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# CURE **committee** report

# CHINA – UK RESEARCH ETHICS (CURE) COMMITTEE REPORT

## Committee members

Professor David Warrell (Chairman), Emeritus Professor of Tropical Medicine, University of Oxford

Dr Nick Bunnin, University of Oxford

Dr Amanda Dickins (rapporteur), King's College, London

Professor Donald Evans, Christchurch, New Zealand

Professor Xin Lu, Director, Ludwig Institute, Oxford University

Professor Tom Meade, Emeritus Professor, London School of Hygiene and Tropical Medicine

Professor Geneva Richardson, Professor of Law, King's College, London

Professor Nikolas Rose, Martin White Professor of Sociology, Chair BIONET, London School of Economics and Political Science

Professor Brian Salter, Professor of Biopolitics, King's College, London

Professor Peter Smith, London School of Hygiene and Tropical Medicine

Dr Hugh Whittall, Nuffield Council on Bioethics

Dr Xiaoning Xu, Clinical Scientist, MRC Human immunology Unit, University of Oxford

## Medical Research Council Head Office

Dr Catherine Elliott: Head of Clinical Research Support and Ethics

Dr Tony Peatfield: Head of Policy

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# EXECUTIVE SUMMARY

## 1. Aims and scope

The principal aim of CURE was three-fold:

1. To analyse the guidelines for research ethics in China,
2. To examine their implementation in actual research settings and
3. To make recommendations for the management of MRC-funded China-UK research collaborations and the development of mutual understanding in the area of research ethics.

In addition to a general overview, the Committee produced more detailed analyses of three areas:

1. Stem cell research
2. Clinical trials relating to emerging infections
3. Research involving Traditional Chinese Medicine

This report was produced following two visits by members of the Committee to Beijing and Shanghai, and a reciprocal visit of China National Centre for Biotechnology Development (CNCBD) delegates to London.

## 2. Summary of findings

Chinese laws and guidelines cover many aspects of medical research. The regulation of research is rapidly evolving in China and many of these guidelines and regulations have been produced within the last decade. Ongoing review of the regulatory situation in China (and indeed the UK) is required to ensure that collaborations are governed appropriately, in accordance with the regulatory systems of both countries.

Recent Chinese guidelines draw extensively on international guidance, such as the International Committee on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice Guidelines (ICH GCP). Chinese regulations bear a marked resemblance to UK regulation in areas such as embryonic stem cell research. Most of the underlying principles governing the conduct of medical research in China are broadly similar to those that guide UK regulation, although there are particular challenges, for example, interpreting individual informed consent in a culture that places high value on family involvement in decision making. However, some aspects of medical research are much more closely regulated in the UK than in China, such as uses of human tissues and data protection.

The key difference between the two countries is in the implementation of regulation: for this reason this Committee recommends close review of potential research collaborations. Although the elite scientists and institutions that we visited in China were committed to implementing international standards, the situation elsewhere remains unclear and the implementation and enforcement of regulation is not as consistent as it is in the UK.

The two countries differ greatly in their approaches to enforcing guidelines for the conduct of research at the national level. In China, although there is some scrutiny of clinical trials, there is comparatively little inspection or review of compliance. Moreover, although sanctions exist for violations of guidelines, it is not clear how they would be applied. The absence of national oversight places the onus on individual institutions and researchers to ensure the appropriate conduct of research. In contrast, the UK has many regulatory agencies overseeing and, in some cases, licensing and inspecting aspects of research – including uses of human tissue and embryos. There are also separate regulatory processes for gene therapy research and some research involving patient data. These additional layers of oversight may be viewed as a burden by the UK research community, but they provide considerable assurance regarding the appropriate conduct of research.

There are also important differences between the UK and China in terms of the institutional structures that conduct ethical reviews. China has followed the US model of institutional review boards (IRBs) and has no equivalent to the UK's National research ethics Service (NRES) to administer these committees and ensure consistency of procedure. Our report details significant differences between review committees in the UK and China. For example, there is a clear requirement in the UK that Research Ethics Committees (RECs) include members who are independent of the research teams, but this is not the case in China. Chinese IRBs are largely composed of professionals associated with the institution and are often chaired by the Director or a senior member of the research staff of that institution.

In addition to its general overview of the regulation of medical research, the Committee undertook a detailed analysis of three areas of particular interest. Their findings were as follows:



1. Stem cell research: Particular attention must be paid to the source of tissue used in research, including embryos, and procedures for obtaining consent, which should be compatible with both Chinese and UK regulation. The situation in China regarding the regulation of human admixed embryos is uncertain and future proposals involving such work need to be assessed in relation to the guidelines in place at that time. Any proposal involving the translation of stem cell research into clinical practice needs to be reviewed with great care, as the regulatory situation in China lacks clarity and it is important to ensure that this is not exploited.
2. Research involving clinical trials: All such research should be reviewed carefully, including the protocol, procedures for approval, recruitment and consent, and the issue of post-trial benefits. The MRC should ensure that there are adequate monitoring mechanisms in place. China's State Food and Drug Administration (SFDA) performs a similar role to the UK Medicines and Healthcare products Regulatory Agency (MHRA) in reviewing applications for clinical trials, but the MHRA has a system of inspection that is more transparent and covers a greater proportion of clinical trial sites. The SFDA is undergoing a programme of reform and further review will be needed in future to determine if this has fully addressed previous concerns.
3. Traditional Chinese Medicine: Attention needs to be paid to the quality, purity and standardisation of product to be used, the selection of participants and the use of placebo and control groups. Consideration should be given to the issue of concurrent traditional or Western treatments being taken by participants.

### 3. Summary of recommendations

The MRC must ensure the highest possible standards of governance of China-UK collaborations. If the UK, or specifically the MRC, is perceived to have been involved in unethical research, the negative effects on the reputation of the MRC and on future China-UK collaborations could be considerable. The following recommendations address how these high standards can be established and implemented in such collaborations.

#### MRC engagement with Chinese research ethics policy

##### Recommendation 1

The MRC should continue to discuss research ethics with Chinese counterparts and maintain the lines of communication developed through the CURE project.

##### Recommendation 2

If there is a lack of confidence in monitoring and inspection procedures in China in areas of strategic relevance to the MRC, the MRC should take steps to remedy this by reviewing the situation and, where necessary, engaging with researchers and policy-makers to improve capacity.

##### Recommendation 3

The MRC should seek to involve China in discussions about how to manage 'first-in-human' trials for innovative therapies.

#### MRC engagement with potential Chinese collaborative partners

##### Recommendation 4

The MRC should focus on established centres of excellence when funding collaborations with China and seek to build durable relationships with these centres.

