SIXTH FRAMEWORK PROGRAMME

Ethical Governance of Biological and Biomedical Research: Chinese-European Co-operation

3rd WORKSHOP REPORT

Clinical Research and Clinical Research Organisations in EU-CN research – ethics and governance issues

Research Center for Bioethics, Peking Union Medical College & Chinese Academy of Social Sciences
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Introduction and background

Since the mid 20th century, clinical trials (especially randomized controlled trials) have emerged as the 'gold standard' for evaluating the efficacy of a drug or treatment. Today, there are an estimated 50,000 clinical trials being run worldwide. In recent years, pharmaceutical companies have increasingly contracted clinical research organisations (CROs), which specialise in carrying out clinical trials, to carry out the bulk of their clinical trials. These CROs, which are often based in America or Europe, have in turn begun 'offshoring' their trials to countries in Africa, Latin America and Asia.

The regulation of drug testing in China has been under increased scrutiny both within the country and internationally since the former first chief of the State Food and Drug Adminstration (SFDA) Zheng Xiaoyu was executed in July 2007 for corruption. At the same time, Western companies have been accused of exploiting human subjects in developing countries in order to make profits. As asked in a recent article: "Are multinational pharmaceutical companies doing mankind a favour by conducting clinical trials (on humans) or are they using Chinese people as guinea pigs to make more money?" (China Daily 2008).

In the last decade, a number of regulations and guidelines have been promulgated in China to oversee clinical trials research. These include the Drug Clinical Trial Administration Norms from September 1999 which stipulate that all drugs that are to be marketed in China must be tested by an authorised medical research institution and all protocols must be reviewed by an Ethics Committee. In 2003, Chinese Good Clinical Practice guidelines were published and in January 2007 Regulations on Ethical Review of Biomedical Research Involving Human Subjects were promulgated by the Ministry of Health. Also in 2007, the SFDA released its latest Measures for the Administration of Drug Registration.

In Europe, the last decade has also seen an increase in regulations and directives governing clinical trials research. In 2001, The European Commission adopted its Clinical Trials Directive 2001/20/EC which made it obligatory for all countries to establish an Ethics Review system. This Directive has consequently been translated into a number of national laws. Some countries have adopted a centralised approach to ethical review while others have a more decentralised approach.

In advanced biological and biomedical research, which is the core focus of BIONET's work on issues of ethical governance, clinical trials increasingly act as an 'obligatory point of passage' in translation work from bench to bedside. While clinical trials have primarily been used to test new drugs since the 1950s and 60s when legislation in America and Europe made it mandatory for drug companies to provide evidence of safety and efficacy, one biotech CEO has predicted that in the 21st century "living cells will be tomorrow's pharmaceuticals" (Geron 2006). And so, as more efforts are made to translate advanced biological research into stem cell and gene therapies, they will become increasingly subject to clinical trials. Finally, with increasing research into pharmacogenomics, clinical trials are being used, not just to test the safety and efficacy of certain drugs, but also to identify genetic markers which might predict those who respond well to a drug from those who do not.

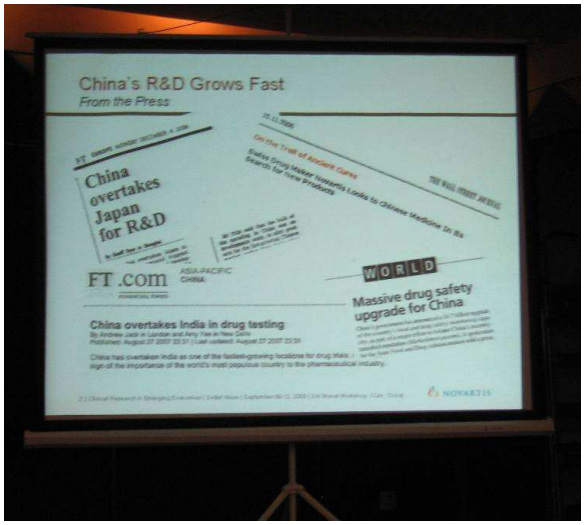
When it comes to the ethical governance of clinical trials research, a number of challenges and questions remain, including:

- What role should local ethics committees play in multi-national, multi-centre clinical trials?
- What are the best ways to ensure synergy, quality and training across China's three-tier ethics review system – national, provincial and institutional ethical review?
- How can conflicts of interest, 'therapeutic misconception' and undue inducement of patients be avoided in an increasingly commercialised context where participation in clinical trials can mean 'free healthcare'?
- Under which circumstances is the use of a placebo arm acceptable?
- In addition, what would be the special challenges that arise from and within collaborative clinical trials, between Europe and China?

It was against this background, that BIONET organised its third workshop on ethical issues surrounding the governance of clinical trials, especially in contexts of international collaboration where European companies or institutions carry out such trials in China. A total of 60 speakers and participants gathered in Xi'an in early September 2008 for a frank and constructive exchange about some of the many challenges 'on the ground' facing partners who engage in clinical trial collaborations. Participants included clinicians, ethicists, regulators, lawyers, medical company representatives, pharmacologists as well as government officials. The key discussions and topics covered are summarised in this workshop report.

Push-pull: clinical trials as an industry in China

In 2007, the Financial Times suggested that China had taken over from India as one of the fastest-growing destinations for clinical trials with 274 of those clinical trials registered on www.clinicaltrials.gov being carried out in China compared to 260 in India. Worldwide, the clinical trials industry has grown in the last decade to an estimated value of over $10 billion and all signs suggest that there is scope for more. How is it that so many companies and institutions are choosing to relocate their clinical trials from Europe and America to Asia, Africa and Latin America?



In a presentation on global clinical trials, Prof. Nikolas Rose pointed to three different sets of factors that make China an attractive country to carry out clinical trials in: 1) large population, 2) good medical and research infrastructure at substantially lower cost, and 3) growing domestic pharma market. The fact that increasing numbers of patients are required per trial – now averaging over 5,000 – to substantiate claims of clinical benefit, and that China's large population make it relatively easy to recruit patients with diseases under investigation, means research can be carried out much more rapidly than in many industrialised countries. Also, the availability of hospitals and clinics to recruit subjects as well as availability of trained

clinicians and researchers at much lower costs, make conducting clinical research in China much more cost effective. Finally, an epidemiological transition brought about through rapid industrialisation and improved living standards means that China has become a potential market for many 'Western' drugs.

