is a clinical trial facility that conducts trials for contract research organisations or, directly, for drug companies. These companies handle records and regulatory issues. The JCDC is described in a press report reproduced on its website⁵⁹ as "an independent company with full time staff dedicated for conducting research". The chief executive officer is Pathik Divate, a chartered

⁵⁵ The company results mention three sites and GSK has stated that the third investigator is D Raghunadharao at the Nizam's Institute of Medical Sciences, Hyderabad, Andhra Pradesh.

⁵⁶ Interview with Shona Nag, JCDC, Pune, September 25, 2008.

⁵⁷ <http://www.rubyhall.com/CancerCenter/Inner/medical1.html>

⁵⁸ <http://www.rubyhall.com/CancerCenter/Inner/research.html>

⁵⁹ <http://www.jcdc.co.in/p1.shtml>

accountant and a Master's degree in Business Administration who has worked in auditing and consulting, outsourcing and the drug industry. In 2007, JCDC signed a five-year contract with Wyeth to undertake clinical research.⁶⁰

The JCDC has positioned itself as a service organisation for company-sponsored drug research. According to information on its website, it is conducting clinical trials for “seven of the top 10 drug companies worldwide” and also “other major international Contract Research Organisations”. It has set up facilities including separate space for archiving records, temperature-controlled drug storage, a fully equipped laboratory and an information technology infrastructure. It has a panel of specialist consultants⁶¹. It is one of two sites selected from 33 in India to recruit patients for clinical trials with reduced administration, management, time and cost, while maintaining quality. It allayed the concerns of a medical device company about the difficulties of conducting clinical trials in India by handling regulation, documentation and conduct of the trial in an efficient way; and it conducted phase 1 studies for a domestic drug company for USFDA approval. “We provided them dedicated space, beds and equipment within Jehangir Hospital and committed personnel. Moreover, our association with the hospital gave us access to its advanced emergency management system and ambulance services which are among the best in the country. Over four years, the study was conducted with extremely close supervision and continuous monitoring. This company has successfully been able to file the results of the study with the Food and Drug Authorities within the stringent timelines mutually agreed with our organization.”⁶²

Shona Nag

In an interview.⁶³ at her office in the JCDC, Dr Nag said that she restricts the number of oncology trials at the centre to 10-12, handled by six coordinators, each handling 2-3 trials. She recruits six to 12 patients per trial per year.

Clinical trial described as a treatment option

Dr Nag apparently views clinical trials as a treatment option for patients. Speaking about the new drugs on the horizon, she said:

“There are herceptin-like drugs and avastin-like drugs in the market – because everybody is in the market, everybody is making them – which are trying to give oral options rather than the IV (intravenous) option, and these are available on clinical trials free to the patient. So patients themselves come to me, the other day I had one on Herceptin, she said, ‘Can’t you put me on a clinical trial?’ They are sensitised and they know that they will get the same, if not better, on a clinical trial. They like to go for the late phase trials where the drug has already proven its mettle in phase II. Phase III is quite easy to recruit.”

⁶⁰ <http://www.jcdc.co.in/p1.shtml>

⁶¹ <http://www.jcdc.co.in/p4.shtml>

⁶² http://www.jcdc.co.in/case_studies.shtml

⁶³ Interviewed at the JCDC, Pune, on September 25, 2008.

Do patients enter trials to get access to drugs that they cannot afford?

When asked if patients might feel compelled to enter trials and put themselves at risk because of the high prices of effective drugs, Dr Nag replied that many patients refuse to enter trials even if they cannot afford the standard drugs.

“There’s one patient of mine who would really benefit from a trial I have ongoing and I don’t know, maybe I didn’t discuss it too much, I tried my best to convince her, because I honestly thought it is the best thing for her. But she has decided to sit at home and take Ayurvedic treatment. She has no money for Herceptin and yet she has opted for Ayurvedic treatment. Maybe it’s foolhardy, maybe she will realise and come back, but she has exercised her choice.”

Dr Nag said she spends a lot of time to ensure that patients who agree to participate in clinical trials have given their informed consent. She insists that patients discuss the trial with their family and family doctor before they consent to enter the trial.

Were poor patients recruited from government hospitals?

Dr Nag also visits the government Sassoon hospital as part of JCDC’s charitable treatment programme which provides cancer drugs free or subsidised to poor patients.

Why did trial participants refuse existing treatment options?

Dr Nag said she recruited seven patients at her site (she said there were only two sites in India, in line with the journal report but contrary to the results on the company website⁶⁴) for the two-dose monotherapy trial. When asked if the women on the trial were asked to refrain from using Herceptin until the trial was over, she said:

“If my patient had chosen Herceptin, I would not put them on the lapatinib trial, which is why I only had seven when I was asked to recruit 10. I couldn’t give them 10. Because I didn’t think it was fair for those who afforded Herceptin to get on to this trial.”

Asked what she thought about the fact that patients were not given Herceptin, the international standard of care, she answered:

“If they can’t afford it then what do you do? Then they go untreated. Then it’s better to give something. According to me, you can’t have the same rules in every country. The situation is completely different, their concerns are different. Who said it’s the standard of care in India? Who has decided Herceptin is the standard of care in India? How can it be when 10 per cent of the population can afford it or five per cent of the population can afford it?”

She also said that some of the patients who went on lapatinib had refused chemotherapy because they wanted oral treatment (trastuzumab or Herceptin must be taken by injection).

The informed consent document for this trial would provide some idea of why participants might have refused existing treatment options, and whether they knew that they were getting

⁶⁴ <http://www.gsk-clinicalstudyregister.com/files/pdf/20700.pdf> last accessed November 12, 2008

an experimental drug. Dr Nag did not provide a copy of this document. GSK has refused to provide a copy of the informed consent form.

What treatment did the women receive after the trial was over?

Dr Nag stated that after the trial was over, women who were responding well to lapatinib were continued on it. Those who stopped responding were given standard chemotherapy.

GSK has stated that after the 12-week treatment was completed, “The protocol provided the option of continuing on the same dose and schedule of the experimental drug for those patients who responded to the treatment during the trial period.” Once women stopped responding to the experimental drug, “they were placed on alternative treatment at the investigator’s discretion.”

Who paid for treatment after the trial was over?

GSK was also asked if patients paid for any treatment during or after the trial. The reply was: “Patients did not pay for their treatment *during* the trial.” [emphasis author’s].

Is lapatinib affordable to Indian patients today?

Dr Nag can think of at least three patients who she feels could benefit from lapatinib but they cannot afford to pay for it.

The Rajiv Gandhi Cancer Institute and Research Centre

The second Indian author listed in the journal article reporting this trial is Dinesh Doval, chief of medical oncology at the Rajiv Gandhi Cancer Institute and Research Centre, New Delhi. The RGCIRC is a private institution recognised by the government department of science and technology as a scientific research centre. The institute has a 15-member research advisory committee and an institutional review board. The website states that so far 70 national and international Phase I to Phase IV clinical trials have been conducted, including the first phase I study in oncology in India. Seventy of the 100 proposals submitted to the Institutional Review Board (IRB) are in medical oncology (drugs). There are 17 active studies, of which seven are enrolling and the rest have patients in various stages of treatment or follow-up. According to the RGCIRC website, “The institution is a rich source of clinical material which can contribute towards the fundamental research into the causes, mechanism, diagnosis, treatment and prevention of cancer.”⁶⁵

Dinesh Doval

Dr Doval discussed the trial in a face-to-face interview on October 1, 2008, in the Rajiv Gandhi Cancer Research Institute in Delhi and over the telephone on November 10, 2008. He stated that he has been conducting drug trials since 1990 and at RGCIRC since 1997. He said the standard of care for this type of breast cancer was trastuzumab (Herceptin), but very few women can afford it.

⁶⁵ <http://www.rgci.org/cancerregistry.pdf>

Did participants enter the trial because they did not want chemotherapy – or because they could not afford it?

Dr Doval said that in this trial, “The scenario would be elderly, terminally ill patients. The eligibility criteria included stage 3 and 4, and HER 2 positive. I screened 40-45 patients. We have a large patient pool. They were not willing for any chemo.”

Why did they not choose chemotherapy?

“There could be many reasons, I don’t know why. One lady, her sister had breast cancer. When we talked about treatment, she cut me short: ‘If you are going to talk about chemotherapy...’ ”

Did they refuse chemotherapy because they could not afford it?

“Rajiv Gandhi is a private institution. Affordability is not an issue for our patients. Not for chemotherapy.”

What are the reasons they did not choose chemotherapy?

“I don’t know. Maybe because of the side effects: hair loss, infectious complications, nausea, vomiting. Maybe they had seen relatives. *There could be patients who could not afford.*”
[emphasis added]

How were patients recruited into the trial?

“Once we found that they met the inclusion criteria, then we told them that a study was available, and they may be eligible for it. Then we tested the patients for HER2 positive. Then those [who] were HER2 positive, we told them they fit the study criteria. We discussed the treatment options when we took their consent.

“We explained the need for chemotherapy. Then we explained that HER2 receptors were present in the body. Only with those patients who had these receptors was the drug given. They opted for it knowing that it was a new treatment. We explain that they can take chemotherapy. What goes on in their minds we cannot say.”

Was the trial legal in India?

The lapatinib trial is a multi-country trial that started in 2004. Before January 2005, Indian regulations normally did not permit concurrent phase international trials. Sadhna Joglekar of GSK has stated that the trial was conducted with the approval of the Drugs Controller General of India. Dr Joglekar was asked for information on the clause permitting a concurrent phase trial before January 2005. She replied: “This was not a concurrent phase trial since lapatinib, as an NCE, was already in phase III of development at the time that this phase II study was conducted in India.” According to Dr Gulhati, “The defence is invalid since the two trials were fundamentally, scientifically and legally entirely different. Exactly the same trial should have undergone phase 3 before phase 2 was permitted by the DCGI in India.”

4.4 Findings on the lapatinib trial

The company has provided little information after repeated requests. It has not given information on the trial sites in each country and the number of patients recruited at each trial site in each country. It has refused to provide the text of the informed consent form, stating: “As standard practice, GSK does not disclose materials submitted to regulators or to ethics committees, nor share personal details of their members or their responses.”

Questions about the informed consent process

We do not know how exactly the women were recruited into the trial, or what they were told. Were they invited to join the trial *after* they stated that they would not choose any of the options available to them?

Nor is it possible to know, from the information available, exactly why the women decided to participate in the trial. Did they refuse all medical options even though these were available to them? Or were these options out of their reach anyway? Did they participate in the trial because they believed it would give them treatment? Did they participate because they felt they had no other option for treatment?

However, at least one investigator described clinical trials as a treatment option and even tried to persuade her patient to enter a trial in order to benefit from the experimental drug. She is likely to have encouraged participants to enter the trial for this purpose. Another investigator has stated that the patients were informed of their options after they were screened for eligibility in the trial.

It has been suggested that a person who cannot afford treatment can be invited to join a trial as long as the decision to ask them is taken independently of the person’s ability to afford the drug. It is not clear how an investigator can separate the two processes. It is also important to ask if a person who cannot afford effective treatment is able to take truly voluntary decisions.

Economic vulnerability exploited

This trial of lapatinib was conducted in several developing countries. In countries such as India, many women with breast cancer are “treatment-naïve”, and very few are likely to have received the international standard of care. The local “standard of care” depends on what the patient can afford.

It is very likely that the trial recruited only those participants who could not afford any treatment. It is reasonable to conclude that the trial tested an experimental drug on women whose economic vulnerability could have led them to view the trial as a treatment option.

One of the trial sites (JCDC) is a site maintenance organisation which runs a charity programme in a nearby government hospital. Patients from this government hospital might have been recruited for this trial. SMOs may include patients from other sites in their trials. However, it is not possible to confirm whether this indeed was the case in this trial.