In evaluating potential collaborations, we recommend that the MRC should look for both an international reputation in research, indicated by publications in international journals and funding from overseas funding agencies known to require tight ethical regulation, and for markers of good institutional governance. Such markers would include an international scientific review committee and well-constructed Institutional Review Boards with an appropriate proportion of independent members recruited from outside the institution.

Outside these established centres of excellence, the MRC will need to take proactive measures in all stages of planned collaborations to ensure that high standards of research ethics are maintained.

##### Recommendation 5

MRC should consider funding research to develop knowledge of institutional governance and matters relating to research ethics in relation to proposed MRC-funded China-UK collaborations.

## Ethics and governance standards in proposed collaborations

### Recommendation 6

Under no circumstances should the MRC fund research that has not been judged acceptable by a UK ethics committee. All proposed collaborations should be fully scrutinised by both countries, following the relevant Chinese and UK procedures.

### Recommendation 7

The MRC must ensure that appropriate procedures for informed consent are in place.

A research proposal could seek to remedy uncertainty in this area by incorporating elements such as reviewing consent procedures. Such additional work would also require approval of the ethics committees in China and UK.

## Pre-funding review

### Recommendation 8

It is important that the MRC seeks clarity, from the outset, regarding the reasons to collaborate on both sides of a proposed collaboration and an understanding about benefit sharing.

### Recommendation 9

The MRC and research ethics committees should review the specific piece of research for which funding and/or ethics approval is sought in the context of the whole programme of research, of which the specific project may be part.

### Recommendation 10

The MRC's pre-funding review process for China-UK collaborations should include review by one or more experts with experience and knowledge of Chinese regulation and science.

### Recommendation 11

The MRC should review research protocols to ensure that they are sensitive to cultural differences and social context.

### Recommendation 12

The MRC should review the level of payments or nature of inducements in any collaborative projects to ensure that they conform with current MRC policy and are not 'undue' inducements.

### Recommendation 13

The MRC should require all participating institutions and researchers to demonstrate that they have all necessary licences from the appropriate Chinese authorities to undertake their proposed programme of research.

## Additional funding

### Recommendation 14

Potential MRC-funded collaborations should be able to apply to the MRC for funding for an initial "Phase Zero", lasting six to twelve months.

This initial phase would be conceived as a period during which relationships and institutional developments might evolve before the research itself commences. It could provide knowledge relating to governance or ethics of the proposed project or allow for a period of capacity-building within the proposed team. Where there is uncertainty regarding governance structures, funding for the research could be made conditional on the satisfactory completion of "Phase Zero".

### Recommendation 15

For larger projects or research in areas of particular concern or sensitivity, the MRC should provide funding for expert evaluation of the research governance structures.

## Strategic issues

### Recommendation 16

The MRC should consider further:

- Strategic issues in the funding of collaborative research – including the evaluation of different models for funding collaborative research in China.
- Possible mechanisms to support capacity building for ethics review in China-UK collaborations.

## FOREWORD FROM PROFESSOR DAVID WARRELL, COMMITTEE CHAIR

Medical and biological science has great historical depth in China. In ancient times, it equalled the achievements of Greece and was far ahead of the rest of Europe. Traditional Chinese medicine evolved and flourished during the Han dynasty (206BC-220AD) and medical botany during the Sung dynasty (960-1279AD) but these traditions were maintained through the 18th century (Unschuld, 1990)<sup>1</sup> and up until modern times. However, it has been the recent surge in the pace, originality, breadth and volume of biomedical scientific research in China that has made us, in Western countries, so eager for greater contact.

The increasing appetite for research collaboration between British and Chinese scientists in the face of a need to understand their apparently differing traditions of research ethics, prompted the MRC to establish CURE. We were given the daunting task of trying to find ways of coming to terms with attitudes and constraints to biomedical research in modern China and to formulate guidelines to facilitate agreement on ethical practice compatible with our own convictions. China has always had the capacity almost to overwhelm one with its immense history, size, complexity and impenetrability. Especially challenging in a subject like medical research ethics was the need for precise understanding of language, philosophical and religious context and aspects of politics, law and commerce. All might be relevant in the assessment of a research proposal.

What has made the seemingly impossible almost attainable has been the enormously high calibre and generous attitude of our Chinese colleagues. Despite the gulf between translation and full understanding (with cultural connotations), we have at least approached enlightenment thanks to the enduring patience of our Chinese-speaking hosts. We are grateful to CNCBD and also the Ministry of Health in China for facilitating many interesting meetings providing invaluable background information. We also had the enormous advantage that BIONET had already identified, recruited, and bonded in intellectual fellowship, a remarkable group of European, American and Chinese ethicists, historians and social scientists. They welcomed the CURE committee members to their itineraries, meetings and lively discussions.

CURE has been a fascinating experience for us all. We have been privileged to be able to discuss fundamental issues with some of China's leading scientists and ethicists and to discover substantial areas of common ground in our beliefs of what can be done ethically in the name of scientific research in our two countries.

### **David A. Warrell (Chairman)**

Emeritus Professor of Tropical Medicine, University of Oxford

## ACKNOWLEDGEMENTS

The CURE committee is very grateful to all of the individuals and institutions who discussed these issues with us. These discussions demonstrated the considerable will of Chinese researchers and policy-makers at all levels to engage openly and promote collaboration in a framework of clear and ethical governance standards.

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<sup>1</sup> Unschuld PU. Forgotten Traditions of Ancient Chinese Medicine: A Chinese view from the Eighteenth Century. Paradigm, Taos, NM, 1990.

# I. INTRODUCTION

The rapid development of science and technology in China has attracted worldwide attention. Over the last decade, China's output of articles in international scientific journals has quadrupled, as has the number of articles with Chinese and UK co-authors.<sup>2</sup> In recent years, China has made a large investment in biomedical research and this is reflected in the rising number of China-UK collaborations in this area.

In response to these trends, the UK Medical Research Council (MRC), in partnership with the Foreign and Commonwealth office and CNCBD convened the China-UK Research Ethics committee (CURE) under the chairmanship of Professor David Warrell. CURE was asked to study the issues relating to research ethics raised by China-UK collaborations in biomedical research involving human participants and to make recommendations to maintain the highest standards of research ethics in such collaborations. Research ethics, in this context, was taken to include research governance as well as questions of bioethics. However, the ethics of animal experimentation were excluded from the committee's remit.

## Aims and scope

The principal aim of CURE was three-fold:

1. To analyse the guidelines for research ethics in China,
2. To examine their implementation in actual research settings and
3. To make recommendations for the management of China-UK research collaborations and the development of mutual understanding in the area of research ethics.