Yet, it is not only, European and American companies who are interested in moving their research to China. As put by Dr. Zhu Dahai, Vice President of the Peking Union Medical College in his introductory remarks to the workshop, "we welcome more clinical trials in China, we are ready". And Li Enchang of the Journal of Chinese Medical Ethics stated that clinical trials can be an important way of building research capacity in China. And so, attracting clinical trials research to China is seen by some as a strategic way to ensure investment and improve medical treatment as well as the domestic pharmaceutical industry in China. That is to say, attracting international clinical trials to China are a means to bring in scarce resources to support medical infrastructure or as a way to bring in expensive medical treatments. In a recent interview, cancer specialist Jiang Zefei from the Military 307 Hospital in Beijing pointed out that:

> Hundreds of my critically ill patients have participated in trials for different drugs to combat breast cancer. Nearly all of them, I should say, have benefited from the trials. Medical ethics is the top concern in a drug trial. Most of the therapies would fail for terminal cancer patients. But clinical trials of the latest potential remedies, provided free, might be effective for them. At least, they can save the patients and their families from the heavy economic burden even if they don't prove efficacious. (Xinhua 2008)

Still, this relatively recent rapid growth in clinical trials research in China has not come without its challenges. To begin with, in his presentation, Prof. Qiu Renzong pointed out that "we have no complete picture of these offshore clinical trials in China". And this lack of clarity was in many ways related to an ongoing development of regulatory mechanisms on the one hand and an infrastructure of ethical oversight on the other. As a result, there are a number of areas where the protection of people participating in clinical research needs to be improved.

Entering the debate

The starting point for ethical concerns about clinical trials is that they raise questions of therapeutic misconception and informed consent, especially among 'vulnerable populations' who may be susceptible to wrongful involvement either because they live under unfortunate socio-economic conditions or because they are in a desperate situation when suffering from certain diseases with little treatment options. Another important general issue with special validity in international constellations is the conflict of interest between researchers and clinicians: a clear differentiation should be made between provision of healthcare and clinical research. Yet, in practice, this has proved very difficult to achieve especially in situations where healthcare resources are scarce and institutions serve both purposes. Moreover, the agenda of this Sino-European forum also includes the principle of relevance of research to the human subjects involved and benefit-sharing: who will ultimately benefit from the clinical research being carried out, and how to prevent from the outset that vulnerable populations in socio-economically deprived areas may end up as 'human guinea pigs' for those who are more well-off. In general, discussions covered questions of the fairness and proper follow-up in clinical trials, from the patient's perspective, and the ethics of using the established double-blind RCT with a placebo arm in clinical studies. Although it is considered to give the most 'authoritative' data, using a placebo is not always ethically acceptable, especially when there

are existing treatments available, or in the case of individualised rather than standardised approaches, e.g. ‘traditional’ medicine.

A principal challenge for multi-national governance is how to deal with diversity of legal and cultural standards. Before this issue can be tackled, it is important to ensure that not only the respective country’s positive legal and ethical codes are taken into account but also the entire system of implementation, the actors’ compliance and adherence and practicality on all relevant levels throughout the process: starting with planning and application for approval, the organising and management of the actual trial, and its ex-post evaluation.

A general lesson was taken from the other fields of BIONET’s study as significant for clinical trials: potential double-standards or conflicting standards should be identified, pro-active measures to avoid abuse or adverse outcome due to poor implementation should be taken and advice should be offered to those who are responsible for governance to clarify and strengthen their respective system according to its own purpose. After all, ‘having a law’ can coincide with significantly different practices, whether in China or in a European country.

In China, revised Regulations on Ethical Review of Biomedical Research involving Human Subjects, have been in force since January 2007. These revisions were promulgated alongside the establishment of a new Ethics Committee of the Ministry of Health and are for “the purposes of standardising human-related biomedical research and relevant application of technology, protecting human life, promoting health, preserving human dignity, and respecting and ensuring the legal rights and interests of human subjects” (Article 1). Article 16 specifies that “project applicants must obtain written informed consent from their subjects prior to submission of an application. In situations where written informed consent is unobtainable, oral consent should be acquired with supporting evidence submitted. For subjects who are legally disabled or incapacitated, written informed consent must be acquired from the subject’s guardian or legal representative”. In this context, special attention goes to research involving children, mentally ill patients and vulnerable populations in an expressed effort to comply with the relevant international guidelines. Accordingly, good governance of clinical trials in China should be based upon researchers’ and physicians’ humane behaviour towards their patients and subjects. This policy follows international standards, by emphasising informed consent, respect of the subject’s dignity and human rights and protection from commercial exploitation and undue incentives.

IRB or ERC?

One of the most important developments and debates on how to ensure ethical oversight of clinical research in China concerns the format and structure of the review committees/boards. While drug trials have been subject to ethical review since the State Food and Drug Administration’s (SFDA) Good Clinical Practice guidelines were adopted in 1999, it was not until January 2007 that ethical review of all medical research on human subjects became mandatory. As a result, the Ministry of Health and its partners are now in the process of

building up a national system of ethical review. And there are currently at least two competing models for building up such a system that are under debate in China.

The first approach involves focusing on institutional ethics committees or institutional review boards at the hospital level. Such a decentralised approach would involve capacity building and training for committee members as well as some kind of accreditation system. During the workshop, one of the liveliest debates was about how accreditation should be organised. Currently, training workshops have been offered by the Bioethics Research Centre of the Peking Union Medical College, Fudan University and the Peking University Health Science Centre, with support from the Harvard School of Public Health, National Institutes of Health, Good Clinical Practice Alliance – Europe as well as the WHO. Moreover, FERCAP – the Forum for Ethical Review Committees in the Asian and Western Pacific Region – also organises training and certification for committees in China. According to its website, FERCAP "welcomes IEC/IRBs who wish to have themselves certified for quality ethical review and compliance with the requirements of the WHO Guidelines on Surveying and Evaluating Ethical Review Practices".