Participants may have paid for treatment once the trial was completed

GSK has stated that the participants were given the option of continuing on lapatinib for as long as they responded to it, even after the trial was over. Women who stopped responding to lapatinib “were placed on alternative treatment at the investigator’s discretion.” When asked if patients paid for treatment during or after the trial, GSK replied: “Patients did not pay for their treatment during the trial.”

Legal status of the trial questioned

GSK has stated that the trial was permissible according to Indian law in 2004. This is contested by an expert on clinical trial regulations who stated: “The defence is invalid since the two trials were fundamentally, scientifically and legally entirely different. Exactly the same trial should have undergone phase 3 before phase 2 was permitted by the DCGI in India.”

In fact, between 1997 and 2005, there have been a number of concurrent phase trials in India that seem to violate the regulations in place at that time. There is no information available on how such trials were permitted. The DCGI has discretion to waive the phase lag requirement for drugs of “special relevance” to India. Dr Gulhati stated that this is applicable to drugs “for diseases which are specific to India. Otherwise all drugs (are) of local relevance whether (for) blood pressure or breast cancer.”

The approved drug is not affordable in India

Lapatinib is available in India after authorisation but at a price that puts it out of the reach of almost everyone who needs it. “If you ask me whether lapatinib represents a major advance in the treatment of cancer, I will say ‘yes and no’,” said an oncologist. “It is a good drug but its cost-benefit is poor, especially since it must be taken lifelong.” Another oncologist said: “Less than one per cent of patients who need this drug will get it.”

There is no indication that the government will insist on the benefits of research being available here at affordable prices. All drugs for cancer are outside the government’s list of price controlled drugs. Indeed, India’s potential as a site for cancer drug trials will likely continue to be exploited for research on drugs that remain out of the reach of people here.

There is no evidence of a reasonable likelihood that Indian women with breast cancer will benefit from the results of this trial.

5. Placebo-controlled trials of psychiatric drugs

Three placebo-controlled trials of psychiatric drugs were chosen for investigation: one of risperidone for acute mania and two of quetiapine (extended release) for schizophrenia. Both drugs are “atypical” or second-generation anti-psychotics.

The first generation of drugs for psychosis was introduced in the 1970s. Of these, haloperidol is an inexpensive and widely used drug. Drugs in the second generation of atypical antipsychotics were approved starting in the 1990s.

These trials were chosen for the following reasons: First, they were conducted on patients who may have lacked the competence to provide voluntary and informed consent. Second, they were placebo-controlled trials for the drugs’ use in medical conditions for which there already existed established and effective treatments. Third, they were conducted almost exclusively in countries where the standard of health care provided might be different from the standards in the US/EU and where regulation of clinical trials may be inadequate.

5.1 Placebo-controlled trial of risperidone for acute mania

Risperidone is an atypical antipsychotic drug marketed by Johnson & Johnson. It was first approved in 1996. In 2003, it received Food and Drug Administration (FDA) approval for use as monotherapy in the short-term treatment of acute manic or mixed episodes associated with bipolar disorder^{66, 67}.

One of the three pivotal trials that was the basis for FDA approval for risperidone in acute mania was a trial conducted exclusively in India⁶⁸. This was a placebo-controlled trial on 290 patients hospitalised during an episode of acute mania. The trial, which was reported as being conducted in eight centres across India, was funded by Johnson & Johnson. The trial was conducted through the CRO Quintiles. The trial was conducted in 2001.

Description and findings of the risperidone trial

Patients with bipolar disorder were admitted to hospital and subjected to a “washout” of all medication (they were taken off all drugs) for up to three days before they were assigned to the risperidone or placebo arm. No other psychiatric drugs could be given in addition as long as they were enrolled in the trial. Lorazepam could be given for control of symptoms, but only for up to the first 10 days of the trial.

Those on the risperidone arm started with a 3 mg dose. Daily doses were then reduced or increased at the discretion of the investigator. The trial lasted for three weeks. When patients entered the trial their symptoms were evaluated on a scale, the Young Mania Rating Scale (YMRS).

⁶⁶ Ketter TA. Advances in treatment of bipolar disorder. *Review of psychiatry*. Volume 24. American Psychiatric Pub: 2005.

⁶⁷ http://www.medscape.com/viewarticle/466794_6

⁶⁸ Khanna S, Vieta E, Lyons B, Grossman F, Eerdeken M, Kramer M. Risperidone in the treatment of acute mania: double-blind, placebo-controlled study. *Br J Psychiatry*. 2005 Sep;187:229-34.

The authors state: "Signed informed consent was obtained for all participants and the study was conducted according to the Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects, in the 1989 version of the Declaration of Helsinki (World Medical Association, 1989)." ⁶⁹

The risperidone trial measured the effectiveness of the drug in patients with acute mania by measuring the change in YMRS in the placebo and the treatment group. It also compared the rate of drop-out in the two groups. The trial found that risperidone was effective in acute mania, and also well tolerated. Extrapyramidal symptoms (involuntary movements) were the most frequently reported adverse effects.

Risperidone trial questioned for doing harm to patients

The ethics of this trial were first questioned in a commentary published in the *Indian Journal of Medical Ethics*⁷⁰ after the *British Journal of Psychiatry* published the study report. The writer of the *IJME* commentary, Vikram Patel, is with the department of international mental health, London School of Hygiene and Tropical Medicine, and on the editorial advisory boards of both publications.

Dr Patel noted that in this trial, seriously ill patients were subjected to harm; they were deprived of effective and available drugs that are "usual care even in government facilities in India". Haloperidol is a conventional antipsychotic that Dr Patel states is considered by many as the standard of care for acute mania.

The trial was conducted on poor patients

The risperidone trial was conducted in four government hospitals and three private hospitals across India. More than 210 of the 290 patients in this trial were recruited in three government hospitals. Patients enter government hospitals because they cannot afford treatment in private institutions. As the lead investigator of this trial pointed out, one reason CROs conduct trials in government hospitals is that patients in these hospitals are the most severely ill.

Patients were severely ill

Describing the condition of people with acute mania, Dr Patel wrote:

"Bipolar disorder is a severe mental disorder, called manic-depressive disorder in older classifications of mental disorders, characterised by severe mood swings. During the manic phase, the person typically becomes irritable, agitated, is unable to sleep, experiences a rapid flow of thinking, and may become psychotic. The hallmark feature of the phase is the loss of insight: the person is unaware of their illness and often needs to be brought to medical facilities by concerned relatives. In severe cases, the person may need a period of hospitalisation to bring symptoms under control. Indeed, acute manic episodes are one of the commonest reasons for hospitalisation in psychiatric care."

⁶⁹ Till October 2008, the USFDA required clinical trials submitted to it for approval to follow the 1989 version of the Declaration of Helsinki.

⁷⁰ Patel V. Ethics of a placebo-controlled trial in severe mania. *Indian J Med Ethics* 2006; 2: 11-2.

India trial had the most severely ill patients

K Kuruvilla, an investigator in the risperidone trial, felt it was justified because the trial provided convincing evidence of risperidone's efficacy in acute mania. "Risperidone was being used as a general antipsychotic but the specific use for acute mania was proved by this study. Both old and atypical antipsychotic drugs were being used. This kind of convincing evidence had not arisen in those times."

He also stated that he participated in the trial because he knew there were other centres in developed countries. "I am particular, personally sensitive about these issues. If somebody had done a trial only here, I would not have consented to that." He is partly right. While this particular trial had sites only in India, another placebo-controlled trial of risperidone for acute mania was conducted in the US and was also used towards USFDA approval. However, the patients recruited in the US trial were not as severely ill as those in India.

Patients in the India trial were more severely ill than in other similar trials conducted in developed countries. Both journal articles on the India trial mention another placebo-controlled trial of risperidone in acute mania⁷¹. This was conducted in the United States and was also used towards USFDA approval. Patients in this trial had a mean YMRS score of 29 compared to 37.2 in the Indian trial. The India trial's lead investigator, Sumant Khanna, described the trial as "a landmark" as "The effect size was the largest in any study in mania with any known drug."⁷²

Dr Patel was asked to explain the significance of the YMRS as a measure of efficacy. He stated: "A lay summary is that the patients in this trial had a severity of illness greater than other comparable trials and, not surprisingly, they showed a marked improvement after treatment with all three treatments. However, the really important question of whether these treatments, all of which are more expensive and have different side-effects from the most widely used treatment, is better than the latter has not been answered."

⁷¹ Hirschfeld RM, Keck PE Jr, Kramer M, Karcher K, Canuso C, Eerdekens M, Grossman F. Rapid antimanic effect of risperidone monotherapy: a 3-week multicenter, double-blind, placebo-controlled trial *Am J Psychiatry*. 2004 Jun;161(6):1057-65

⁷² Interview with Sumant Khanna, Delhi, October 1, 2008

The trial may not have been required for marketing approval in India

Risperidone was used as a general antipsychotic, according to one of the trial investigators. Drug approval in India is often for broad indications such as “for psychosis” which would include acute mania.

Johnson & Johnson was asked what role the trial played in risperidone’s approval for use in acute mania in India. The company did not answer this question.

The trial violated the Declaration of Helsinki

The trial violated the Declaration of Helsinki 2000 which was in effect at that time. This states that placebo controls are unethical when an effective treatment exists. Second, the illness, especially in its acute phase, would very likely make it difficult for patients to make informed decisions.

The drug company’s response

A representative of Johnson & Johnson India replied to a letter and e-mail asking them for information on this trial (Appendix II). The letter does not contain any information on the trial.

Trial sites and investigators

The trial sites were identified from journal articles. The article by Khanna et al, which triggered the debate on the risperidone trial, does not contain any information on the trial sites or investigators. This is given in an article discussing another aspect of the study results, which was published in the *Journal of Clinical Psychiatry*⁷³. The trial was conducted by the clinical research organisation Quintiles.

The trial was conducted by investigators located at four large government hospitals and three smaller private institutions. The eighth investigator dropped out of the trial before it was completed.

Sumant Khanna was with the National Institute of Mental Health and Neuro Sciences (NIMHANS), Bangalore, when the study was conducted. NIMHANS is an autonomous institute for patient care and academic work in mental health and neurosciences. It functions under the direction of the state and national government ministries of health. Dr Khanna is now based in Delhi where he is advisor for CliniRx Research, a contract research organisation.

V Palaniappan is with the Institute of Mental Health in Chennai, Tamil Nadu. The IMH is a government institution attached to the Madras Medical College and is described (on its website) as the second largest institute in India.

⁷³ Gopal S, Steffens DC, Kramer ML, Olsen MK. Symptomatic remission in patients with bipolar mania: results from a double-blind, placebo-controlled trial of risperidone monotherapy. *J Clin Psychiatry*. 2005 Aug;66(8):1016-20.

Ethical concerns in clinical trials in India: an investigation

R Sathianathan is additional professor of psychiatry at the Madras Medical College, Chennai, also a government institution.

Jitendra Trivedi is professor at the department of psychiatry at the government's King George Medical College, Lucknow. The department of psychiatry has a 120-bed hospital.

Dr Trivedi is a principal investigator for a large number of psychiatric drug trials. The KGMC website⁷⁴ lists 31 "ongoing research projects" by Dr Trivedi. Of these, 26 are sponsored by drug companies (two by Johnson & Johnson, four by Pfizer, two by Lundbeck India and one by Torrent Pharmaceuticals) or the CRO Quintiles (19 trials)⁷⁵. It was in response to the large number of trials in the institute that the vice chancellor of KGMC put a cap to the number of trials that a single faculty member can run at any given time⁷⁶. Dr Trivedi was principal investigator for the three psychiatric drug trials examined in this report.