First, CURE was asked to investigate the principles, frameworks and methods of regulation applied to biomedical research in the Peoples' Republic of China (PRC). The results of this investigation are contained in Section II of this report, where the ethical regulation of medical research in China is presented and explained in relation to its social and cultural context, and the framework of governing institutions. Translation of full texts of the Chinese guidelines, where available, are included in the Appendix. The report also notes the principal similarities and differences between the situation in the PRC and that encountered by researchers in the UK.

Secondly, CURE was asked to examine the implementation of research ethics in China, by examining how the mechanisms of ethics review operate in specific research environments, highlighting the similarities and differences between these and their UK equivalents. The fruits of this work may be found in Section II under the heading of "Implementation". Further detail on specific fields of research contained in Section III. It should be emphasised, however, that this report is not a comprehensive review of the implementation of research ethics in China. There is considerable variation in the implementation of research ethics in different regions and institutions. CURE chose to focus its site visits on Beijing and Shanghai, research hubs that present some of the greatest opportunities for research collaborations between China and the UK.

Certain areas of scientific research raise specific ethical concerns and it was clear that CURE would need to investigate some of these in greater depth. The MRC requested that CURE focus its energies on those fields in which there was particular potential for developing collaborations between the Chinese and UK research communities. The fields selected for special attention were: (1) stem cells and (2) clinical trials and vaccines, with a focus on emerging infections. A third area was added at the request of the Chinese partners CNCBD and this was research involving Traditional Chinese Medicine (TCM). Each of these fields is discussed in detail in Section III of the report.

Thirdly, CURE was asked to make recommendations for future policy, including suggestions about ways of maintaining the communication and exchange of experience between China and the UK. The Committee's recommendations are addressed to the MRC, although these recommendations may be relevant to other UK funding bodies, ethics committees and researchers involved in collaborations with China. The recommendations are discussed in Section IV, which contains the conclusions to this report.

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<sup>2</sup> Wilsdon J and Keeley J. China: the next science superpower. Demos 2007



## Method of working

CURE was fortunate to be able to draw on a wide range of experience and skills amongst its committee members. The members of CURE included active research scientists alongside experts on law, bioethics, social science and Chinese science policy.

The initial stages of the committee's work included investigations by individual members of the committee of the situation in China, including the collation, translation and preliminary analysis of written materials, such as legislation and policy documents as well as articles from scholarly journals and the mass media on research and the regulation of research in China. In conducting these preliminary investigations, the committee drew on the work of the Global Biopolitics Research Group (King's College, London) and the intellectual resources of BIONET, a collaborative network of Chinese and European researchers working on the ethical governance of biomedical research in the context of potential EU-China collaborations, coordinated by the BIOS centre at the LSE. We were also very grateful for the initial assistance of Professor Tony Hope of the University of Oxford – particularly in mapping out the systems in the UK.

Following completion of this preliminary stage, a working party of committee members visited China to investigate how guidelines on research ethics were being implemented in actual research environments. CURE visited China twice, in April and October 2007. They met scientists, policy-makers and bioethicists, and visited a range of research sites including a vaccine trial and a stem cell research institute as well as several universities and hospitals. (Further details of their site visits and other meetings may be found in the Appendix.) The committee has drawn extensively on these discussions in the writing of this report and we are very grateful to the many individuals who gave generously of their time and knowledge and, without whom, this report would not have been possible.

The working party's visits coincided with two workshops organised by BIONET. The CURE delegation was extremely fortunate to be able to attend these meetings and wishes to record its gratitude for the very valuable assistance provided by BIONET. We wish them success in their future endeavours to develop European-Chinese exchange and understanding in bioethics, efforts which are complementary to our own. Participation in the discussions with Chinese researchers, practitioners and bioethicists at the BIONET workshops provided the CURE delegates with valuable insights into the actual practice of research regulation, in addition to knowledge of the formal guidelines and structures of regulation in China.

The findings contained in this report have also benefited from discussions with the CNCBD, the MRC's partner in the CURE project. Part of the remit of the CURE project was to find ways of developing mutual understanding between China and the UK on questions of research ethics. In keeping with this aspect of CURE, CNCBD were invited to lead a delegation of Chinese policy-makers and scientists to visit the UK to discuss these matters as well as the findings of this report. This delegation met representatives of regulatory authorities (the Human Fertilisation and Embryology Authority (HFEA), Human Tissue Authority (HTA) and Medicines and Healthcare Products Regulatory Agency (MHRA)), the National Research Ethics Service (NRES) and UK scientists, as well as senior officials from the Department of Health and the MRC.

## Structure of the report

The report begins with an overview of the regulation of research in China, including an introduction to the organisations involved in the regulation and funding of research. This is followed by separate discussions of research ethics in the specific fields of stem cell research, clinical trials (and vaccine research) and TCM. In each case, we have endeavoured to evaluate implementation on the ground as well as the formal guidelines and structures of regulation. Our recommendations for MRC policy and suggestions for future exchanges with Chinese partners conclude the main body of the report. The committee has also produced a "toolkit" containing guidance for UK scientists who might be considering collaboration with Chinese researchers. This document may be found appended to the report's conclusions. In addition, the Appendix contains translated texts of the relevant Chinese guidelines, information on Chinese organisations involved in the governance of research ethics, an overview of UK legislation, background information on stem cell science and details of the working party's visits to China.

## II. GUIDANCE ON BIOMEDICAL RESEARCH IN CHINA

This section surveys and analyses Chinese guidance on the conduct of biomedical research. In order to build a more complete picture of this guidance, it begins by introducing the cultural and social context and the government bodies involved in biomedical research in China. Chinese guidelines and laws are outlined and the means by which they are monitored and enforced. We note the similarities and differences between China and the UK and key differences are discussed in detail in the final part of this section.

### I. Background: cultural and social context

In order to create a full picture of the Chinese system of regulation of research ethics, this section introduces three important aspects of the cultural and social background:

- a The healthcare system,
- b Confucian tradition and the role of the family, and
- c The development of bioethics in China.

#### (a) The healthcare system

The Chinese healthcare system is currently in a state of change, caught in an awkward transition as it moves towards a market-based system. The result of these changes is that a considerable proportion of income for hospitals and professionals is derived from the sale of services and medication.

The opportunity to earn extra money by, for example, collaborating in clinical trials is, therefore, an important incentive for both clinicians and hospitals. The cost of medical treatment remains beyond the reach of many people, most of whom are not covered by any form of medical insurance, with the result that they find it difficult or impossible to get adequate healthcare.<sup>3</sup> Provision of medical care during a research study is therefore of considerable benefit to many subjects and is a possible inducement to participation. The national government has made reform of the healthcare system a priority and so the situation may improve. In the meantime, however, the condition of China's healthcare system must be taken into account when planning any biomedical research involving human participants. Our recommendations include practical suggestions for the responsible management of clinical trials and other research involving human participants.