While all workshop participants welcomed support for capacity building and training, there was considerable debate about how any accreditation/certification system should be organised, especially since China's Regulation on Certification and Accreditation which was adopted by the State Council on 1 November 2003 stipulated that organizations outside of China cannot accredit or certify Chinese institutions. Nevertheless, a number of participants pointed to advantages arising from international cooperation in building ethical review capacity.

As Francis P. Crawley of the Good Clinical Practice Alliance – Europe (GCPA) noted in his presentation, Europe has been and is currently going through a similar process of capacity building for achieving best practices in the ethical review of research involving human subjects. His presentation focused on the role of ethics committees in contributing to a societal framework of trust in health science and technology. Starting in the 1960s, the United States and Europe began the *ad hoc* establishment of institutional 'IRBs', leading progressively to societal and governmental recognition of the need for best practices in ethical review. In 1995 *Guidelines and Recommendations for European Ethics Committees* were published and in 2001 the European Parliament and European Council passed the the Directive on the Implementation of Good Clinical Practice (2001/20/EC). These two instruments helped to develop a European focus for common standards in ethical review. In particular, Article 6.1 of the Directive stated: "Member States shall take the measures necessary for the establishment and operation of Ethics Committees". Nonetheless, Member State practices continue to vary widely as can cursively be indicated by the examples of how the Directive has been implemented into national legislation in the United Kingdom through a law on clinical trials involving medicines, in Belgium through a law concerning experiments on human subjects, and in France through a law concerning public health. And so, in Europe, while the Directive has set a general framework and obligation to

form ethics committees, member states continue to organise ethical review practices diversely.

Dr. Tade Spranger, member of the Ethics Committee of the University of Bonn, gave workshop participants a concise overview of how ethical review of clinical trials research is currently organised in Germany. The EU Clinical Trials Directive has been implemented in Germany through a Medicinal Products Act. According to this Act, a "clinical trial of a medicinal product on human beings may only be commenced by the sponsor if the competent Ethics Committee has issued a favourable opinion on it". Moreover, it also stipulates that "an application […] shall be submitted by the sponsor to the independent, interdisciplinary Ethics Committee responsible under Land law for the investigator".

The following points were highlighted as possible reasons for refusing a favourable opinion:

- Missing analysis of benefit and harm
- Possible adverse effects of GMOs
- No adequate protection of persons without the capacity to consent / minors
- Unsatisfying qualification and knowledge of the investigator
- No adequate insurance protection

Out of 260 applications received, 95% failed to meet legal standards. However, only 9 have been rejected by the Ethics Committee in Bonn, which demonstrated that the Committee was having a definite impact on improving practice. Dr. Spranger underlined how "the members of the ethics committee are independent concerning their tasks and are not bound by instructions. They shall carry out their tasks according to their best will and conscience."

The debates and discussions at the workshop focused on the benefits and shortcomings of centralised as opposed to decentralised approaches to ethical review. In China, the Ministry of Health is currently working on the format and structure of a national system for ethical review which will be three-tiered: national, provincial and institutional. According to Prof. Qiu Renzong, provincial and national committees will have the role of providing guidance to, and oversight/monitoring of institutional Ethics Committees. There is also discussion of whether or not smaller hospitals could pool their resources together and form provincial ethics review committees.

Another key point raised in discussions concerned the ethical review of multi-centre trials. Dr. Chen Pei asked "in multi-centre trials, what is the say of a local ethics committee? Do they have a right to review the research?". Francis P. Crawley pointed out that in Europe, the Clinical Trials Directive states "for multi-centre clinical trials . . . Member States shall establish a procedure providing . . . for the adoption of a single opinion for that Member State." In Germany, Dr. Spranger showed how this has been translated into national law as: "If the clinical trial is to be conducted by several investigators, the application shall be submitted to the independent Ethics Committee responsible for the principal investigator or the chief investigator".

These examples were rendered lessons from national experience, which need to be further analysed and discussed in the light of the guiding question of problems and needs for governance of clinical trial involving humans, in collaborative European-Chinese projects.

Capacity building

Whatever the format and structure, virtually all workshop participants highlighted the importance of training and capacity building for ethics committee members, in general, and in particular under the conditions of the emerging Chinese governance system. While some of the larger institutions in bigger cities like Beijing and Shanghai were described as having had good experience with forming and running Ethics Committees, as the requirement of having an Ethics Committee is rolled out throughout the country, many of the medium-sized to smaller hospitals and institutions are having to learn from the beginning. As put by Prof. Chen Pei of the Shanghai Renji Hospital, "there is good practice in top hospitals, but more problems in less-resourced hospitals". She reported that in many Chinese regions the grassroots-level is very engaged in their attempts to implement laws and regulations. Ethics bodies are mushrooming in hospitals and research institutions all over the country. However, the middle levels, especially the provincial governments should lend more support. Participants took the cautionary conclusion that international oversight should be regarded as temporarily impractical in China.

According to Dr. Detlef Niese of Novartis which carries out clinical research in China, the different levels of capacity of ethics committees in China observed that there is today "significant competition for the most experienced trial sites as preferred partners". And Xu Ning from Jansen pharmaceuticals pointed out that the variation in IRB's made it difficult some times to know what criteria would be used to evaluate research proposals. Dr. Niese highlighted the fundamental principles as they have been layed out early in the Belmont Report (Respect to Persons, Beneficence, Non-Maleficience, Justice) and addressed, how they are challenged under contemporary conditions of high-tech and market development. He observed that, "A heated economy always carries the risk that the needs of the individual may be lost", namely due to the focus of companies on cost savings when considering Clinical R&D in emerging economies and the perception of poor protection of trial participants and exploitation by multinational companies. He called for an advanced understanding among company leadership of the impact of Chinese culture and society on Clinical R&D and vice versa and acknowledged that, while Ethical Review Capacity in China is still developing while Clinical R&D activities expand quickly. A recommended tool to support good governance could be an independent consultant that would serve as an interface between policies and practice. Niese introduced an Ethics Council that has started operation in the summer of 2008, in collaboration with Beijing University's Health Science Center, to advise the company on ethical, societal and cultural issues as well as on policies regarding the conduct of clinical research and other research in humans in China. Its focus also covers research on human biologic material, such as tissue or blood, in the context of developing new medicines for the Chinese and global market. Optimistically, Niese suggested, "the China Ethics Council may serve as a model for similar institutions in other emerging countries."