On April 9, 2007, Dr Trivedi was submitted to an audit by the USFDA⁷⁷ at which questions were raised about the data quality in his trials. The auditors concluded that he had failed to follow investigational plans. While "objectionable conditions were found", the auditors judged that these did not justify further regulatory action.

Podila Sharma is with the department of psychiatry at the Kasturba Medical College, Manipal, a private medical college attached to the Kasturba Hospital which has a capacity of 1,475 beds, and 15 specialty and 15 super specialty departments including a department of psychiatry and clinical psychology. Dr Sharma was principal investigator for the three psychiatric drug trials examined in this report.

Kurien Kuruvilla is emeritus professor, PSG Institute of Medical Sciences, Coimbatore, in the southern state of Tamil Nadu. PSG Institute is a private medical college set up by a charitable trust in 1985.

G K Vankar is professor and head, department of psychiatry, B J Medical College, Ahmedabad and is attached to the Civil Hospital, Ahmedabad, a tertiary care centre with 600,000 outpatients and 70,000 inpatients annually.

Vijay Debsikdar is director of Kripamayee Institute of Mental Health, a private clinical care institution in Miraj, a city in interior Maharashtra. Dr Debsikdar's name was not among the investigators listed in the journal article, but he was interviewed by a journalist.⁷⁸ when the controversy about this trial broke out. He says he withdrew from the trial before it was completed.

⁷⁴ <http://www.kgmcindia.edu/research.htm>

⁷⁵ Dr Trivedi is an investigator in all five quetiapine trials in the shortlist given by SOMO.

⁷⁶ Statement made by Shelley Awasthi in interview in Lucknow, September 30, 2008.

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<http://209.85.175.104/search?q=cache:JkEOgEMnh0cJ:www.accessdata.fda.gov/scripts/cder/CLIL/in dex.cfm%3Ffuseaction%3DBrowse.Browse%26NameFirstLetter%3DT%26SortField%3DPostalCode %26SortRequest%3D1+jitendra+trivedi+clinical+investigator&hl=en&ct=clnk&cd=1&gl=in>

⁷⁸ Mudur G. Indian study sparks debate on the use of placebo in psychiatric trials. *BMJ* 2006. Mar 11; 332: 566.

Two placebo-controlled trials of quetiapine extended release formulation

Schizophrenia is a psychiatric disorder in which the person has abnormal perceptions including hallucinations, delusions and disorganised speech and thinking.

Quetiapine

One of the new atypical anti-psychotic drugs approved to treat schizophrenia is quetiapine fumarate (brand name Seroquel), manufactured and marketed by AstraZeneca. The drug was first approved in 1997 by the USFDA for the treatment of schizophrenia in adults. In 2003 it was approved for mania associated with bipolar disorder. In October 2006, the USFDA approved its use for depressive episodes associated with bipolar disorder.

In May 2007, the USFDA approved an extended release version for the acute treatment of schizophrenia in adults. In August 2007, the Medicines Evaluation Board of the Netherlands approved the extended release formulation for the treatment of schizophrenia in adults and granted market authorisation via the Mutual Recognition Procedure across Europe⁷⁹. In November 2007, it was approved for maintenance treatment of schizophrenia in adults.

5.2 Placebo-controlled trial of quetiapine extended release for acutely ill patients with schizophrenia

The first study (described as study 132 in EPAR⁸⁰) was a six-week, randomised trial of quetiapine extended release (XR) formula in the treatment (efficacy and tolerability) of acutely ill patients with schizophrenia. A summary of the results was published on the company website in June 2007⁸¹ and the study is reported in the *Journal of Clinical Psychiatry* in 2007⁸².

Trial description

Patients with a diagnosis of “acute schizophrenia” were considered for the trial. They had to have a minimum Positive and Negative Syndrome Scale (PANSS) score indicating that the condition was severe. A total of 588 patients were taken off their regular antipsychotic medication (as well as other supportive drugs like mood stabilisers and antidepressants) at

⁷⁹ Schipper Irene, Weyzig Francis, op cit.

⁸⁰ The Public Assessment Report of the Medicines Evaluation Board in the Netherlands. EU-procedure number: NL/H/0156/08-011/MR Registration number in the Netherlands: RVG 34625-8 2008 Apr 10.

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<http://www.astrazenecaclinicaltrials.com/sites/133/imagebank/typeArticleparam528363/D1444C00132.pdf>

⁸² Kahn R, Schulz C, Palazov V, et al. Efficacy and tolerability of once-daily extended release quetiapine fumarate in acute schizophrenia: A randomized, double-blind, placebo-controlled study. *J Clin Psychiatry* 2007;68:832–42.

least 48 hours before being randomly assigned to quetiapine extended release (XR), quetiapine immediate release (IR) or placebo. The primary endpoint was the change in the patient's state over the six weeks of the study. The study was also designed to identify a clinically relevant dose range for the extended release version of quetiapine. 446 patients completed the study. Patients were recruited at 39 centres in Bulgaria, Romania, Russia, Greece, South Africa, the Philippines, Indonesia and India (three sites). The study was conducted between November 2004 and December 2005.

Ethics review and monitoring

The authors state: "The study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with International Conference on Harmonization/ Good Clinical Practice." The study was approved by local institutional ethics committees and patients or their legal representatives provided informed consent before they entered the study. There is no mention of a data safety monitoring board.

Trial findings

The study concluded that the extended release version of quetiapine was as effective as the immediate release version of the drug, and both were more effective than placebo in patients with acute schizophrenia. The drug was well tolerated.

Death in trial

One participant, a 42-year-old man in the immediate release arm, died "of unknown cause" on the last day of the trial. The authors report that this death was "not considered to be related to treatment."

Trial sites and investigators

The sites for the trial were identified from the journal article⁸³ reporting it. The trial was conducted by the clinical research organisation Quintiles.

Jitendra Trivedi is professor at the department of psychiatry at the government's King George Medical College, Lucknow.

Podila Sharma is with the department of psychiatry at the Kasturba Medical College, Manipal, a private medical college attached to the Kasturba Hospital.

Jitendra Nagpal is a senior consultant psychiatrist with the Vidyasagar Institute of Mental Health and Neurosciences, New Delhi, a private institution with a 120 bed hospital and a 28 bed ICU facility, providing psychiatric and drug de-addiction services.

⁸³ Kahn R, et al. Op cit.

5.3 Placebo-controlled trial of quetiapine XR for maintenance in schizophrenia

The second trial was a placebo-controlled study of quetiapine XR, also mentioned in the assessment report of the Netherlands as one of the trials towards the drug's approval (study 004 in the National Public Assessment Report (NPAR)⁸⁴). This study is a randomised, placebo-controlled trial of quetiapine XR as maintenance therapy in patients with schizophrenia. The results were reported on the AstraZeneca website⁸⁵ in September 2006 and in the journal *Psychiatry MMC*⁸⁶.

Trial details

327 clinically stable patients with schizophrenia were enrolled in the study. They were first taken off all drugs and stabilised on quetiapine XR over a period of 16 weeks. 197 of them completed this phase and were randomly assigned to the quetiapine XR arm (94) or the placebo arm (103). The primary endpoint was the time that it took for the patient to have a relapse episode. Secondary endpoints included risk of relapse at six months. Patients were enrolled in 26 trial sites in five countries: Poland, Russia, Bulgaria, the Ukraine and India (five sites). The study was conducted between March 2005 and April 2006.

Ethics review

The journal article states that the study design included a Data Safety Monitoring Board to address ethical considerations and minimise the potential risk to patients receiving placebo. It also states that the study was approved by local ethics committees and signed consent was taken from all participants or their authorised representatives.

Trial findings

The study was terminated after an interim analysis after 45 relapses found that relapses were more likely for patients on a placebo than for those on the drug. They relapsed sooner, and at the end of six months they were significantly at more risk of relapse. The study concluded that quetiapine XR was effective in preventing relapse in patients with stable schizophrenia, and the drug was well tolerated for long term use.

⁸⁴ The Public Assessment Report of the Medicines Evaluation Board in the Netherlands. EU-procedure number: NL/H/0156/08-011/MR Registration number in the Netherlands: RVG 34625-8 2008 April 10.

⁸⁵ <http://www.astrazenecaclinicaltrials.com/sites/133/imagebank/typeArticleparam528363/D1444C00004.pdf>

⁸⁶ Peuskens J, Trivedi J, Malyarov S, Brecher M, Svensson O, Miller F, Persson I, Meulien D, on behalf of the Study D1444C00004 investigators. Prevention of schizophrenia relapse with extended release quetiapine fumarate dosed once daily: a randomized, placebo-controlled trial in clinically stable patients. *Psychiatric MMC*. 2007 Available from: <http://www.psychiatrymmc.com/prevention-of-schizophrenia-relapse-with-extended-release-quetiapine-fumarate-dosed-once-daily-a-randomized-placebo-controlled-trial-in-clinically-stable-patients/>

Patient commits suicide

One patient in the placebo arm committed suicide during the trial. According to the journal article, this death was “not considered treatment related”.

Information on trial sites and investigators in India

The sites for the trial were identified from the journal article⁸⁷ reporting it. The trial was conducted by the clinical research organisation Quintiles.

Jitendra Trivedi is professor at the department of psychiatry at the government’s King George Medical College, Lucknow.

Podila Sharma is with the department of psychiatry at the Kasturba Medical College, Manipal, a private medical college attached to the Kasturba Hospital which has a capacity of 1,475 beds, and 15 specialty and 15 super specialty departments including a department of psychiatry and clinical psychology.

G Prasad Rao is a consultant psychiatrist and director in the psychopharmacology and schizophrenia division, Asha Hospital, in Hyderabad, the capital of the southern state of Andhra Pradesh. The Asha Hospital is a private psychiatric hospital run by a group of psychiatrists. It has 130 beds, and provides comprehensive psychiatric care.

Nagesh Pai was head of the department of psychiatry, K S Hegde Medical Academy, Mangalore, a trust institution established in 1999, and affiliated to the Rajiv Gandhi University of Health Sciences, Bangalore. It has a 720-bed teaching hospital, the Justice KS Hegde Charitable Hospital. Dr Pai has reportedly moved to Australia.

Shiv Gautam is a professor with the department of psychiatry at the Sawai Man Singh Hospital, a government medical college in Jaipur, Rajasthan, established in 1947 and affiliated to the University of Rajasthan⁸⁸. Dr Gautam also has his own private mental health clinic in Jaipur.

5.4 Issues of concern in the risperidone and quetiapine trials

Placebo controls

The trials of risperidone and quetiapine discussed here had a placebo arm though an established treatment existed. Risperidone was approved in India for psychosis which includes acute mania. Haloperidol is a commonly used drug for the same purpose and also the drug recommended by the World Health Organization. The immediate release version of quetiapine was already approved for schizophrenia and the extended release formulation should have been tested against the immediate release formulation.

⁸⁷ Peuskens J, et al. op cit.

⁸⁸ http://smshospital.rajasthan.gov.in/dpt_psychitry.jsp

The Declaration of Helsinki is held as the benchmark for research ethics and also as a standard for regulatory agencies such as the EMEA. The version amended in 2000 would have been applicable in the risperidone trial and stated clearly that new drugs should be tested against the best available drugs; placebos should be used only when there are no proven treatments. A clarification in 2004 (therefore applicable to the quetiapine trials) stated that placebos could be used only if there was a compelling scientific reason *or* if the condition was minor and the trial participant would not be harmed.

Are placebo controls necessary?