#### (b) Confucian tradition and the role of the family

Traditional Confucian philosophy emphasises the importance of filial piety. Chinese bioethicists have interpreted this as implying that the body of a child remains under the control or influence of its parents, even in adulthood: a conclusion with implications for healthcare decisions, including participation in clinical research. China's "Regulation on the governance of medical institutions" specifies that informed consent must be obtained from the family as well as from the individual (see Appendix). However, it is unclear to what extent Confucianism is influencing research ethics in China today: the committee heard conflicting views on this subject. Some bioethicists argue that Confucianism is still the strongest influence, or is at least strong enough to make China significantly different from the West. However, there are complex transitions in religious and social concepts currently underway in China and there are many competing ethical traditions and regimes in China, as there are in many countries, including the UK.

However, the family retains an important influence over healthcare decisions for many patients in China. This is particularly important amongst less well-educated, traditionally minded communities found in rural areas.<sup>4</sup> In many areas of China, family consent is sought for medical treatment or for research and some prominent Chinese bioethicists promote the idea of "family-assisted" individual consent for clinical trials. Information is provided to family members who have time to discuss the decision about participation. However, the ultimate decision remains with the individual patient.

Chinese attitudes towards the family and sensitivity to issues of heredity may help to explain the Chinese regulatory position on the disposal of "supernumerary" embryos, i.e. those remaining after a successful IVF cycle has resulted

3 Only 29% of the population has health insurance. David Blumenthal and William Hsiao, "Privatization and Its Discontents – The Evolving Chinese Health Care System", *New England Journal of Medicine*, 353 (11) 2005.

4 Despite China's rapid economic development, most of China's population continues to live in rural areas. Official government statistics estimate that the rural population is 58% of the whole population. <http://www.china.org.cn/e-changshi/index.htm> accessed 14 January 2007.

in a live birth. This issue is faced by many couples, because a result of China's one-child policy<sup>5</sup> is that most couples undergoing IVF treatment will not be able to use these embryos for further reproduction.<sup>6</sup> Chinese regulation forbids the transfer of supernumerary embryos to another couple for use in reproduction: such embryos must either be destroyed or donated for research. Donation for research is regulated by government guidelines. (For further discussion, please refer to the section on stem cell research.) During discussion with Chinese bioethicists and scientists, we heard contrasting views on the ethical status of the embryo. Such differing views would also be encountered in the UK, but China has not had the widespread public discussions about the moral status of an embryo or fetus that have occurred in the UK. China, like the UK, prohibits embryo research beyond 14 days, as set out in the 2003 Ethical Guiding Principles for Research on Human Embryonic Stem Cells from the Ministry of Health (MOH) and Ministry of Science and Technology (MOST) (see Appendix).

### (c) The development of bioethics in China

The field of bioethics has developed with impressive speed in China and there is a small but important community of bioethicists. The creation of bioethics centres and programmes has begun to provide the institutional support and professional development necessary to allow independent bioethical review. Important centres and programmes include the Research Centre for Bioethics run by the Chinese Academy of Medical Sciences and Peking Union Medical College, and the Medical Ethics Programme at the Peking University Health Science Centre. We were told that the Chinese Government was increasingly serious about ethics, although the level of interest varies across different Ministries. The MOH has played an important role, funding bioethics research and, in 2001, establishing an expert bioethics committee to provide advice on bioethics and the development of ethical review.<sup>7</sup>

International guidelines and guidelines from other countries have influenced the development of Chinese policy: Chinese policy documents often include a statement to the effect that research must comply with international guidelines, and China has accepted the main relevant international declarations and guidelines in bioethics, such as UNESCO's 1998 Universal declaration on human rights and biomedicine.<sup>8</sup> However, many of our Chinese colleagues pointed to the disparity that often exists, especially outside the major centres, between formal commitments and their domestic implementation, we discuss the issue of implementation in detail below.

Chinese bioethicists actively participate in global as well as regional bioethics networks, where they have introduced distinctive perspectives, particularly around family issues and the role of cultural values in bioethical practice. However, they share many of the values promoted by Western bioethicists. Their training and affiliations illustrate the important role that the US has played in the development of Chinese bioethics. Harvard University and the National Institutes for Health (NIH) have actively promoted the development of bioethics in China, disseminating a distinctively US approach that has shaped the theory and the practice of bioethics in China. In developing its system of ethics review, China has followed the US system of the "institutional review board" (IRB). In China, as in the US, bioethics appears to be the domain of professionally designated experts.<sup>9</sup>

## 2. Government bodies involved in biomedical research in China

This section provides an overview of the government bodies involved in biomedical research in China. The guidelines issued by these bodies are a key element of the regulation of research ethics in China. For further details and background information on these bodies, please refer to the Appendix.

Many government bodies are involved in the management and funding of biomedical research in China. There has been major reorganisation in recent years and this appears to be continuing. Figure 1 illustrates their functions and inter-relationships, in October 2007.

5 We were told that the one-child policy now applies only to urban Han families whereas rural and Tibetan communities are allowed more children

6 This policy is subject to change and may be abolished in the near future. There are already some circumstances under which exceptions to the one-child policy may be permitted: for example, for couples whose first child has an incapacity that is judged to be severe, or where the parents themselves come from one-child families or are from minority groups. University of California - Irvine. "China's One-child Policy Reveals Complexity, Effectiveness". ScienceDaily. Accessed 14 January 2008 <http://www.sciencedaily.com/releases/2007/04/070418115227.htm>