Dr. Li Hongying, a member of the Institutional Review Board at Suzhou University Hospital gave a very frank account of some of the many challenges they faced at the University. Since the introduction of ethical review procedures has been relatively new in her institution, the IRB has met some internal resistance. Indeed, she remarked that it was not uncommon to hear doctors complaining that requirements for informed consent to take biological samples would negatively impact on their ability to carry out research. Up until very recently it had been common for doctors to take as many biological samples (e.g. blood) as were needed for therapeutic/diagnostic as well as research purposes without obtaining informed consent.

Overall, workshop participants pointed towards training needs on especially two fronts: training of ethics committee members and training of clinical researchers. In a presentation on "Challenges facing ethical review committees in China", Dr. Shan Yuandong of the Peking Union Medical College Hospital highlighted a number of critical areas that need to be addressed through training. These included:

- Lack of independence – many ethical review committees were chaired by the heads of hospitals and external members often did not have voting rights
- Conflicts of interest arising from researchers' financial interests
- Lack of resources to monitor and follow up once research has been approved
- Researchers tend to give yes/no answers with insufficient commentary on issues of researcher qualifications, risk-benefit analyses, informed consent and compensation
- Lack of qualified members for ethical review committees, members may have basic training in GCP but not in ethics
- Lack of resources for ethics committees to train researchers
- There are still large discrepancies in the quality of informed consent, examples range from half a page to 4-5 pages – insufficient explanation of randomisation, placebo, other available treatments, risks, adverse effects
- No attention to insurance questions – the most frequent source of dispute comes from disagreement about compensation if adverse or harmful effects result from participating in a clinical trial

Dr. Chen Yixin of the State Food and Drug Administration (SFDA) highlighted that one way to improve the situation was to ensure that Ethics Committees talk to each other by establishing systematised lines of communication and feedback. Other workshop participants also made their case for allowing smaller hospitals to pool their resources by forming joint Ethics Committees so as to be able to benefit from each others experiences. Prof. Li Benfu of the Peking University Health Science Centre underlined that while the key objective of ethical review was to protect the dignity, rights and safety of human subjects participating in research, ethical review was also important for protecting researchers, especially in cases where disputes about compensation might arise. This, he pointed out, was important for clinical researchers to understand, that it is in their own best interests to have a robust ethical review system.

Another point raised around capacity building and training concerned the technical knowledge that was often needed to make a judgement about the relevance and necessity of research. In Germany, Dr. Spranger explained that Ethics Committees did not evaluate the scientific merit of a research proposal (which was usually evaluated institutionally by the chief investigators' peers) but rather solely focused on ethical issues. In China, however, Li Benfu explained that it was considered a part of

ethical review to consider whether a research project was at all scientifically sound and worthy. This meant that it was important to have members on ethical review committees who had the competence to peer review research proposals as well for their scientific merit.

Reporting, quality of data and misconduct

One of the most important aspects of clinical trials research concerns the collection and reporting of data about safety, quality, efficacy and, in a post-marketing phase, also adverse effects. Prof. Hu Ch'ing-li argued that poor reporting, mis-reporting, selective reporting and withholding of data were all unethical practices as they compromised scientific integrity and potentially also the safety of people. This sentiment was echoed by Liu Qiyan from the Ministry of Science and Technology who, in a talk on "Governance in science and technology in China" said that faking of data – fraudulent science – was a critical problem that his Ministry's recent Regulation on Scientific Misconduct from 2007 had sought to address. Since they came into force, some 70 cases of misconduct had been brought to the Ministry's attention, primarily through a 'whistle-blower' website.

Professor Zeng Fandian, who is the Chair of the IRB of Tongji Medical College in Wuhan, pointed out that clinical trials organisation and management can pose serious problems that challenge best practice, according to stated regulations and intentions. These problems include short observation time for drug effects; poor understanding of substance interaction owing to single-drug trials, with no combined multiple drug applications. Multi-causal drug effects including unforeseen adverse reaction can only be seen after market introduction (a phenomenon euphemistically referred to as wild life trial). Zeng explained that currently a system for "spontaneous reporting" is implemented. Yet greater attention ought be paid to other issues, beyond risk and health, such as privacy and data protection, which remain as insufficiently considered in China. He also addressed the potential benefits from international collaboration in governance. On practical questions, such as how to organise and conduct evaluations of ongoing trials, advice from Europeans was invited, as it is expected to draw from longer experience with trial oversight systems. This exemplary account gave rise to passionate debates, e.g. about the comparative disadvantage between a national filing system and a registry with the additional capacity to stimulate self-control and enforcement of standards, the implications of which were observed to reach far beyond technicalities.

Li Enchang, editor of the Journal of Chinese Medical Ethics argued that data integrity is in the interests of all – industry, scientists, research subjects and governments, and that the journals had a role to play in assuring data integrity by insisting that articles reporting research results must have been subject to ethical review.

And both Chen Yixin of the SFDA and Zeng Fandian of Tongji Medical College highlighted wide national disparities in the quality of post-marketing surveillance and adverse effect

reporting. Poor quality of post-marketing data could compromise patient safety if drugs were not withdrawn from the market quickly.

In a presentation on the problem of the placebo effect, Dr. Ayo Wahlberg from LSE pointed out that as the effectiveness of more and more drugs targeting chronic and lifestyle diseases was measured against subjective scores, careful reporting and interpretation of data was crucial. The Randomised Controlled Trial itself relies on Standardised diagnostic criteria for patient recruitment, a standardised drug or treatment to put on trial (chemical compound or repeatable intervention) as well as standardised outcomes (e.g. quality of life rating scores, biological markers, clinical events). While the measurement of a prolonged life or number of clinical events (e.g. stroke, heart attack, death) might be relatively straightforward, measuring whether or not a drug or intervention has improved a patient's life through quality of life scores was open to plenty of interpretation.