Psychiatrist Vikram Patel states: “My position on trials for conditions for which there are existing and available effective treatments is that any new treatment must be evaluated against that existing and available treatment. However, many country drug controller authorities demand a placebo-controlled trial and this is often why companies are compelled to carry trials such as the ones you have sent are permitted.” Further, he points out that from the scientific question is not whether a new drug works better than a placebo; it is “whether the new treatment being tested is better than the existing, approved, treatment.”

All but one of the investigators interviewed stated that there were strong methodological reasons to have a placebo arm. The primary argument was that psychiatric conditions can be self-limiting, and there is also a significant placebo response to psychiatric drugs. A placebo arm will enable the researcher to isolate the effect of the drug. Kurien Kuruvilla, one of the investigators in the risperidone trial, stated that the trial provided definitive information on the value of this drug in acute mania.

Trial investigators’ reservations about placebo controls

Interestingly, researchers in the risperidone and quetiapine trials have themselves expressed reservations about the use of a placebo.

Sumant Khanna, lead investigator of the risperidone trial, stated that a placebo is not necessary to establish the efficacy of drugs when an effective treatment exists; equivalence trials can obtain this information but they require larger sample sizes. Such placebo-controlled trials (when a treatment exists) are “on their way out”, he said. “In 2000 placebo-controlled studies were the norm and were regulatory requirements by FDA and EMEA. These studies were done according to these requirements. The regulatory authorities need to change their stand on placebo-controlled studies.”⁸⁹

The authors of the quetiapine XR for maintenance in schizophrenia trial state: “An important consideration for future relapse trials is that although the use of a placebo arm is important to demonstrate efficacy or lack of efficacy for any treatment, its use in schizophrenia clinical trials is being questioned owing to the severe nature of the condition and the considerable negative impact of relapse on illness severity and future treatment. [3] However, it is notable that the regulatory authorities in the countries in which this study was conducted required the use of a placebo in this study to determine the absolute efficacy of quetiapine XR in reducing the risk of relapse. In the present study, the risk to patients was minimised by the Data and

⁸⁹ Sumant Khanna interviewed in New Delhi, October 1, 2008

Safety Monitoring Board (DSMB) conducting pre-planned interim analyses after 45 and 60 observed relapses, as well as having persons monitoring the safety of the patients to enhance clinical care during this study. For future studies, it may, therefore, be appropriate to investigate the differences between formulations of the same antipsychotic or versus an active comparator.⁹⁰

Harm minimisation in trials using a placebo

Psychiatrist Prathap Tharyan, professor of psychiatry at the Christian Medical College, Vellore, and coordinator of South Asian Cochrane Network, has also commented on placebo-controlled trials in psychiatry⁹¹.

When a treatment already exists, Dr Tharyan writes, the acceptability of a placebo control is determined by whether the patient will be harmed by deferring therapy. The potential harm of withholding treatment includes “distress and disruption produced by the continuation of manic or psychotic symptoms, the progression of the illness with the potential for poorer recovery from an episode and the risk of suicide.” It is possible to minimise these harms, he wrote, by “careful evaluation of all participants for worsening, non-response in a reasonable period of time, or adverse effects, and the protocol permitted withdrawal of any participant at the discretion of the investigator”.

Clinical pharmacologist Urmila Thatte stated that in psychiatric conditions, without a placebo control, it may not be possible to know whether the improvement associated with the new treatment is due to the drug itself or due to a placebo response. Adjusting for this placebo response with a larger sample size will require a very large sample and this puts many more patients at risk, rather than minimising it. However, the use of placebo must be justified on a case by case basis and all steps must be taken to minimise the risk to the patient. There is no justification, she said, for the use of a placebo to test the efficacy of an extended release formulation of an approved drug. This can be done by bioequivalence studies which compare the blood levels of the two formulations to confirm that they have the same biological impact. Dr Vikram Patel stated that he was not sure “why the risk of giving placebo to people who are very sick and for whom there is an effective treatment is not considered a risk. The placebo effect is universal in medical care, perhaps barring infectious diseases. If we accept that placebo controls are therefore needed for all medical intervention trials, then what is the point about the Helsinki principles which clearly state that the control group must have the best available care, except under very exceptional circumstances?”

Informed consent in psychiatric patients

Dr Tharyan notes that informed consent is a particular concern for patients with compromised competence and even competent patients have difficulty understanding the concept of placebo and randomisation. It is also known that patients participate in trials because they expect to benefit. Finally, he writes, “The pressure of competitive recruitment in industry-sponsored multi-centre trials, the substantial emoluments that trial recruitment confers, and the stringent data monitoring associated with many such trials, makes obtaining

⁹⁰ Peuskens J, et al. op cit.

⁹¹ Tharyan P. Placebo-controlled trials in psychiatry on trial. *Indian J Med Ethics* 2006; 2: 13-6.

valid informed consent, the component of the trial that is supervised and evaluated the least, the most likely to be compromised.”

The investigators in these trials have stated that informed consent was obtained from the patient and legally authorised representative. It must also be remembered that the families of patients needing health care may also be vulnerable to giving consent for a relative to participate in a trial. The basic services provided in a clinical trial might actually serve as an inducement for patients to participate in trials as a way to get health care.

Vulnerability of patients in government hospitals

Five of the centres in these trials were in government hospitals which house the most seriously ill patients, according to one of the investigators. In the risperidone trial, government hospitals are believed to have recruited more than 210 of the 290 patients in this trial. At least two-thirds of the patients – possibly more – were in government hospitals which house the economically most vulnerable patients, and where the quality of care can be poor. Jitendra Trivedi, who runs a large number of psychiatric drug trials in a government hospital, acknowledges that for psychiatric patients in government hospitals, the concern is whether you are taking truly informed consent. Consent can be compromised by patients’ medical condition, their education levels, and poverty. “This can influence their desire to take part, their ability to understand.”

The investigators’ comments strongly suggest that patients in public hospitals enter trials to obtain care. Sumant Khanna who was lead investigator in the risperidone trial, said, “You also get free treatment (in public hospitals). So a lot of poor people go there. Many of them required hospitalisation and with the limited number of beds they may not have been hospitalised. Entering a trial gets them priority.” According to Dr Trivedi, patients who have been part of one of his trials actually ask if there are others they can enter “because of the amount of care which they get, the focus and the attention which they get.”

R Sathianathan, who ran a site for the risperidone trial in a government hospital, acknowledges that psychiatric patients, especially in government hospitals, are particularly vulnerable, but such vulnerability is not unique to psychiatric trials. “We cannot do any research without this. This is the question of any general hospital, government hospitals have poor patients only. It is true for all trials. There is no question of vulnerability.” Did placebo controls exploit psychiatric and financial vulnerability of patients in public hospitals? “I strongly disagree.”

Vulnerability of patients in private hospitals

On the other hand, patients in private institutions are also vulnerable as trials can be promoted as an opportunity to get free treatment. Vijay Debsikdar, who recruited some patients for the risperidone trial, said: “Well affording patients will not go for clinical trials because it offers free treatment. People who can afford treatment don’t join clinical trials.”

Prasad Rao who ran a site in quetiapine XR for maintenance treatment for schizophrenia said about informed consent: “For an average patient, he or she is getting the opportunity to

take this drug. There is an opportunity for the patient to get free treatment. They get all other investigations free.”

Why would people join the trial even when they know that they could receive a placebo instead of the active treatment? “I don’t know why,” said Dr Rao. “They will be told about the placebo. And 50 per cent of those who are asked don’t come. For a patient who is chronically ill and taking treatment, one thing is they are getting something free. Some might say the new drug might be better than what they have been taking altogether. We explain that there is a placebo.”

5.5 Findings on the risperidone and quetiapine trials

The trials were conducted for approval in the US and EU

These trials were conducted for approval in the US or in EU countries. The journal article reporting the risperidone trial states that the trial (conducted in 2001) was conducted according to the 1989 version of the Declaration of Helsinki when the 2000 version would have been applicable. The USFDA and the EMEA require placebo-controlled trials of drugs submitted to them for approval. The USFDA required adherence to the 1989 version of the Declaration, and not any later revisions (it no longer requires adherence to the Declaration). Before January 2005, the office of the Drugs Controller General of India gave a drug marketing approval following the drug’s approval in other countries. Approval of drugs developed and approved in other parts of the world required small phase 3 trials on the Indian population. In January 2005, the DCGI’s requirements for marketing approval have changed. However, it does not require placebo-controlled trials for drugs submitted to it for approval, says S D Seth, chair of clinical pharmacology at the ICMR. The decision to permit or disallow placebo-controlled trials rests with the local ethics committees at the trial sites⁹². As a member of a local ethics committee, Dr Seth rejected a three-arm ⁹³ placebo-controlled trial of an extended release version of a psychiatric drug (not quetiapine). “Another drug had already been tested against placebo for this condition and found effective. The new drug should have been tested against the established drug.”

A placebo-controlled trial was not methodologically necessary to test the efficacy of quetiapine XR. Dr Urmila Thatte, clinical pharmacologist, states that since the immediate release formulation had already been approved, the efficacy of the extended release formulation could have been proven through a bioequivalence trial.

At least one expert has stated that risperidone’s efficacy for acute mania could have been proven through a trial comparing it to the existing standard of care, haloperidol. Even the lead investigator of this trial has stated that the information could have been obtained by comparing risperidone to another drug rather than to a placebo.

⁹² Interviewed in Mumbai on October 4, 2008.

⁹³ Extended release drug, standard drug and placebo

These trials exploited the vulnerability of patients who cannot afford quality medical care

It is not known how many patients in the quetiapine trials were recruited from government hospitals, but more than two-thirds of patients in the risperidone trial were recruited in government hospitals. The poor quality of care in government hospitals would encourage patients to view trial participation as a way of getting better quality care.

Patients in private hospitals are also vulnerable. Barely five per cent of people in India have insurance coverage. Patients in private hospitals may view trial participation as a way of obtaining free care.

These trials harmed the participants

There is no doubt that patients in the placebo arms of these trials were harmed by their participation. In the risperidone trial seriously ill patients – worse than patients in similar trials in the US – were taken off treatment to prove the efficacy of a drug when an effective treatment was available.

In the trial of quetiapine XR for long-term maintenance for schizophrenia, a serious psychiatric condition, patients were put on placebo despite the existence of an effective drug. More patients on placebo suffered a relapse than patients on the active drug of proven efficacy. Patients on placebo suffered serious harm because of participation in the trial.

A patient in one of the quetiapine trials committed suicide after 173 days of being on placebo or no treatment. The authors of the journal article reporting on this trial have stated that this suicide is “not considered treatment related”. Suicide is a known risk for patients with schizophrenia. The investigators do not explain how they concluded that the suicide was unrelated to the treatment. The possibility cannot be ruled out that the patient committed suicide because s/he was deprived of effective treatment.

There were deaths in both the quetiapine trials. No information is available on where these deaths took place. Nor is there information on whether compensation was paid to the families of the patients.

6. Overview of findings and concluding remarks

Limited information could be obtained on these trials as we have been unable to obtain documents that should be in the public domain, such as the informed consent document. However, the following issues emerged in this exploratory study of three clinical trials in India.

These trials exploited the fact that most Indians do not have access to good quality and affordable care and therefore may accept offers that provide better quality and free treatment. They were conducted on people who were vulnerable because they could not afford high quality treatment or the most effective drugs. They were also vulnerable because they were seriously ill. These trials caused harm to the patients who participated in them. These trials also violated national and international ethical guidelines.

Lapatinib

GlaxoSmithKline, the company marketing lapatinib, has refused to provide important information such as a copy of the informed consent form and patient information sheet, or information on how many patients were recruited at each site in the 10 countries where the trial took place. GSK has refused to give information “as standard practice”. Still, certain concerns are apparent from the available information.

The phase 2 trial of lapatinib monotherapy on chemotherapy naïve patients with metastatic breast cancer was searching for new information and may have genuinely led to new information on the drug’s efficacy and safety.