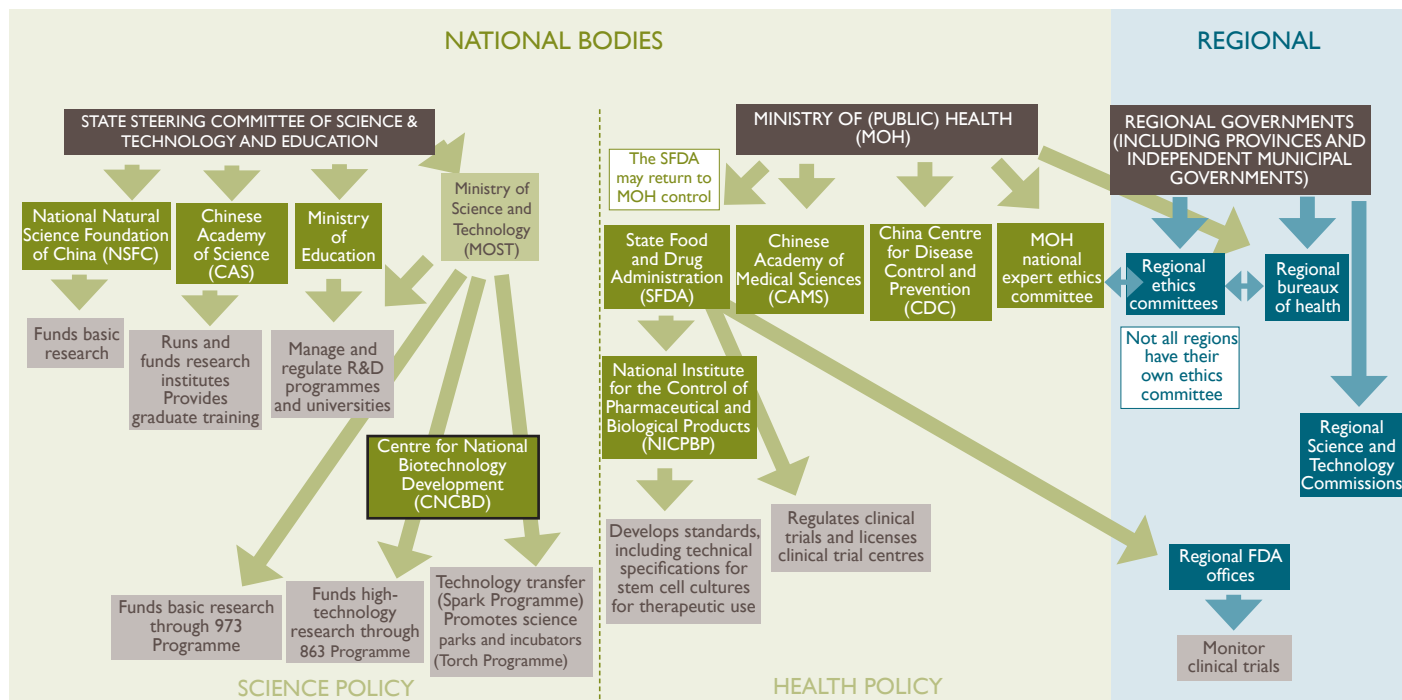
7 See <http://www.moh.gov.cn/newshtml/17503.htm> (in Chinese)

8 China co-authored the WHO Guidelines on ethics in medical genetics (1998), UNESCO's Universal declaration on human rights and biomedicine (1998) and the UNESCO International Bioethics Committee's statement on Human embryo research and international solidarity and cooperation (2001). China also endorsed the Helsinki Declaration on Ethical principles for medical research involving human subjects (2000) and supported a UN ban on human cloning for reproductive purposes.

9 David Dickson and Jia Hepeng, editorial on "Bioethics Reporting in China: a case for bold action", SciDev.Net, 5 October 2006. Accessed 2 July 2007.

As in other countries, the bodies involved in biomedical research have different remits. Some were set up to promote science and technology; others focus on health.

Figure 1: Government bodies involved in the regulation and funding of biomedical research in China.



### Science and technology policy

Science and technology is ultimately the responsibility of the State Steering Committee of Science & Technology and Education, but this committee works indirectly by guiding the work of other organisations and does not seem to be directly involved in either the funding or regulation of research. The MOST, together with the Chinese Academy of Sciences (CAS), control most research funding in China.<sup>10</sup>

The China National Centre for Biotechnology Development (CNCBD) is an agency of MOST with responsibility for biotechnology and medical technology. It administers the biotechnology portion of the '863' high technology programme', one of China's large national funding programmes. CAS is a huge and highly prestigious organisation, controlling over a hundred research institutes, a university, a graduate school, various enterprises and information and publishing services.

The National Natural Science Foundation of China (NSFC) is a smaller organisation that focuses on basic research. It has a reputation for transparent governance and we were told that it reviews rigorously ethics issues relating to biomedical research.

Of the bodies involved in science and technology policy, MOST has the most important role in developing regulation of basic and laboratory research. Guidelines promulgated by MOST have nationwide scope, whereas the rule-making powers of NSFC and CAS affect only their own institutions and research projects. This allows for a potentially more structured implementation of governance in the limited number of facilities funded by these bodies. In keeping with its focus on science and technology, MOST's primary interest in research ethics is scientific integrity. At the beginning of 2007, MOST set up a special office to deal with cases of misconduct. The director of the policy and regulation department said that the government was planning to establish a committee, including international and national experts, to promote scientific integrity.<sup>11</sup>

### Health policy

Health issues are the responsibility of MOH. This Ministry thus has responsibility for research involving patients and the regulation of the ethics of such research. The Chinese Academy of Medical Sciences (CAMS) operates under MOH, as does the China Centre for Disease Control and Prevention (CDC). In keeping with its remit to protect and promote the health of Chinese citizens, MOH has taken the lead in initiating regulations to govern biomedical research and protect human participants in such research. MOH funds bioethics research and guided by its committee of expert

<sup>10</sup> Nature editorial (2005). "New Accountability in China", Nature, 434, p.1053.

<sup>11</sup> <http://www.scidev.net/content/news/eng/china-sets-up-rules-to-combat-scientific-misconduct.cfm>

bioethicists. The Minister of Health, Professor Chen Zhu, was actively engaged with bioethics as a vice president of CAS, prior to his appointment as Minister. There are a number of new regulatory initiatives in this area but their impact is not yet certain. In China, as in the UK, it can take a long time to develop policy: for example, guidelines on the application of innovative health technologies have existed in draft form since 2001, but have yet to be promulgated.

#### Pharmaceutical regulation

The SFDA bridges science and technology policy and health policy. The government is keen to promote the development of China's pharmaceutical industry and the agency was set up with this aim. However, the SFDA is currently undergoing radical reform after the exposure of massive high level corruption at the agency: SFDA was placed under MOH control in March 2008, a move that may signal a greater emphasis on public health rather than economic development (the SFDA is discussed further below in the section on clinical trials.) The National Institute for the Control of Pharmaceutical and Biological Products (NICBPB), an agency of the SFDA, will play an important role as stem cell products are applied clinically. NICBPB worked with Beijing University researchers to develop technical specifications for China's first SFDA-licensed clinical trial of a stem cell therapy.

#### Regional government

China is a large and very diverse country, with powerful "provincial level" governments in the provinces and in the four "direct-controlled" municipalities: Beijing, Tianjin, Shanghai, and Chongqing. These regional governments have considerable autonomy: the old saying that "the mountains are high and the Emperor is far away" still resonates. Regulation and policymaking at regional level reproduces much of the structure found at national level. There are regional science and technology commissions, food and drug administrations, centres for disease control and bureaux of health. Regional bodies are usually accountable to their national counterparts, but there are often stronger ties with officials in the regional government. As a result, it is sometimes difficult for the national ministries to get accurate data about what is happening in remote regions, let alone to govern them.