Also in the context of Traditional Chinese Medicine, Guo Xinfeng of the Guangzhou TCM University suggested that the quality of evidence was very poor because of poor quality study design, trial reporting and selective bias. In short, raising research capacity in China as well as reporting and monitoring practices was considered to be crucial for ensuring that research is also ethical.

The challenges remain huge indeed, starting not only with governance culture, but already with science and ethics basics. Professor Qiu Renzong from Beijing, made a plea to embrace a fundamentally scientific attitude: clinical trials should be clearly defined, plausibly designed, and conducted with honesty and integrity.

These challenges were on the table, not only for domestic action but also for concerted international governance initiatives. This workshop explored, how Europe and China could work together more effectively towards a better understanding of what is going on in this area of research, how to respond with proper legislative action and install apt mechanisms to implement good standards of science and ethics through a cooperative system of good governance.

Protecting patients: vulnerability and researchers' obligation to care

The key objective of ethical review in biological and biomedical research is to protect (especially vulnerable) patients from coercion or exploitation. This is all the more important in contexts where human subjects are recruited from socio-economically disadvantaged areas. Many of the speakers at the workshop pointed out that since medical care has become increasingly commercialised in China and only a minority of people are sufficiently covered

by health insurance, participation in clinical trials is seen by many as a way to get free 'health care'.

In China, Prof. Qiu Renzong suggested that "patients, physicians/ investigators and health care administrators regularly confused clinical trials with medical care" and also that "some physicians/investigators seem deliberately to treat clinical trials as medical care", raising many questions about the quality of informed consent in clinical trials research. Qiu's sketch of the present situation was: there is widely spread therapeutic misconception, often intended to lure subjects into trial participation. Administrators, such as in the Ministry of Health, did not always fully understand the science and the ethics of trial approval. In China, with difficulties to hold individual administrators accountable, formal approval could be given more easily than justified.

In his presentation on Indian perspectives on Clinical Trials, Dr. R. Kishore proposed a taxonomy of population sub-groups and indicated that recruiting human subjects for clinical research from the bottom two groups was not ethical because their vulnerability put in question their ability to give free and informed consent:

A	The educated, advanced and economically sound sections where individual, free and informed consent can be obtained after adequate enlightenment.
B	Educated /semi-educated and economically weaker sections, living under traditional set-up where decision-making process is a collective exercise with dominant participation of father or husband and the individual's choice is subordinated to family perspectives or even to extraneous considerations.
C	Uneducated, economically backward and "primitive" groups/populations where head of the tribe or the religious seer commands authority even in matters relating to individual's private life and it is not possible for the individual to give a free and informed consent.
D	The rank impoverished and deprived whose only concern is to safeguard his survival and free, informed consent does not carry any meaning to him. He can be lured into any kind of intervention.

Many participants recommended introducing quality assurance audits and site visits as a way to ensure quality of informed consent procedures. Dr. Detlef Niese spoke of the need for international companies who come to China to carry out research to make a careful selection of partners through pre-inspections, audits as well as training of staff as a means of quality assurance. He pointed out that while ethical review capacity is important, so too is the capacity of researchers to carry out proper informed consent procedures, an area that also requires training.

Also, Prof. Zhai Xiaomei argued that, just as in Europe, personal and / or commercial interests on the part of researchers in China was a key problem leading some to exaggerate the benefits and to downplay possible adverse effects. Examples could be seen on television and

newspaper advertisements. Prof. Du Zhizheng from Dalian had carried out a small sample of interviews with patients who had participated in a clinical trial in Beijing. From his interviews he noted that the major reason that patients had participated was to get therapeutic benefit or to cure their disease. Some also suggested that they had agreed to participate in order to ensure a better relationship with their doctors. In China, there are no regulations covering the relationship between drugs/equipment manufacturers and physicians/investigators or IRB members which means that commercial interests may come before patient interests in some cases.

Finally, despite the increasing amount of regulations and guidelines covering clinical trials research in humans, Prof. Qiu Renzong pointed out that apart from medical drugs, devices and vaccines, it is not explicitly specified which other medical interventions should be subject to clinical trials. And so, for example, it is not clear how innovative therapies, e.g. stem cell therapies, nanotech or gene therapies are to be tested on humans.

This situation leaves many questions open and challenges ethical governance in EU-Chinese collaborations involving clinical trials.

Issues arising for international collaboration

The rich presentations and discussions among workshop participants raised a number of issues which were relevant for international research collaboration focus of BIONET. Acknowledging the international dimensions of clinical trials, the workshop heard reports from different European countries and from India. Dr. R. Kishore, an advocate at the Supreme Court of India and Delhi High Court and the president of the Indian Society for Health Laws & Ethics summarised that “industry can play a vital role by minimizing the possibilities of exploitation and research induced injuries. The best way to achieve this goal is integrity and self-regulation on the part of the Industry. There is no substitute for good governance.” He explained that good governance means to explore scientific promise with minimum risk to the research participants. The workshop agreed that a clinical trial is an activity where scientific, socio-economic, legal, ethical, moral, cultural and religious factors must be taken into account. In such an area, the Industry should have to ensure that the benefits to the population outweigh the risks involved.

But, how to achieve such a governance culture? Dr. Catherine Elliott, Head of the Clinical Research and Ethics department of the Medical Research Council, UK proposed that, in international research it needs to be clarified, whether, standards of most rigorous participant or national participants should be prioritised. She recommended making sure that true partnerships and benefits to all collaborators could be achieved and that cultural differences should be carefully considered, e.g. regarding consent or placebo trials. She outlined her agencies requirements for applicants who apply for funds to carry out international research. The MRC emphasises that easier patient recruitment, cheaper costs and/or different ethics governance procedures are not sufficient arguments to get funding for research outside of the UK. Instead, applicants are expected to demonstrate the expectations of all contributing partners about roles, responsibilities, intellectual property, publication plans as well as data access and sharing. The MRC also required that health and safety requirements were met for protection of participants, protection of investigators, employer responsibilities as well as research staff contracts. Moreover, the ethical standards of the most rigorous participant in the partnership were to be adhered to while also ensuring that local cultural frameworks were

taken into consideration. For border-crossing projects, international registries would be helpful.