2. The majority of breast cancer patients in India cannot afford proper treatment. This trial required seriously ill patients who had not received treatment for their condition. Their economic vulnerability forces patients in India to take part in trials in order to get access to treatment and to disregard the potential risks that participating in clinical trials entails. By carrying out this clinical trial in India GlaxoSmithKline took advantage of the vulnerable position of breast cancer patients.

There is reason to believe at least in one case that the principal investigator who was also the patients’ physician presented the trial to patients as a treatment option.

GSK’s reply suggests that patients, who stopped responding to lapatinib, were not assured treatment once the trial was completed.

The trial started before January 2005 when regulations did not permit concurrent phase trials. There is no indication that GSK received any special permission to bypass this regulation. GSK’s statement that this was not a concurrent phase trial is disputed by an expert on regulatory issues.

The approved drug is not affordable to the vast majority of Indians who could benefit from it.

Risperidone

Johnson & Johnson’s reply to a letter seeking information shed no light on the conduct of this trial. However, the information that is available highlights certain concerns.

Ethical concerns in clinical trials in India: an investigation

This placebo-controlled trial of risperidone for acute mania was conducted for regulatory purposes in the US. All sites of this trial were in India.

It used a trial design required by US regulatory authorities which many have argued is unnecessary.

Patients in this trial were recruited from both government and private hospitals. However, more than two thirds of patients were recruited from government hospitals where the most severely ill patients are found.

The comments of investigators clearly indicate that patients in government hospitals may view trial participation as a way to get improved care as clinical trials require monitoring for efficacy and safety. Investigators have also indicated that patients from private hospitals may view trial participation as a way to get free care.

The patients in this trial were much more severely ill than similar trials of risperidone conducted in the US and other developed countries.

Patients in this trial were suffering from an acute attack of a psychiatric condition that would have caused them much distress. They were harmed because they were taken off all treatment before they were put on either the active drug or a placebo. Those on the placebo were also harmed because they were deprived of an effective treatment.

The use of placebo for a serious condition when an effective treatment exists is a clear violation of the Declaration of Helsinki that was applicable at the time of this trial.

Quetiapine fumarate extended release

Astra Zeneca has not responded to requests for information. However, the information that is available highlights certain concerns.

Two placebo-controlled trials of quetiapine extended release were conducted on patients with schizophrenia. An immediate release formulation of the drug had already been approved and these trials were of an extended release version of the drug, for its impact on patients with acute schizophrenia and for long-term use.

These trials were not required to establish the efficacy of the drug. Nor were they required by regulatory authorities in India.

Patients in these trials were recruited from both government and private hospitals. The comments of investigators clearly indicate that many patients in private hospitals may view trial participation in order to obtain free treatment. Further, patients in government hospitals may view trial participation as a way to get improved care as clinical trials require monitoring for efficacy and safety.

Patients in one of the quetiapine trials were harmed when they were taken off all treatment before being put on either the active drug or a placebo. Those in both trials on the placebo were also harmed because they were deprived of an effective treatment. This constitutes a violation of DOH regarding placebo-controlled trials

The official explanation of the two deaths in these trials is unacceptable. One death is described as “due to unknown causes” but also “unrelated to treatment. In the other trial, the suicide by a patient on placebo – no treatment – is explained away with the statement that suicide is a known risk for patients with schizophrenia.

Conclusion

These trials violated the the Indian Council of Medical Research's *Ethical guidelines for biomedical research on human subjects* and the World Medical Association Declaration of Helsinki: *Ethical principles for medical research involving human subjects*.

The trial designs do not seem to have violated regulations for the conduct of clinical research in India. The existing regulatory apparatus therefore permits unethical trials of no benefit to Indians.

Clearly, trials are being conducted in India that could not be conducted in developed countries, taking advantage of people's lack of access to affordable, good quality care. The benefits of research do not reach the community as drugs found effective following these trials may not be affordable to the community in which they were tested.

Such practices are in violation of the Declaration of Helsinki as well as the general principles laid down in the Indian Council of Medical Research's ethical guidelines for biomedical research.

The infrastructure for regulation, ethics review and monitoring is insufficient.

The government's priority seems to be ensuring that clinical research in India produces good quality data according to Good Clinical Practice standards. Ethical guidelines – including its own ethical guidelines – seem to be of secondary importance.

The ethical concerns raised by these clinical trials; the weak regulatory apparatus to protect trial participants, government policy to encourage international clinical trials without taking active steps to put in place a system to protect participants from harm; people's desperation for affordable health care – all this will only worsen the harm being done to trial participants in India.

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This report was revised after comments from Annelies den Boer, project coordinator, medicines, Wemos Foundation, Amsterdam, The Netherlands; Francis Weyzig, Centre for Research on Multinational Corporations (SOMO), Amsterdam, The Netherlands; Bebe Loff, department of human rights and bioethics, school of public health and preventive medicine, Monash University, Melbourne, Australia; S Srinivasan, managing trustee, LOCOST Standard Therapeutics, Vadodara, Gujarat, India, and Amar Jesani, Centre for Studies and Ethics and Rights, Mumbai. Ruth Macklin, department of epidemiology and population health, Albert Einstein College of Medicine, New York, USA, commented on the issues raised in the lapatinib trial. CM Gulhati, editor MIMS India, commented on the section on regulation of clinical trials in India.

Amar Jesani and Neha Madhiwalla, Centre for Studies in Ethics and Rights, gave regular inputs into the investigation and also provided ethics consultation for this purpose

I take responsibility for the content of this report.

Ethical concerns in clinical trials in India: an investigation

The experts who were interviewed for this report include: Vasantha Muthuswamy, former deputy director of the Indian Council of Medical Research; CM Gulhati, editor, Monthly Index of Medical Specialities (India); Arun Bhatt, president, Clininvent Research, Mumbai; S D Seth, chair, clinical pharmacology, Indian Council of Medical Research. and advisor to the Clinical Trials Registry-India; Urmila Thatte, head, department of pharmacology, KEM Hospital, Mumbai, Nithya Gogate, department of pharmacology, KEM hospital, Mumbai; Vikram Patel, reader in the department of psychiatry, London School of Hygiene and Tropical Medicine; Amit Sengupta, Delhi Science Forum and YK Sapru and Shubha Maudgal, Cancer Patients Aid Association, Mumbai. Some of them are quoted here.

Expert opinions on the trials were sought from a number of specialists including Soumitra Pathare, psychiatrist, Ruby Hall Clinic, Pune; Yash Lokhandwalla, cardiologist, Mumbai; Roop Gursahani, neurologist, Hinduja Hospital, Mumba; Nagesh Simha, palliative care specialist; Sunil Pandya, neurosurgeon, Jaslok Hospital, Mumbai; Meenal Mamdani, neurologist, Pune and Chicago, USA, and Bashir Mamdani, physician, Pune and Chicago, USA. Their opinions are not necessarily reflected in this report. They and many others who are not named have contributed their very valuable insights to this report.

Sandhya Srinivasan is an independent journalist and researcher based in Mumbai. She is consultant at the Centre for Studies in Ethics and Rights, Mumbai; executive editor of the Indian Journal of Medical Ethics (www.ijme.in), and consulting editor for the development website www.infochangeindia.org .

Appendix I: Contact and correspondence with investigators and institutions

Contact with trial investigators

Shona Nag and Dinesh Doval were interviewed at their offices about the lapatinib trial. The third Indian investigator in the lapatinib trial could not be contacted. In the psychiatric drug trials, efforts were made to contact all the researchers in the three trials. The director of the National Institute for Mental Health and Neurosciences, one of the sites for the risperidone study was sent an e-mail asking for an interview. Face to face interviews were conducted with Jitendra Trivedi and Sumant Khanna. A second interview with Dr Khanna was conducted on the telephone. Telephone interviews were conducted with Kurien Kuruvilla, R Sathianathan, V Debsikdar, and Prasad Rao. Podila Sharma and G K Vankar were sent a list of questions by e-mail. Dr Sharma acknowledged the e-mail. Shiv Gautam was contacted but could not be interviewed. R Palaniappan, J Nagpal and Nagesh Pai were not contactable. Dr Pai has reportedly migrated to Australia.

The following were sent an e-mail with the quoted statements, informing them that they were being quoted: Shona Nag, Dinesh Doval, Prasad Rao, Jitendra Trivedi, Sumant Khanna, R Sathianathan and V Debsikdar.

Dr Debsikdar's e-mail obtained from his residence bounced back. Dr Kuruvilla was phoned for his e-mail address but did not give it on the phone and then refused to answer phone calls.

Dr Nag, Dr Doval, Dr Khanna and Dr Trivedi gave their consent to their statements quoted in this report.

Contact with institutions

After the interviews with investigators, letters were sent by courier on October 31, 2008, to the directors of the institutions where the trials were conducted. The letter to James Pandian, dean of the Madras Medical College (a site of the risperidone trial) was returned as "refused".

Mail from PSVN Sharma on October 24, 2008

"Dear Madam

"I am in receipt of your mail. I have worked on the two trials that you have mentioned. The correspondence and data regarding these studies has been archived. After receiving your mail I have been in touch with my Institution, the Institutional ethics committee and the sponsors of the trials regarding the matters raised by you and am awaiting their response. I need to clarify with them as to what information and documents I can release without breaking the confidentiality clause of the trials. It would be discourteous on my part not to reply to you, hence this letter. I can assure you that the trials were conducted at our site in accordance with the DCGI and ICMR requirements.

"Yours sincerely

"PSVN Sharma"

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Ashok Panagariya, principal of the SMS Medical College in Jaipur wrote back to state that he had asked the ethics committee to provide information relevant to the ethics committee, and that the principal investigator, Shiv Gautam, should be contacted regarding other information.

P Sripathi Rao, dean, Kasturba Medical College, Manipal, wrote back stating that all information, material and documents related to the trial were confidential and the property of the sponsor.

Satheesh Rao, head of the department of psychiatry of the KS Hegde Medical Academy, wrote back in detail and also provided the DCGI approval documents, informed consent documents and details of the ethics committee.

Appendix II: Contact and correspondence with the companies

During the shortlisting of trials, efforts were made to obtain an interview from the companies conducting the trials. Two of the five companies (Eli Lilly, manufacturing exenatide, and Nycomed Pharma, manufacturing ciclesonide) responded stating that they would not provide any information.

After the interviews with investigators in the four trials, efforts were made to contact a representative in the three companies, GlaxoSmithKline, Johnson & Johnson and AstraZeneca. Following this second round of telephonic contact, e-mails were sent to the the medical director of GlaxoSmithKline, Mumbai, the director (corporate communications), Johnson & Johnson, Mumbai and the director (corporate communications), Astra Zeneca, Bangalore. These letters were also delivered by courier.

The letters asked for details on the trials including the number of patients recruited at each site, economic background of patients and the information given to patients. A copy of the informed consent form, regulatory approval and details of the local ethics committee were also sought.

Efforts to speak to the the director (corporate communications), Astra Zeneca, were fruitless and the company did not respond to were did not respond to e-mails sent to the e-mail company address or to Sheshendra Bhadauria, the director, corporate communications, whose name and e-mail address were obtained from the Bangalore head office. The company did not respond to the letter delivered by courier.

The correspondence with GSK and J&J is reproduced below.

GlaxoSmithKline

E-mail sent to GSK October 17, 2008-12-31 Dear Dr Joglekar,

I am a freelance journalist and am working with my colleague Sachin Nikarge on a story regarding clinical trials in India. We would like to meet you or any other representative GSK for information on the following trial:

This is a phase 2, two-dose monotherapy study involving chemotherapy naïve participants to observe the effect of the drug Lapatinib on breast cancer with doses of 500 mg twice daily and 1,500 mg once a day. The NCT number is NCT00089999. The trial was recently reported in the Journal of Clinical Oncology (Gomez HL et al. Efficacy and safety of lapatinib as first-line therapy for ErbB2-amplified locally advanced or metastatic breast cancer. J Clin Oncol. 2008 Jun 20;26(18):2999-3005).