Researchers involved in collaborations with China should bear in mind these political divisions as well as the enormous diversity and disparities in wealth across the country.<sup>12</sup> Clearly, caution is required and it is important to obtain permissions from and establish working relationships with provincial as well as national regulatory authorities.

### 3. Law and guidelines affecting biomedical research

This section provides a general introduction to Chinese regulation. Specific regulations about stem cell research, clinical trials and traditional Chinese medicine are covered in the relevant sections of the report.

China's regulatory approach to biomedical research consists of laws, regulations and guidelines, of which Ministerial guidelines play the most important role. China does have some laws that set out general regulations for medical practice and for the use of pharmaceuticals, areas relevant to biomedical research. However, even in these areas, guidelines still play an important role because laws (enacted by the National People's Congress) are high-level statements of principles that are expanded in regulations from the State Council and ministry guidelines.

Reliance on ministry guidelines means that responsibility for research regulation is divided between different agencies, the most important being the MOH, the MOST and the State Food and Drug Administration (SFDA). These agencies bring different perspectives to their regulatory role. As discussed above, MOST's mandate dictates its focus within research ethics on scientific integrity. Both MOST and MOH fund areas relating to research ethics. Many of our Chinese colleagues believe that the central government is becoming more committed to the ethical regulation of research, with the possibility of more rigorous governance and regulation of research and of experimental treatments in future.

China's abundance of guidelines covers many of the most important issues in research ethics, though not all: for example, they have yet to promulgate guidelines about application of innovative health technologies although draft

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<sup>12</sup> The US Embassy suggests that "the ability of Chinese provinces to address health issues correlates closely with their development and educational level. The coastal cities rank highest, followed at a considerably lower level by the first-tier eastern provinces (for example, Jiangsu, Zhejiang and Guangdong) and the second-tier (such as Henan and Anhui). Much poorer again than these are the true Western regions such as Qinghai, Tibet, Gansu and Xinjiang." They emphasise that research in these last provinces should be undertaken only "under exceptionally tight supervision by the US contracting entity". US Embassy, "Human Research Subject Protection in China: Implications for US Collaborators" 2000. Available at <http://www.usembassy-china.org.cn/sandt/humanresearchsubjectprotection.htm> accessed 21 February 2008.



guidelines have been under discussion for a number of years. China introduced guidelines for the protection of human research subject in the 1990s, which facilitated collaboration with foreign organisations.<sup>13</sup> China has since developed a sizable body of regulation pertaining to medical research, including the recent guidelines on biomedical research involving human subjects, specific guidelines on clinical drug trials and embryonic stem cell research, as well as provisions for good clinical practice (GCP) and good laboratory practice (GLP).<sup>14</sup> A list of some of the most important regulations relevant to biomedical research is laid out in table 1. Informed consent features prominently in the regulations for clinical treatment as well as research. The regulations contain provisions for review by ethical review committees. In China, such reviews are usually the responsibility of Institution Review Boards (IRBs), the operation and structure of which is discussed in detail in the next section.

**Table 1: Laws, regulations and guidelines relevant to biomedical research in China**

	DATE	PROMULGATOR	KEY PROVISIONS RELATING TO BIOMEDICAL RESEARCH
Management Methods on Clinical Application of Medical Technologies	2009	MOST	Relates to introduction of 'Class III' technologies, including autologous and allogeneous stem cells and cloned stem cells into clinical practice
Regulation on Ethical Review of Biomedical Research Involving Human Subjects	2007	MOH	Contains detailed prescriptions regarding informed consent procedures and includes explicit rules on the organisation, membership and procedures of ethics committees. Regional ethics committees to be formed in the provinces.
Regulation on Misconduct in Scientific Research	2006	MOST	
Ethical Guiding Principles on Human Embryonic Stem Cell Research	2003	MOST, MOH	Requires institutions to set up an ethics committee. Proscriptions mirror the UK legislation, although there is no framework for enforcement to match the UK's licensing system. See section on "Stem Cell Research".
Guidelines on Human Assisted Reproductive Technologies (ART)	2001	MOH	Stipulates that institutions providing ART must set up an ethics committee. See section on "Stem Cell Research".
The Drug Administration Law / Regulations for Implementation of the Drug	2001 2002	National People's Congress	Covers the use of pharmaceutical products in both research and practice. States that the principles of GCP and GMP must be followed in clinical trials
Administration Law of the People's Republic of China	1999 2003	SFDA	Emphasises informed consent and "Strict review by ethics committee". Includes provisions regarding the composition of Institutional Review Boards.
Drug Clinical Trial Regulations Law on Practicing Doctors	1999	National People's Congress	States that a doctor who violates a patient's privacy or conducts experimental clinical treatment without consent must "bear the legal accountabilities".
Interim Measures for the Administration of Human Genetic Resources	1998	MOST, MOH	Includes provisions regarding: licence system; mutual respect; benefit-sharing; informed consent; ethical review.
Regulation on the Governance of Medical Institutions	1994	State Council	Stipulates that informed consent should be obtained prior to the performance of "surgical operation, special examination or special treatment".

(Please refer to the relevant sections for further details of these regulations. The Appendix contains a full list of regulations, together with further information on their contents and, where available, translations of the text.)

<sup>13</sup> There are parallels between this history and events in the UK, where pressure from holders of US NIH grants played a key role in establishing the UK system of research ethics committees. Adam Hedgecoe, "Research Ethics Committees as Political Technologies of Trust", presentation to London Medical Sociology Group, 9 January 2008.

<sup>14</sup> Rao Chunming (NICBP, Beijing), "Regulatory Issues for Cell and Gene Therapy in China" presentation to workshop on "Global Harmonization of Cell Therapy-The Regulator's Perspective", Sydney, Australia, 2007

[http://www.celltherapysociety.org/files/PDF/Meetings/ISCT\\_2007/Post\\_Conference\\_Slides/Thurs\\_I300\\_2\\_Rao\\_I04.pdf](http://www.celltherapysociety.org/files/PDF/Meetings/ISCT_2007/Post_Conference_Slides/Thurs_I300_2_Rao_I04.pdf)

### UK legislative framework (table 2)

The UK system of legislation shows similarities with that of China. Primary legislation is passed as Acts of Parliament. Secondary legislation in the form of Regulations is also passed by Parliament. As the UK is part of the EU, some UK legislation represents the implementation of Europe-wide legal requirements – European Directives, such as the Data Protection Act 1998 and the Medicines for Human Use (Clinical Trials) Regulations 2004.