Another bridge-building attempt was offered from an Eastern European perspective. Dr. Alicja Laska-Formeister, a sociologist from the University of Lodz (Poland), based on empirical case studies thus summarised the ongoing development in her country. “As admitted by doctors, and despite many precautions, ethical and organizational faults of researchers play a significant role with an impact on the final results of clinical studies. The most frequent ones include: results are not published when deemed unfavourable by the PI; studies are performed without due respect for the patients’ interest; diagnostic investigations are conducted too frequently; the general efficiency of newly developed drugs is overstated, causing further risks of complications. Undoubtedly, during clinical studies bad practice is common. The fact that a group of doctors and researchers is paying attention to this situation and stimulate public debates is a positive sign.” Laska-Formeister argued for the need for good laws that would support scientists. “However, without a clear ethical attitude among the researchers and doctors, even the best law would not ensure safety for the participants in clinical studies.”

European and Chinese participants found it easy to relate to such descriptions with observations from their own experience, re-emphasizing the BIONET’s agenda towards ethical governance. Integrating law and ethics within a governance system that encourages adherence and implements best practice is a shared goal, for each country and in collaborations.

Some of the questions and debates that arose out of the discussions with regard to international collaboration were:

- What say do local ethics committees have in multi-centre international clinical trials?
- Where and who should ethically review a clinical trial involving international partners?
- How can international companies coming to China know whether the ethical review capacity as well as research capacity is sufficient?
- How can informed consent procedures be quality assured?
- How should training of ethics committee members as well as ethics training of researchers be carried out to ensure better research collaboration?
- How can issues of fairness, relevance and follow-up vis-à-vis trial participants be addressed in the context of international clinical trials?
- In which situations is it ethically appropriate to test drugs against a placebo arm (e.g. what is the benchmark for standard available treatment)?

Participants shared many observations and values and had similar ideas about instruments in their assessments of the ethical problems in clinical trials. There was agreement that for EU-Chinese collaborations, the development of a joint governance agenda appears both timely and welcome which would incorporate at least the following key elements:

- Building ethical review capacity throughout China by training ethics committee members as well as by providing ethical training for clinical researchers – government, hospitals as well as (international companies) should support this

- Building research capacity to improve study designs, quality of reporting and peer review, and also to prevent misconduct ('fake science')

- Quality assurance of informed consent procedures

- Addressing conflicts of interest by clarifying the independence and authority of ethical review committees at national, provincial and institutional levels as well as by clarifying any commercial interests that researchers may have

- Ensuring some kind of overview of all international clinical trials taking place in China

Media Release

15 September 2008

European and Chinese scientists, regulators and ethicists meet to address ethics of clinical trials

BIONET's third International Workshop on International Clinical Drug Trials in Xi'an took place from 9th to 12th September 2008.

BIONET, the European-Chinese consortium on the ethical governance of biomedical research, has concluded its third international workshop in Xi'an, PRC. The focus of this workshop was on clinical trials for drugs and other treatments for diseases, and the role of clinical research organizations. Since the mid 20th century, clinical trials (especially randomized controlled trials) have emerged as the gold standard for evaluating the efficacy of a drug or treatment, and as an 'obligatory point of passage' in translation work from bench to bedside. There are an estimated 50,000 clinical trials being run worldwide today. In recent years, pharmaceutical companies have increasingly contracted clinical research organisations (CROs), which specialise in carrying out clinical trials, to carry out the bulk of their clinical trials. These CROs, which are often based in America or Europe, increasingly 'offshore' trials to Eastern Europe, Latin America and Asia. The reasons for such offshoring can range from an economic drive to rationalise and save costs, the growing difficulty of finding 'treatment naïve' populations in western countries, and a perception that ethical standards are lower in some countries. The value of the worldwide clinical trial industry has been estimated at $50 billion, and China has now overtaken India in the number of trials conducted, not least because it is forecast to be the world's fifth-largest pharmaceuticals market by 2010.

Such a situation raises numerous ethical and regulatory issues: not simply the scientific standards for the conduct of such trials and the integrity of the data produced, but also the nature and meaning of informed consent of subjects, especially when drugs are trialled on vulnerable populations; conflicts of interest between researchers and clinicians; benefit-sharing, and the need to avoid developing country populations becoming 'human guinea pigs' for those who are more well-off; and the direction of flow of economic benefits of the drugs or treatments developed as a result of such trials. At the same time it is clear that, if appropriately conducted and regulated, clinical trials can work to improve the scientific infrastructure, regulatory oversight, and treatment availability in China as well as to stimulate the process of drug discovery.

It is with these ethical and regulatory challenges in mind, that 50 Chinese and European experts met in the ancient city of Xi'an, 9-12 September, to exchange views and develop proposals for the ethical oversight and governance of clinical trials in China- Europe collaborations. The workshop heard presentations from industry, researchers, clinicians and regulators from the Chinese State Food and Drug Authority, the Ministry of Health and the Ministry of Science and Technology and gathered a unique body of information on the historical and current situation in China, the regulatory problems and developments, and

future prospects in this vital area. A valuable comparative perspective was added by presentations from Eastern Europe and India, where similar problems for regulation are arising. The results of the workshop will soon be available on the BIONET website at www.bionet-china.org

Short description of BIONET

BIONET is a network of European and Chinese social scientists, lawyers, bioethicists and biomedical researchers from 20 institutions across Europe and China, which organizes research, training, workshops and conferences on the ethical governance of research in the life sciences and biomedicine within and between China and European countries. BIONET commenced its work in October 2006 and has held workshops in China on assisted reproductive technologies, and on stem cells, and one international conference on reproductive medicine and stem cells in research and treatment. Following the Xi'an workshop, there will be one further workshop in China on genomic research and biobanking in April 2009, and a final Conference will be held in September 2009. A key outcome of BIONET will be a set of recommendations on standards and guidelines for best practice in the Ethical Governance of EU-China Research collaboration in the Life Sciences and Biomedicine.

BIONET is funded by the European Commission's Sixth Framework Project, with additional support from the UKs Medical Research Council.