The questions are as follows:

Ethical concerns in clinical trials in India: an investigation

1. Which countries was this trial conducted in? How many sites were there in India?
2. How many patients were recruited at each site, in India as well as in the other countries?
3. When exactly was this trial started in India?
4. What was the information sought in the trial? What role has the information obtained in the trial played in higher phase trials and in the drug approval process?
5. In India, what are the details of the ethics review committees that reviewed and approved this protocol? Which of these are institutionally based? Which are private or independent committees? May we have the names of the members? May we have the names and contact details of the EC secretaries?
6. In India, was the trial protocol rejected by any ethics review committees?
7. What is the standard of care for patients with this stage of the disease? Was this standard provided to the women in this trial?
8. What was the economic background of the women in the trial?
9. What information were they given about the trial?
10. What treatment was given to them once the trial was over?
11. Did they pay for any treatment during or after the trial?

We would also appreciate the following:

1. A copy of the document from the DCGI giving approval for the trial.
2. A sample copy of the patient information sheet and informed consent form.
3. Membership details of all the ethics committees that reviewed and approved the trial protocol, a list of members, and contact details of the secretaries.
4. The document from the various ethics committees approving the trial.
5. Details of the deliberations of the ethics committees regarding this trial, and any modifications that they might have requested regarding the trial protocol.

Thank you very much for calling me back and for agreeing to respond by e-mail by Monday October 20. As I said on the phone, if you would prefer a face-to-face interview, I will need it within this week as well. I do appreciate your willingness to spend time with me discussing this subject.

Looking forward to hearing from you,

Ethical concerns in clinical trials in India: an investigation

Sincerely,

Sandhya Srinivasan
www.infochangeindia.org
www.ijme.in
www.cser.in
8 Seadoll, 54 Chimbai Road
Bandra (W), Mumbai 400 050
INDIA
Tel: (91 22) 2651 4211
Cell: (91) 98204 10849

E-mail received from GSK October 28, 2008

Dear Ms Srinivasan,

Thank you for your enquiry. I have pleasure in responding to your request for information.

Study NCT 00089999 was set up by GSK to evaluate and compare the efficacy and tolerability of oral Lapatinib at 1500 mg once daily and 500 mg twice daily in patients with advanced or metastatic breast cancer.

The study was part of a global clinical development programme for lapatinib, which has since been approved in many countries, including India. The objective of this study was to assess the efficacy and tolerability of two lapatinib administration schedules as first-line monotherapy in women with ErbB2-amplified locally advanced or metastatic breast cancer. Lapatinib is a targeted therapy against both the ErbB1 and ErbB2 receptors. Regrettably, patients with advanced or metastatic breast cancer cannot yet be cured – but inhibition of the ErbB2 receptor in this sub-set of patients has been shown to delay tumour progression – either as monotherapy or in combination with chemotherapy. This study was designed to compare two different dose regimens i.e. all patients received active therapy. Lapatinib was provided free of charge to all patients in the study.

In the development of all medicines, it is important to ensure that appropriate efficacy and safety data is collected to ensure continued benefit to patients. This development may include the combination of medicines or a medicine used as monotherapy, in an effort to identify the most effective and tolerable regime for patients. In this study, patients in both treatment arms received lapatinib until week 12, unless their disease had progressed or they had withdrawn from the study. After week 12, patients with clinical benefit had the option to continue their treatment for as long as they responded to treatment (i.e. until disease progression) provided the treatment was tolerated. Once their tumour had progressed i.e. they were not responding to or had become resistant to lapatinib, they were placed on alternative treatment at the investigator's discretion. This was to minimise the risk of side effects when there was no clear benefit to the patient of remaining on lapatinib.

Ethical concerns in clinical trials in India: an investigation

The study commenced in June 2004 in 10 countries including the United States, Chile, Hong Kong, India, Malaysia, Mexico, Pakistan, Peru, Singapore and Taiwan. Three centres in India participated in the study and 27 of the total 138 randomised patients came from India.

The clinical study was established in accordance with the standard ethical and regulatory frameworks and further information about this trial is available on ClinicalTrials.gov.

In accordance with ICH GCP (International Committee on Harmonisation, Good Clinical Practice), GSK provides patients with thorough and appropriate information prior to participation in any clinical study, in a language which they can understand. All participating study centres obtain approval of the research protocol and patient information via their local institution-based Ethics Committees prior to initiation and selection of patients. In order to act with due diligence, GSK in conjunction with the responsible Primary Investigator ensure patients are fully able to give their informed consent prior to enrolling in any study.

GSK ensures that it selects investigators and research centres that offer the required level of qualification, experience and resources appropriate to properly conduct the clinical trial. Standards of care may differ across the varying regions of the world depending on whether specific medications have been approved by each country's Regulatory Authority. Global study protocols are therefore designed to ensure appropriate standards of care are provided to eligible participating patients. These standards are evaluated and approved by each participating local institution-based Ethics Committee (IEC) prior to commencement. Before signing the informed consent forms, patients were informed that approved alternatives with chemotherapy, hormones, radiation therapy, or new anti-cancer options were available for their treatment that they should discuss with their doctor. These forms were approved by the local IRB/IEC prior to implementation.

GSK works within the regulatory framework of all participating countries when establishing research studies. Study NCT00089999 was approved locally by the Drugs Controller General of India. Documentation regarding the study is held by the regulatory authorities.

Regrettably, we cannot make available to you materials submitted to regulators or to ethics committees, nor share personal details of their members or their responses.

If we can be of further assistance, please let me know.

With best wishes

Dr Sadhna Joglekar
V P, Medical and Clinical Research
GSK Pharmaceuticals Ltd.
Mumbai

E-mail reply sent to GSK November 4, 2008

Dear Dr Joglekar,

Thank you for your response to my questions. I do appreciate the trouble

Ethical concerns in clinical trials in India: an investigation

that you have taken to respond to my questions. Unfortunately, few of my questions have been answered and I must therefore restate them with some elaboration in case they were not clear.

1. Could you please provide the names of the institutions and investigators at each site in each country? What are the names of the institutions and investigators at the three sites in India?
2. How many patients were recruited -- at each site -- in India as well as in the other countries?
3. Were patient characteristics identical in all sites?
4. By what clause in the law was permission given to conduct this concurrent phase trial before January 2005?
5. In India, what are the details of the ethics review committees that reviewed and approved this protocol? Which of these are institutionally based? Which are private or independent committees? May we have the names of the members? May we have the names and contact details of the EC secretaries?
6. In India, was the trial protocol rejected by any ethics review committees?
7. What is the international standard of care for patients with ErbB2 amplified locally advanced or metastatic breast cancer?
8. What is the local standard of care, in India, for patients with ErbB2 amplified locally advanced or metastatic breast cancer?
9. What were the different treatment options for women in the Indian trial sites?
10. What is the explanation, as given in your documentation, for these women not to choose one of these treatment options and to choose to take an experimental drug instead?
11. What was the decision-making process by which the investigators invited these women to participate in the trial?
12. What was the economic background of the women in the trial?
13. What information were they given about the trial?
14. Did they pay for any treatment given to them once the trial was over?
15. Did they pay for any treatment during or after the trial?
16. What steps were taken to ensure that patients gave their informed consent?
17. Were the primary investigators also the patients' physicians? Who invited the women to participate in the trial?
18. What exactly was stated in the patient information sheet and the informed consent form?

I would greatly appreciate your answers to all these questions. If for any reason you are unable to provide answers to any of these questions, I would appreciate your explanation for your decision in each case. For example, the patient information sheet, the informed consent form and the details of ethics committee members are surely public information.

Ethical concerns in clinical trials in India: an investigation

I will need your response by Monday November 10 at the very latest.

Looking forward to hearing from you,

Sincerely,

Sandhya Srinivasan

E-mail received from GSK November 11, 2008

Dear Ms Srinivasan,

Thank you for your e-mail of 4 November 2008.

GSK is committed to its mission of helping people to do more, feel better and live longer and our primary focus is on developing and providing medicines which help patients live better lives.

As you will appreciate, we receive many requests like yours and decide on a case-by-case basis whether the provision of the information over and above what is publicly available or available from other sources will be consistent with and not distract us from the pursuit of our overall mission.

You will also appreciate that responding to every request is not possible and many considerations come into play when considering such requests. To help us better understand the context of your request, please could you send me further details as to the nature of your article? You mention that you are working on a story regarding clinical trials in India: Is it a general article covering different aspects of conduct of clinical trials in India or is it focused on a particular therapeutic area such as oncology or a particular new medicine?

The clinical trial in question relates back to 2004. Like other large research-based companies, GSK carries out a number of clinical studies every year. This results in generation of a large volume of documentation, the retrieval of which is time consuming and cumbersome and hence our request to understand the context of your query.

Thank you for your understanding and I look forward to hearing from you.

With best wishes

Regards,

-Sadhna

Dr Sadhna Joglekar.
VP, Medical & Clinical Research,
GSK Pharmaceuticals Ltd.,
Mumbai.

Ethical concerns in clinical trials in India: an investigation

E-mail sent to GSK November 11, 2008

Dear Dr Joglekar,

This report is about ethical issues in clinical trials. It covers different aspects of the conduct of clinical trials in India.

I appreciate the difficulties in retrieving documentation from a trial that was conducted in 2004. But I imagine that most of my questions can be answered by your office.

My questions were first sent to you on October 17 which is more than three weeks ago. You will understand that I must meet my deadline for filing my report. So if you have any response to the questions that I have listed below, I will need them right away.

Looking forward to hearing from you,

Best,

Sandhya Srinivasan

E-mail response received from Jeroze Dalal, general manager, clinical operations, GSK, November 15, 2008

Q1. Can you provide the names of the institutions in India and investigators at each site in India for the NCT 00089999 study?

A1. Three sites in India participated in the study. The participating centres were as follows:

- Dr. D.C. Doval, Rajiv Gandhi Cancer Research Institute & Research Centre Delhi, India, 110085.
- Dr. D. Raghunadharao, Nizam's Institute of Medical Sciences, Hyderabad, Andhra Pradesh, India 500482.
- Dr. Shona Nag, Jehangir Hospital, Pune, India, 411001.

Q2. How many patients were recruited at each site in India, as well as in other countries?

A2. A total of 27 patients from India took part in the study which enrolled 138 patients worldwide.

Q3. What were the patient characteristics at each site?

A3. For all our clinical trials, GSK adheres strictly to an approved study protocol, which outlines inclusion and exclusion criteria for patients eligible to take part in the trial. The inclusion/exclusion criteria for eligibility into study NCT 00089999 is available on <http://clinicaltrials.gov/ct2/show/NCT00089999>. These were the agreed criteria, against which study investigators would recruit patients.

Q4. By what clause in the law was permission given to conduct this concurrent phase trial, before January 2005?

Ethical concerns in clinical trials in India: an investigation

A4. GSK complies with all applicable laws regarding the conduct of clinical trials, including study NCT 00089999. This was not a concurrent phase trial since lapatinib, as a new chemical entity (NCE), was already in phase III of development at the time that this phase II study was conducted in India.

Q5. What are the details of the ethics review committees that reviewed and approved this protocol. Which of these are institutionally based? Which are private or independent committee? May we have the names of the members? May we have the names and contact details of the EC secretaries?

Q5. As standard practice, GSK does not disclose materials submitted to regulators or to ethics committees, nor share personal details of their members or their responses.