Individual Government Departments, such as the Department of Health or Ministry of Justice, produce Codes of Practice or Guidelines expanding on how legislation should be interpreted and implemented. For example, the recent Mental Capacity Act 2005 has its associated Code of Practice produced by the Ministry

of Justice.<sup>15</sup> The Department of Health has also produced Guidance on aspects of the Act's implementation in medical research.<sup>16</sup> In UK terminology, a Code of Practice would usually be seen as being of higher standing than Guidelines<sup>17</sup>. Researchers would be expected to adhere to all such documents although, in the case of guidelines, they may deviate from the advice if there were strong justification.

The Departments of Health have also produced Research Governance Frameworks<sup>18</sup> which set out the requirements for research in the NHS and social care systems. Since most research involving patients occurs within the NHS, compliance with these frameworks is mandatory for most clinical projects. Amongst other aspects, the frameworks set out the obligations of funders, sponsors and researchers in such projects.

Table 2: Key UK statutes relating to medical research involving human participants.

	DATE	SCOTLAND	NORTHERN IRELAND
The Medicines for Human Use (Clinical Trials) Regulations 2004 (CTR)	yes	yes	yes
Adults With Incapacity (Scotland) 2000 (AWIS)	no	yes	no
Mental Capacity Act 2005 (MCA)	yes	no	under review
Human Tissue Act 2004	yes	mostly no	yes
Human Tissue (Scotland) Act 2006	no	yes	no
Data Protection Act 1998	yes	yes	yes
Human Fertilisation and Embryology Act 1990 as amended 2008*	yes	yes	yes

\* The 1990 Act has been amended by the 2008 Human Fertilisation and Embryology Act 2008 as discussed further below

## 4. Implementation

In this section we discuss China's framework for implementing its guidelines on research ethics. We outline the available sanctions, including the more rigorous sanctions when research involves human subjects, and discuss the lack of monitoring mechanisms for all types of research. This is followed by a discussion of the role and structure of China's ethics committees, on which depend the burden of interpretation and enforcement.

Implementation is a key issue in assessing the ethical regulation of research in China. China's regulations consist mostly of guidelines promulgated by the relevant ministries, which could be considered to constitute 'soft law', even though there are sanctions available to punish violations of the guidelines. The UK also relies on much 'soft law' (including

<sup>15</sup> <http://www.justice.gov.uk/guidance/mca-code-of-practice.htm>

<sup>16</sup> Guidance on nominating a consultee for research involving adults who lack capacity to consent. Department of Health. February 2008

<sup>17</sup> A Code of Practice, as under the Mental Capacity Act, is typically required by the parent statute: a statutory obligation is placed on the relevant minister to produce one. In contrast departmental guidelines may simply be issued as part of the department's on going obligations. Neither is likely to be directly enforceable by a court, though both will be taken into account and any failure to follow will have to be justified.

<sup>18</sup> England: [http://www.dh.gov.uk/prod\\_consum\\_dh/groups/dh\\_digitalassets/@dh/@en/documents/digitalasset/dh\\_4122427.pdf](http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_4122427.pdf)

Codes of Practice from regulators, Good Practice guidance from the MRC and reviews by the Nuffield Council on Bioethics) to govern the conduct of research. However, China's formal system for licensing and oversight of regulation is much less developed than the system in place in the UK and so the impact of China's 'soft law' is less clear.

#### (a) Sanctions for violation of research guidelines

We were told that ministry guidelines do have "reasonable force", but have less authority and carry lesser sanctions than rules promulgated by the State Council (the highest organ of the central government) or laws passed by the National People's Congress. Indeed the sanctions for breaching ministry guidelines are often unclear. Researchers applying for funding from major state funding programmes (such as the 863 or 973 programmes<sup>19</sup>) must state that they will follow relevant guidelines in their proposed research. Although the guidelines do not carry the same precise status as law, it was suggested to us by researchers and by the Ministry of Health that researchers who failed to comply with the relevant guidelines could face a warning, lose their funding or even face a fine or lose their job. Where research involves human subjects, the most recent guidelines state that violations by individuals or institutions will be punished.<sup>20</sup> The range of potential punishments includes "open criticism" or the withdrawal or termination of qualifications or work.

The withdrawal of licences would be a serious punishment because it is illegal for clinicians or medical institutions to operate without a government licence.<sup>21</sup> The withdrawal of licences has been used to punish violations of, for example, the guidelines on Human Assisted Reproductive Technologies. However, the use of licences as a means for enforcing ministerial guidelines is complicated by the role of local and provincial governments, which are responsible for issuing licenses to institutions, clinics and laboratories. The withdrawal of such licenses as a means of enforcement will depend on the capabilities and willingness of local and provincial governments to judge and act accordingly.

The task of establishing suitable sanctions as part of a bioethical regulatory regime in China is a task for the Chinese Government through consultation with Chinese scientific researchers, lawyers, bioethicists and other concerned parties. Although Western experience shows that sanctions must be serious to be effective, this Committee believes that punishment for violating laws and regulations in this area should be fair and proportionate.

#### (b) Monitoring mechanisms

In terms of provisions for monitoring, medical establishments (such as IVF clinics) are required to hold a licence for their clinical work. There is also a system of licensing for clinical trials, regulated by the SFDA, which can (and does) inspect the copious documentation generated by trials. Some of this function is undertaken by regional offices. (For a detailed discussion of specific regulations regarding clinical trials, please refer to section III.) However, there are serious concerns about governance of the SFDA, based on its recent history, and the organisation is undergoing radical reform.<sup>22</sup>

Outside the field of clinical trials, there are no other specific provisions for licensing or inspection to ensure that researchers adhere to regulations. Thus, although the regulations appear quite comprehensive, there is a lack of formal systematic procedures in place across China to monitor compliance, identify failures and enforce sanctions.

In the absence of monitoring by external bodies or regulators, adherence to guidelines depends on the integrity and governance structures of individual institutions and their staff. The Chinese system relies on Institutional Review Boards (IRBs) to maintain and monitor research ethics at each institution.

#### (c) Ethics committees: the composition and functioning of IRBs

The operation of ethics review in China gives some cause for concern, even though the formal structure of the Chinese system has been modelled on international guidelines, in particular CIOMS/WHO International Ethical Guidelines on Biomedical Research Involving Human Subjects.

IRBs bear the burden of reviewing and monitoring research in China, but there is little oversight of the IRBs themselves. The MOH's national committee of bioethics experts operates in an advisory capacity and, according to recent guidance from MOH, it is the responsibility of provincial departments of health to overview the IRBs in their

19 These are large programmes of government funded research dealing with specific areas: 863 is the 'High Tech Research and Development programme' and 973 the 'National Basic Research programme'.