More details of BIONET, and copies of publications, can be obtained from: www.bionet-china.org

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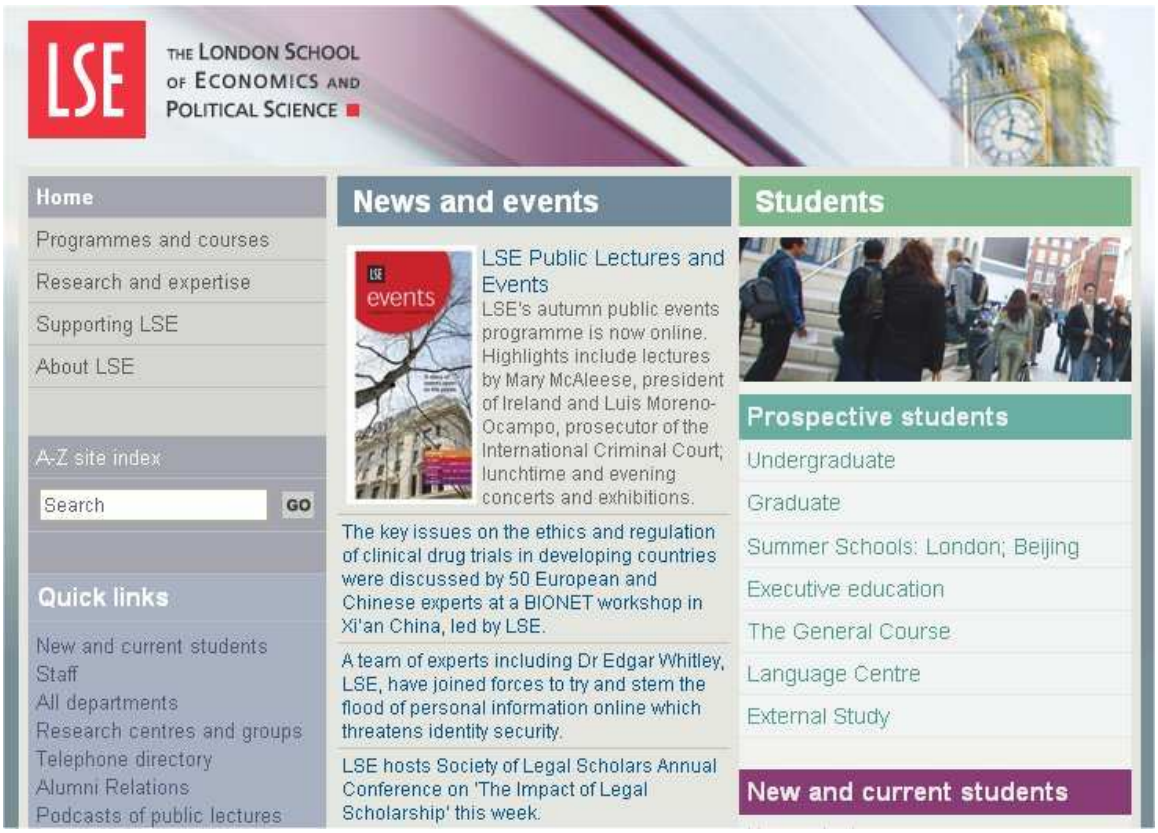

Programme

Tuesday, 9 September

Registration

09/09/2008 Tuesday	Registration	All participants	09:00-21:00

Pre-Workshop Meetings

09/09/2008 Tuesday 16:00-17:00	Steering Committee meeting Workshop preparation	Members of Steering Committee	60 m
17:00-18:30	Expert Committee meeting	Members of Expert Committee	90 m

Day 1: Wednesday, 10 September

Opening Ceremony

10/09/2008 Wednesday Morning	Opening Ceremony		
08:30-09:00	Ministry of Health Ministry of Science and Technology State Food and Drug Administration President, Xian Jiaotong University BIONET	He Wei/Yu Xiucheng (MOH) Liu Qiyan (MOST) Chen Yixin (SFDA) Yan Jianqun (Jiaotong) Nikolas Rose (Bionet)	30 m
09:00-09:20	Photo and break		20 m

Session I

10/09/2008 Wednesday Morning	An Overview of Ethics and Governance of Clinical Trials in Europe and China: *Status quo* and Challenges	Chairs: Hu Ching-Li/ Nik Rose	
09:20-09:50	Ethics and governance in clinical research in China	Yu Xiucheng (MOH)	30 m (25 m presentation, 5 m (Q & A) same below
09:50-10:20		Francis P. Crawley	30 m

	The Development of Systematic Approaches to Ethical Review in Europe: Lessons for International Cooperation in Research Ethics and Bioethics	(Good Clinical Practice Alliance [GCPA])	
10:20-10:50	Governance in science & technology in China	Liu Qiyan (MOST)	30 m
10:50-11:20	Adverse Drug Reaction Monitoring in China	Chen Yixin (SFDA)	30 m
11:20-12:00	Discussion and comments: • Establishing the system of research ethics framework; • Models of regulating clinical trials; • Basic values in ethics and governance of clinical trials; • What is good governance of clinical trials; • National laws/regulations and international guidelines: how to solve inconsistency? etc.		40 m
LUNCH			

Session II

10/09/2008 Wednesday Afternoon	Ethics and Governance in Clinical Research: International Perspectives	Chairs: Hans Galjaard/Lu Guangxiu	
13:30-14:00	Ethics and governance in clinical research: WHO perspectives	Hu Chingli (Shanghai Jiaotong University)	30 m
14:00-14:30	Improving ethics and governance in clinical Research under international cooperation	Catherine Elliot (Medical Research Council, UK)	30 m
14:30-15:00	Ethics and governance in Biomedical Research under	Zhu Dahai (Institute of Basic Medicine Chinese Academy of Medical	30m

	international cooperation	Sciences)	
15:00-15:10	Discussion		10m
15:10-15:20	Break		10m