Q6. In India, was the trial protocol rejected by any ethics review committees?

A. Yes. We know that the Ethics Committee of the All India Institute of Medical Sciences, New Delhi, rejected the study. It is not unusual for a particular EC to reject research protocols. This can be for a number of reasons, which may be unrelated to the formal content of the study.

Study NCT 00089999 was not conducted at any site without ethics approval from the relevant committee and institution.

Q7. What is the international standard of care for patients with ErbB2 amplified locally advanced or metastatic breast cancer?

A7. Standards of care may differ across the varying regions of the world depending on whether specific medications have been approved by each country's Regulatory Authority. Global study protocols are therefore designed to ensure appropriate local standards of care are provided to eligible participating patients. It is GSK policy that the standard of care required by the study design is, as a minimum, consistent with local standards of care. These standards are evaluated and approved by each participating local institution-based Ethics Committee prior to commencement.

Q8. What is the local standard of care, in India, for patients with ErbB2 amplified locally advanced or metastatic breast cancer?

A8. At the time of conducting study NCT 00089999 in 2004-2005, the standard of care in India for majority of patients with advanced or metastatic breast cancer was primarily chemotherapy. For those who could afford it, trastuzumab was the standard of care.

Q9. What were the different treatment options for women in the Indian trial sites?

A9. At the time of conducting study NCT 00089999, women with advanced or metastatic breast cancer had a number of treatment options.

The informed consent process and the form given to patients make it explicit that this study was being carried out with an experimental medication, which has not been hitherto proven to help cancer patients. Furthermore, the informed consent made it clear that the patient's physician will discuss other treatment options and the advantages and disadvantages of participating in such a study.

Q10. What is the explanation, as given in your documentation, for these women not to choose one of these treatment options and to choose to take an experimental drug instead?

A10. The informed consent form given to patients makes it very clear that those invited are under no obligation to participate in the study. This documentation also makes clear the risk associated with participation in this study.

The informed consent form makes it explicit that this is a study with an experimental medication, which has not been proven to help cancer patients. Furthermore the informed consent makes it clear that the patient's physician will discuss other treatment options and the advantages and disadvantages of participating in such a study. The informed consent form clarifies that the patient has the right to withdraw from the study at any time without giving a reason.

Q11. What was the decision-making process by which the investigators invited these women to participate in the trial?

A11. The inclusion/exclusion criteria for eligibility into study NCT 00089999 are available on <http://clinicaltrials.gov/ct2/show/NCT00089999>. These were the agreed criteria, against which study investigators would recruit patients after receiving Ethics Committee approval for conducting this study.

Q12. What was the economic background of the women in the trial?

A12. GSK does not collect this information in clinical trials. Our focus is on medical information.

Q13. What information were they given about the trial?

A13. As standard practice, all study participants are given a copy of the informed consent form. In this study, before signing the informed consent forms, patients were informed that approved alternatives such as chemotherapy, hormones, radiation therapy, or new anti-cancer options were available for their treatment, which they should discuss with their doctor. During the consent process, patients were informed about the potential risks and possible benefits associated with participation in this study. Patients were also assured of being kept informed of any new significant findings that could affect their willingness to continue participation in the study. These forms were approved by the local IRB/IEC prior to implementation.

Q14. Did they pay for any treatment given to them once the trial was over?

A14. The protocol provided the option of continuing on the same dose and schedule of the experimental drug for those patients who responded to the treatment during the trial period.

Q15. Did they pay for any treatment during or after the trial?

A15. Patients did not pay for their treatment during the trial.

Q16. What steps were taken to ensure that patients gave their informed consent?

A16. In accordance with ICH GCP (International Committee on Harmonisation, Good Clinical Practice), GSK provides patients with thorough and appropriate information prior to participation in any clinical study, in a language which they can understand. All participating

Ethical concerns in clinical trials in India: an investigation

study centres obtain approval of the research protocol and patient information via their local institution-based Ethics Committees prior to initiation and selection of patients. In order to act with due diligence, GSK in conjunction with the responsible Principal Investigator ensures patients are fully able to give their informed consent prior to enrolling in any study.

For the study in question, before signing the informed consent forms, patients were informed that approved alternatives with chemotherapy, hormones, radiation therapy, or new anti-cancer options were available for their treatment that they should discuss with their doctor. These forms were approved by the local IRB/IEC prior to implementation.

Q17. Were the primary investigators also the patients' physicians? Who invited the women to participate in the trial?

A17. As standard practice, GSK is not able to disclose physician / patient information. That is a question for the study centre.

Q18. What exactly was stated in the patient information sheet and the informed consent form?

A18. The key contents of the patient information sheet and informed consent form appear in answers to questions 8, 9, 10, 13 and 16.

Johnson & Johnson India

E-mail sent to J&J November 7, 2008

-----Original Message----- From: sandhya srinivasan [mailto:sandhya199@mtnl.net.in] Sent: Friday, November 07, 2008 5:04 PM To: Nayak, Anil [JNJINBO]; sandhya srinivasan Subject: request information regarding a clinical trial sponsored by Johnson & Johnson

Mr Anil Nayak

Director, Corporate Communications

Johnson & Johnson India

30, Forjett St, Mumbai 400 036

Tel: (022) 6664 6464

E-mail: anayak1@its.inj.com

Dear Mr Nayak,

I am a freelance journalist and am working with my colleague Sachin Nikarge on a story regarding clinical trials in India. I am writing to ask for information regarding the following multi-centre clinical trial conducted by your company:

"A double blind, placebo-controlled trial of risperidone monotherapy for the treatment of acute mania."

The report of this trial was published in 2005 (Khanna S, Vieta E , Lyons B , Grossman F, Eerdeken M, Kramer M. Risperidone in the treatment of acute mania: double-blind, placebo-controlled study. Br J Psychiatry 2005 Sep;187:229-34).

My questions are as follows:

Ethical concerns in clinical trials in India: an investigation

1. How many placebo-controlled trials have you sponsored of risperidone in acute mania? Which countries were these trials conducted in?
2. In the India trial reported by Khanna et al, how many patients were recruited at each site? How many were recruited in each government hospital?
3. When exactly did this trial start and end?
4. What is the name of the contract research organisation that conducted this trial?
5. What was the information sought in the trial? What role has the information obtained in the trial played in the approval of this drug for use in acute mania in India? What role did it play in the approval process in the US and/or EU?
6. What are the details of the ethics review committees that reviewed and approved this protocol? Which of these are institutionally based? Which are private or independent committees? May we have the names of the members? May we have the names and contact details of the EC secretaries?
7. Were there any other sites identified for the trial but which did not participate because the trial protocol was rejected by the ethics review committee?
8. What is the standard of care for patients with this condition? Was this standard provided to the participants in this trial?
9. What was the economic background of the participants in the trial?
10. What information were they given about the trial?
11. What treatment was given to them once the trial was over?
12. Did they pay for any treatment during or after the trial?

We would also appreciate the following:

1. A copy of the document from the DCGI giving approval for the trial.
2. A sample copy of the patient information sheet and informed consent form.
3. Membership details of all the ethics committees that reviewed and approved the trial protocol, a list of members, and contact details of the secretaries.
4. The document from the various ethics committees approving the trial.
5. Details of the deliberations of the ethics committees regarding this trial, and any modifications that they might have requested regarding the trial protocol.

Looking forward to hearing from you,

Best,

Sandhya Srinivasan

www.infochangeindia.org , www.ijme.in , www.cser.in

8 Seadoll, 54 Chimbai Road, Bandra (W), Mumbai 400 050

Cell: (91) 98204 10849

sandhya_srinivasan@vsnl.com

E-mail received from J&J November 13, 2008

Hi Sandhya,

Thanks for your mail.

Ethical concerns in clinical trials in India: an investigation

Our response is as follows:

Our primary responsibility has always been focused on delivering the highest-quality care and patient safety. Our actions continue to be driven by the core values that are at the heart of the Johnson & Johnson Credo, which states that "...Our first responsibility is to the doctors, nurses and patients, to mothers and fathers and all others who use our products and services."

Johnson & Johnson recognizes the immense contribution of the patients who participate in our clinical trials, and we provide them the information and freedom necessary to give informed consent. We have well trained physicians and scientists to explain protocols to patients and answer any questions to obtain and document informed consent. We ensure that all participating physicians receive training and guidance on informing patients about the trial and documenting their informed consent in complete accordance with established guidelines and with particular attention to relevant language, literacy, cultural and societal issues. Our trials are open to internal and external audit. We don't enroll anyone for whom appropriate consent is not given.

Warm Regards,

Anil Nayak
Director - Corporate Communications
Johnson & Johnson Limited, India
30, Forjett Street, Mumbai - 400 036
Phones: Off: +91 22 66646732 Mob: +91 9987059524

Appendix III: Summary of the process identifying four drug trials for investigation

In the first stage of this work, various searches were conducted of the database www.clinicaltrials.gov using the keywords India, placebo control, mania, schizophrenia and depression, to identify ongoing trials with India sites whose trial design was likely to be of concern. This was not meant to provide an objective list, or a list that allowed for generalisability, as the objective of the study was only to document types of unethical research practices.

After a discussion with Wemos and SOMO, it was decided that while a search for ongoing trials would be important, the objective of highlighting concerns in drugs approved for the EU would best be served by looking at completed trials that might have been used for approval by the European Medicines Agency (EMA). The rest of the work was based on a shortlist sent by SOMO of trials with at least one site in India, and related to drugs that had been approved in the EU after 2004.

The trials were:

four placebo-controlled phase 3 trials of quetiapine, a psychiatric drug marketed by Astra Zeneca;

three phase 2 trials of lapatinib, a drug for breast cancer marketed by Glaxo Smithkline;

three phase 3 trials of ciclesonide, an inhaled steroid for asthma marketed by Nycomed Pharma/ Altana Pharma;

one phase 3 trial of pregabalin for neuropathic pain marketed by Pfizer,

one phase 3 trial of exenatide, an injectable drug for diabetes marketed by Eli Lilly,

and one phase 3 trial of amlodipine/atorvastatin, a combination drug for hypertension and high cholesterol marketed by Eli Lilly.

In the first stage, available information was assembled about the trials: journal publications and other results obtained through www.ClinicalTrialResults.org, the company sites, and google searches of the trial titles.

The India offices of the companies⁹⁴ were contacted by phone and e-mail, The representative of each company was informed that that we (Sandhya Srinivasan and Sachin Nikarge) were researchers with the Centre for Studies in Ethics and Rights and were interested in learning more about a trial of a drug manufactured by the company. The details sought were: the sites where the trial was conducted; the start and end dates of the trial; contact details of the institutions; the name of the CRO if one was involved; the names and contact details of the principal investigator, and membership and contact details of the ethics committee that reviewed the trial protocol.

The representative of Eli Lilly (exenatide) replied on the telephone, refusing to provide details. The representative of Nycomed Pharma (ciclesonide) asked for an e-mail to be sent to the head office in Germany. Dr Christian Biberger, Director Clinical Trial Management

⁹⁴ Astra Zeneca, Eli Lilly, Pfizer, Altana Pharma and Glaxo Smith Kline.

Ethical concerns in clinical trials in India: an investigation

Konstanz, of Nycomed Pharma, replied: “thank you for your inquiry. We understand that this request is neither coming from a regulatory body, nor from a IEC body involved in the study. We therefore ask for your understanding that we cannot disclose to you more information than posted in clinicaltrials.gov.”

The other three companies did not respond to telephonic or e-mailed requests.

A search was conducted for the results of each trial, on the company’s website, another registry, or as journal articles. This was done simultaneously with contacting the companies and getting expert feedback on the trials, so searches were pursued only if the trial looked as if they were worth following.