Session III

10/09/2008 Wednesday Afternoon	Informed Consent in Clinical research in Europe and China	Chairs: Qiu Renzong/ Ayo Wahlberg	
15:20-15:50	Developments in diagnosis and treatment of disease	Hans Galjaard (Erasmus, Netherlands)	30 m
15:50-16:50	*Panel discussion: Informed consent in China*		60 m
15:50-16:10	Process of informed consent and consent form: *status quo* and challenges in China	Zeng Fandian （Tongji Medical College）	20 m
16:10-16:30	Quality assurance for informed consent in China	Liu Chuntao （Huaxi Medical College）	20 m
16:30-16:50	Does Chinese culture constitute challenges to informed consent?	Zhu Wei （Fudan University）	20 m
16:50-17:20	Discussion and comments: • Cultural influences in the practices of informed consent; • Individual vs. family/community in informed consent; • Roles of family and community in the practices of informed consent; • Oral and written consent; • Monitoring the process of informed consent		30 m

Day 2: Thursday, 11 September

Session IV

11/09/2008 Thursday Morning	Ethical Review Committees in Europe and China	Chairs: Dominique Memmi/ Zhu Dahai	
08:30-09:00	The function of ERCs according to German Law (with special emphasis on clinical trials)	Tade Spranger (Institute of Science and Ethics, Bonn)	30 m
09:00-09:30	Challenges facing ethical review committees in China	Shan Yuandong (PUMC Hospital)	30 m
09:30-09:40	Break		10 m
09:40-11:00	*Panel Discussion: Status quo and issues in ethical review committees in China*		100 m
09:40-10:00	Ethical review in clinical research: experiences and challenges	Li Benfu (Peking University)	20 m
10:00-10:20	Ethical review in clinical research: experiences and challenges	Yang Lan (Affiliated Hospital of Xi'an Jiaotong University)	20 m
10:20-10:40	Ethical review in clinical research: roles of specialists	Wang Liyu (China Medical University)	20 m
10:40-11:00	Ethical review in clinical research: experiences and challenges	Li Hongying (Suzhou University Hospital)	20 m
11:00-11:20	Ethical review in clinical research: experiences and challenges	Chen Pei (Shanghai Renji Hospital)	20 m
11:20-11:30	Break		10 m
11:30-12:00	Discussion and comments: • Constitution, composition and organization of ERC; • Scope of ethical review; • Capacity of ethical review; • Capacity building and		30 m

	training; • Recognition and accreditation of ERC; • Oversight of ERC etc.		
LUNCH			

Session V

11/09/02008 Thursday Afternoon	RCTs in China and Europe	Chairs: Herbert Gottweis/ Yang Huanming	
13:00-13:30	Randomized controlled trials and the placebo problem in Europe	Ayo Wahlberg (LSE)	30 m
13:30-14:00	Ethical Issues in RCT in China	Qiu Renzong (CASS)	30 m
14:00-15:00	*Panel discussion: RCT and TCM*		60 m
14:00-14:20	On clinical trials of TCM	Wang Xiaoyun (Guangzhou TCM University)	20 m
14:20-14:40	On clinical trials of TCM	Guo Xinfeng (Guangzhou TCM University)	20 m
14:40-15:00	Discussion and comments: • Perspectives on significance of, and justification for RCT; • The placebo problem; • Can and should traditional medicines be subjected to RCT? • Status quo and controversies regarding clinical trials in traditional medicine, etc.		20 m
15:00-19:00	Tour: Fu Rong Park, Dinner & Song-and-Dance Performance – "A Dream Return To Tang Dynasty"		

Day 3: Friday, 12 September

Session VI

12/09/2008 Friday Morning	Surveillance and clinical trials (phase VI) in post marketing stage in Europe and China	Chairs: Cong Yali/ Ole Doering	
08:30-09:00	Title TBC	John Telford (IRIS-Chiron)	30 m
09:00-09:30	Issues in phase VI clinical trials	Zeng Fandian （Tongji Medical College）	30 m
09:30-09:40	Discussion and comments: • Issues in phase VI clinical trials		10 m
09:40-09:50	Break		10 m

Session VII

12/09/2008 Friday Morning	Conflicts of Interest	Chairs: Du Zhizheng/ John Telford	
09:50-10:20	Clinical Research in Emerging Economies: The Role of Industry in Governance and Protection of Research Participants	Detlef Niese (Novartis)	30 m
10:20-10:50	Ethical Issues: Conflicts of Interest in China	Zhai Xiaomei (PUMC)	30 m
10:50-11:20	Clinical trials: Indian perspectives	R. Kishore (Indian Society for Health Laws & Ethics)	30 m
11:20-11:35	Discussion		15 m
11:35-11:45	Break		10 m
11:45-12:00	Towards ethical governance of translation in stem cell science in Britain and China	Thomas Streitfellner	15 m

LUNCH			

Session VIII

12/09/02008 Friday Afternoon	Clinical Reseach: Patient's perspectives in Europe and China	Chairs: Li Benfu/ Margaret Sleeboom-Faulkner	
13:00-13:30	The power of knowledge and the law, courage of speaking about doubts, ethical responsibility. A reflection about clinical studies from the patient's perspective in Poland	Alicja Laska-Formejster	30 m
13:30-14:00	Clinical Research: Patient's perspectives in China	Prof. Du Zhizheng (Dalian University)	30 m
14:00-14:10	Discussion		10 m
14:10-14:20	Break		10 m

Session IX

12/09/02008 Friday Afternoon	*Panel discussion: Roles of industries and journals in ethics and governance of clinical trial*	Chairs: Wolfgang Hennig/ Zeng Fandian	
14:20-14:40	Roles of industries in ethics and governance of clinical trial	Xu Ning (Xi'an Ganssen Pharmaciutical Ltd)	20 m
14:40-15:00	Roles of industries in ethics and governance of clinical trial	Mao Jimin (Astrazeneca)	20 m
15:00-15:20	Roles of journals in ethics and governance of clinical trials	Li Enchang (The Journal of Chinese Medical Ethics)	20 m
15:20-15:40	Discussion and comments: • Roles of industries in ethics and governance of clinical trials; • How to regulate the		20 m

	relationships between physicians/investigators and pharmaceutical companies; • Ethical responsibilities of pharmaceutical companies		

Closing Session

15:40-16:00	Reflections and Conclusion	Nikolas Rose	20 m

Post-Workshop Meetings

12/09/2008 Friday 16:00-17:00	Steering Committee meeting	Members of Steering Committee	60 m
17:00-18:30	Expert Committee meeting	Members of Expert Committee	90 m

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