Three drugs were then excluded for the following reasons:

Pregabalin: Two specialist responses said the trial did not pose ethical concerns and it does not seem to have put people at “unacceptable risk”. The trial was probably done to meet Indian regulatory requirements for marketing the drug in India. The drug seems to have been approved in India before the Indian Patent Act amendments came into effect so it is available in India in generic versions that are not considered inordinately expensive by the neurologists. The drug is commonly prescribed for neuropathic pain. But in any case the approval date in the EU predated the trial. This trial may be worth following (though not for the purposes of this study) because the European assessment report reports a number of deaths, some of which are *not* related to the condition for which the drug is taken.

Amlodipine/Atorvastatin. The clinical trial details (for Amlodipine/Atorvastatin) given to us did not match the European Pharmaceutical Assessment Report (which was for Amlodipine/valsartan) and further investigations by SOMO found that there was nothing to link the drug to an Indian trial site. The drugs Amlodipine and Atorvastatin were commonly used separately, and out of patent.

A drug manufacturer speculated that the trial may have been conducted to rule out significant drug interactions but one cardiologist stated that the two drugs are regularly prescribed together, meaning that there are no major interactions. The combination drug is not very expensive. Third, one specialist response identified no ethical concerns with the trial itself. A search of www.clinicaltrials.gov identified one closed trial of amlodipine and valsartan with sites in India, NCT00548067. This is a phase 3, India-only study that started in September 2007 and ended in March 2008. The combination was approved in the EU in January 2007. (Journal reports of the trial could not be located.) Still, this may be worth following at a later stage given the recent report of infant deaths in an Indian centre in trials that included valsartan⁹⁵.

Exenatide: The initial specialist (diabetologist) response was that the placebo control was not problematic because diabetes drug prescription is individualised. A pharmacologist who has been tracking unethical trials concurred (on the basis of the information he was given; he

⁹⁵ Sinha Kounteya, TNN 49 babies die during clinical trials at AIIMS *The Times of India* 2008 Aug 18 http://timesofindia.indiatimes.com/India/49_babies_die_during_clinical_trials/articleshow/3374492.cms

Ethical concerns in clinical trials in India: an investigation

said he could not comment further without the detailed trial protocol). (Journal reports on the trial could not be located.)

This needs to be explored further at some stage, as the use of a placebo control is potentially of concern. Further, exenatide is a relatively expensive drug compared to insulin (the drug used for diabetes) in India. Further, according to www.clinicaltrials.gov the trial took place in India, China, Korea and Taiwan, countries where concerns have been raised about the quality of regulation of such trials. However, it is not useful to Wemos as the trial took place (Jan 2006-September 2007) after EU approval (Nov 2006) and India approval (July 2007).

Of the nine remaining trials of three drugs, we chose to focus on one trial of each drug, each identified as having ethical concerns based on one or more of the following criteria: the trial took place almost exclusively in countries with poor regulatory systems, it involved a vulnerable population (children, people with psychiatric conditions, perhaps cancer patients), the trial design may have put participants at risk, and the drug may not be affordable for the people on whom they were tested in India. In addition, all the drugs were for chronic conditions particularly important in developed countries. The drugs in this list that seem to satisfy these criteria are: one of the trials for quetiapine extended release, the trial comparing ciclesonide and fluticasone and one of the three trials of lapatinib.

The ciclesonide/fluticasone trial was an India-only trial. According to information available on www.clinicaltrials.gov⁹⁶, it was carried out in eight sites (Delhi, Chandigarh, Jaipur, Ahmedabad, Kolkata, Pune, Bangalore, Coimbatore) in India in 2003. It was considered for follow-up because it was conducted on children aged 4-15, it was an India-only trial, and it is already known that steroids can cause stunting, for which reason it is not approved for under 12. It is therefore of concern that all the trial sites were in India and there were no sites in developed countries.

However, there is nothing to link this trial with the EU registration process and we were unable to trace the article reporting the results, so we could not learn about the investigators and sites. Still, this trial is worth pursuing further because it was conducted on children.

Of the three trials of lapatinib, the two-dose monotherapy of lapatinib (<http://www.clinicaltrials.gov/show/NCT00089999>) seemed most worthy of follow-up. The trial results were located on the website of the manufacturer, GlaxoSmithKline, and also the journal article reporting it. The journal article reporting the pivotal trial was also located. The trial was done in developing countries only, it involved a vulnerable group, the drug itself is very expensive and therefore unaffordable for most people who would need it. In addition, a major factor in deciding to pursue this trial was the statement by an oncologist who was shown the [ct.gov](http://www.fda.gov) summaries of all three trials that patients who entered this trial were denied the standard of care for breast cancer.

Based on the journal article, two India centres, in Pune and in Delhi, were identified and further opinions were sought from experts.

⁹⁶ Trial sites given on www.clinicaltrials.gov do not always correspond to the trial sites given in the journal publications of these trials, presumably because a site with poor patient recruitment may be dropped another site added to recruit the target number of patients.

Ethical concerns in clinical trials in India: an investigation

Another trial chosen for follow-up was the placebo-controlled trial of an extended release version Quetiapine, an approved drug, <http://clinicaltrials.gov/show/NCT00206115> . This trial had sites in India and was used for approval in the EU/Netherlands. It had already been discussed in an earlier report by SOMO. The trial results mention a report of a serious adverse event and most of the trial sites were in developing countries. During the journal search a second placebo-controlled trial of quetiapine XR was identified that also had India sites. This was followed up as well.

One trial was followed up that was not included in the SOMO shortlist. This was an India-only placebo-controlled trial of risperidone (marketed by Johnson & Johnson) for acute mania. A specialist commentary on this trial was published in the *Indian Journal of Medical Ethics* in 2006, along with another specialist and a response from the lead author of the journal article reporting the trial. A search revealed another journal article reporting the same trial, which gave the investigators' names and affiliations.

Appendix IV: Trial details

The list of trials sent by SOMO is given below.

I. Quetiapine Fumarate (*AstraZeneca*)

<http://clinicaltrials.gov/show/NCT00314184>

“Multicenter, Randomized, Parallel-Group, Double-Blind, Placebo-Controlled Phase 3 Study of the Efficacy and Safety of Quetiapine Fumarate and Lithium as Monotherapy for up to 104 Weeks Maintenance Treatment of Bipolar I Disorder in Adult Patients.”

II. Quetiapine Fumarate (*AstraZeneca*) <http://www.clinicaltrials.gov/show/NCT00227305>

A 26-Week, Multicenter, Open-Label Phase **3b** Study of the Safety and Tolerability of Quetiapine Fumarate (SEROQUEL™) Immediate-Release Tablets in Daily Doses of 400 mg to 800 mg in Children and Adolescents With Bipolar I Disorder and Adolescents With Schizophrenia (Abbreviated) Treatment, Randomized, Open Label, Uncontrolled, Parallel Assignment, Safety/Efficacy Study

III. Quetiapine Fumarate (*AstraZeneca*)

<http://clinicaltrials.gov/show/NCT00206115>

A 6-Week, Multicenter, Double-Blind, Double-Dummy, Randomized Comparison of the Efficacy & Safety of Sustained-Release Formulation Quetiapine Fumarate (SEROQUEL) & Placebo in the Treatment of Acutely Ill Patients With Schizophrenia
Outcomes: clinical impact: randomisation to relapse; change in PANS scale, etc.

IV. Quetiapine Fumarate (*AstraZeneca*)

<http://clinicaltrials.gov/show/NCT00090324>

A 6-Week, Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled, Phase 3b Study of the Efficacy and Safety of Quetiapine Fumarate (SEROQUEL™) Immediate-Release Tablets Compared With Placebo in Adolescents With Schizophrenia (Abbreviated)

V. Exenatide (*Eli Lilly/Amylin*)

<http://www.clinicaltrials.gov/show/NCT00324363>

Safety and Efficacy of Exenatide in Patients With Type 2 Diabetes Using Metformin or Sulfonylureas and Metformin Treatment, Randomized, Double Blind (Subject, Investigator), Placebo Control, Parallel Assignment, Safety/Efficacy

VI. Amlodipine/Atorvastatin (*Pfizer*)

<http://www.clinicaltrials.gov/show/NCT00143234> Clinical Utility of Amlodipine/Atorvastatin to Improve Concomitant Cardiovascular Risk Factors of Hypertension and Dyslipidemia treatment, Non-Randomized, Open Label, Uncontrolled, Single Group Assignment, Safety/Efficacy Study phase 3, ND

VII. Pregabalin (*Pfizer*)

<http://www.clinicaltrials.gov/show/NCT00631943> A Study to Evaluate the Efficacy and Safety of Pregabalin (Lyrica) for the Treatment of Nerve Pain

VIII. Ciclesonide and Fluticasone Propionate (*Nycomed/Altana Pharma*)

<http://www.clinicaltrials.gov/show/NCT00163410>

Efficacy of Ciclesonide Inhaled Once Daily Versus Fluticasone Propionate Inhaled Twice Daily in Children With Asthma (4 to 15 y) (BY9010/M1-205)

IX. Ciclesonide (*Nycomed/Altana Pharma*)

<http://www.clinicaltrials.gov/show/NCT00163436>

Efficacy and Safety of Ciclesonide Administered With or Without Different Spacers in Patients With Asthma (12 to 75 y) (BY9010/M1-145)

X. Lapatinib (GSK)

<http://www.clinicaltrials.gov/show/NCT00089999>

This phase II study will evaluate and compare the efficacy and tolerability of two dose schedules (1500 mg QD and 500 mg BID) of oral Lapatinib as treatment for patients with advanced or metastatic breast cancer.

XI. Lapatinib (GSK)

<http://www.clinicaltrials.gov/show/NCT00371566>

This is a study comparing the activity of lapatinib versus placebo followed by chemoradiation. This study is designed to explore the effects of lapatinib monotherapy on apoptosis/necrosis, in pre-treatment and post-treatment tumour tissue samples in subjects with locally advanced squamous cell carcinoma of head and neck.

XII. Lapatinib (GSK)

<http://www.clinicaltrials.gov/show/NCT00263588>

Phase II Study of Lapatinib for Brain Metastases in Subjects With ErbB2-Positive Breast Cancer Following Trastuzumab-Based Systemic Therapy and Cranial Radiotherapy.

Abbreviations and acronyms

CRO	Contract Research Organisation
CSER	Centre for Studies in Ethics and Rights
DCGI	Drugs Controller General of India
DoH	Declaration of Helsinki
DSMB	Data and Safety Monitoring Board
EC	Ethics review Committee
EMA	European Medicines Agency
EPAR	European Medicines Agency's Assessment Report
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
HER2	Human Epidermal growth factor Receptor 2
ICH	International Conference on Harmonisation
ICMR	Indian Council of Medical Research
ICRI	Institute of Clinical Research (India)
IEC	institution-based Ethics Committee
IMH	Institute of Mental Health
IR	immediate-release
IRB	Institutional Review Board
J&J	Johnson & Johnson
JCDC	Jehangir Clinical Development Centre
KGMC	King George Medical College
NCE	New chemical entity
NEJM	New England Journal of Medicine
NIMHANS	National Institute of Mental Health and Neuro Sciences
NPAR	National Public Assessment Report
OPD	out patient department
PANSS	Positive and Negative Syndrome Scale
RGCIRC	Rajiv Gandhi Cancer Institute and Research Centre
NGO	Non-Governmental Organisation
SAG	Scientific Advisory Group
SMO	Site maintenance organisation
SOMO	Centre for Research on Multinational Corporations
WHO	World Health Organisation
WMA	World Medical Association
UK	United Kingdom
US	United States
USFDA	United States Food and Drug Administration
XR	extended-release
YMRS	Young Mania Rating Scale