20 Regulation of Biomedical Research Involving Human Subjects, 2007.

21 Special licenses are required to conduct clinical trials: these are issued by the SFDA. For a detailed discussion of specific regulations regarding clinical trials and recent concerns about the governance of the SFDA, please refer to section III.

22 See [http://www.chinadaily.com.cn/china/2007-03/29/content\\_839153.htm](http://www.chinadaily.com.cn/china/2007-03/29/content_839153.htm)

region.<sup>23</sup> We understand that there are proposals to monitor the implementation of research regulation, but no details were available.

Chinese rules on the composition of IRBs, issued by the SFDA in 1998 and MOH in 2007, adhere to most of the International Committee for Harmonisation (ICH) recommendations. The ICH stipulates that an IRB should have a minimum of five members, including at least one member whose primary area of interest is non-scientific.<sup>24</sup> The Chinese guidelines specify that the IRB should have at least five members including both men and women, and “members from non-medical profession, law and other institutions”.<sup>25</sup> It is claimed that most IRBs comply with these rules as did the IRBs that we met on our site visits.<sup>26</sup>

However, Chinese guidelines are notably less specific than international guidelines in ensuring the independence of IRBs from the institutions they are scrutinising. The ICH guidelines specify that the IRB should have at least one member who is independent of the institution or trial site.<sup>27</sup> In contrast, the Chinese guidelines merely state that the composition and work of Ethics Committee shall be relatively independent from the researcher.<sup>28</sup> Therefore, the Chinese guidelines do not require IRBs to include a member independent of the institution.

We discussed the composition of the IRBs at a number of institutions. It is clear that they are composed with insufficient regard to conflicts of interest. In many cases, they lacked any member who was entirely independent of the institution. Most IRB members were drawn from medical staff at the institution (clinicians, hospital managers, nurses and, in one case, a psychologist). The “lay people” included were generally associated with the institution (such as a lawyer, financial manager or pharmacist who works for the hospital). Some IRBs included a bioethicist, who might be expected to be more independent (as well as having a clearer idea of the purpose and conduct of ethical review) in view of their professional training / ethos.<sup>29</sup> In no case did an IRB include a patient representative (such representation is a relatively recent development in the UK).

In China, many IRB members lacked specific training in ethics. Without a necessary understanding or awareness of the purpose of ethics review, some committees may review scientific rather than ethical aspects of the proposed research.

We visited institutions that were among the national leaders in their fields and might, therefore, be expected to have the best developed ethics practice. We were told that most well-established institutions had “well-organised” ethics committees and it appears that some areas, such as the Beijing and Shanghai municipalities, have good standards, but that practices vary widely across China. Most of our interlocutors thought that ethical governance of research outside the major metropolitan centres was probably much less developed. Since Chinese bioethicists, policymakers and scientists have great difficulty in getting information about the situation outside major research centres, it is likely that potential research partners outside China would find proper assessment even more elusive. It is thus important in any proposed collaboration to evaluate the membership and operation of the IRB governing the Chinese partner.

Clearly, IRB structures are still evolving in China. In some cases, the composition of the committee has changed in recent years, sometimes more than once. The UK system is also evolving. Before the 1990s, ethics committees in the UK did not have their present role in research approval but, following a review of ethics committees and their function in the early 1990s, there have been changes in the organisation of RECs and their governance.

From discussions with research scientists, we gained the impression that leading researchers were responsive to suggestions about improving their ethics review processes and structures and were keen to learn about policies and experience in other countries. Recent guidance has required the development of regional ethics committees at provincial or municipal level.<sup>30</sup> None of the people we met was familiar with the UK’s National Research Ethics Service (NRES) model of central coordination. As discussed in our conclusions, we felt that it could be beneficial to both sides if the UK were to make available in China more information about UK institutions and processes for reviewing research ethics.

23 Regulation of Biomedical Research Involving Human Subjects, 2007. We were informed that the MOH had asked provincial bureaux of health to report on the structure and functioning of IRBs in their region.

24 ICH Harmonised Tripartite Guideline for Good Clinical Practice

E6(R1), available from <http://www.ich.org/LOB/media/MEDIA482.pdf> accessed 21 February 2008.

25 Article 9, SFDA Drug Clinical Trial Guidelines. For full text and source, please refer to the Appendix.

26 For example, Xu observes that most IRBs have between seven and 15 members. Jiaqi Xu et al “Human Subjects Protections in Clinical Drug Trials in China”, *International Journal of Pharmaceutical Medicine* 20 (2006), p.368.

27 ICH Harmonised Tripartite Guideline for Good Clinical Practice

E6(R1), available from <http://www.ich.org/LOB/media/MEDIA482.pdf> accessed 21 February 2008.

28 Article 9, SFDA Drug Clinical Trial Guidelines. For full text and source, please refer to the Appendix.

29 In some (but not all) cases the bioethicist was employed by the same institution, but often in a centre for bioethics or within some other administrative structure, such as a medical ethics programme, that might afford them some protection from pressure to approve research proposals.

30 Regulation of Biomedical Research involving Human Subjects, 2007 (Article 5).

### UK National Research Ethics Service

In the UK, systematic oversight of the NHS research ethics review process is provided by NRES. There is no equivalent to NRES in China. There are three main types of research ethics committee (REC) in the UK; those dealing with NHS research involving NHS patients, staff or premises; University RECs dealing with all other research requiring ethical approval and Independent Ethics Committees (IECs) authorised to review Phase I clinical trials involving healthy volunteers. The NHS RECs are administered through NRES, so that procedures and governance are broadly consistent across all recognised committees. RECs require annual reports on the progress of approved projects. Individual NHS RECs may be authorised ('flagged') to deal with clinical trials involving adults who lack capacity (as defined by the Mental Capacity Act 2005). There are local and multi-centre committees (LREC and MRECs), the latter dealing with research across multiple research sites. IECs are appointed by the Appointing Authority for Phase I Ethics Committees (AAPEC).<sup>31</sup>

## 5. Key differences between China and the UK

Over the last decade, China's guidelines governing biomedical research have been shaped to bring the country formally into line with international regulations, where they exist, or with national regulations accepted by major research centres in countries such as the USA and the UK. China and the UK have similar background legislative and governance frameworks for many areas of medical research.

However, there are some marked differences in the systems for their implementation. In China, the formal system for implementation and oversight is underdeveloped. Important differences between the UK and China include the (greater) number of statutory regulators in the UK and the sanctions specified by UK statutes. The lines of authority are more clearly drawn in the UK: there can be considerable variation between the different provinces in China and there is no equivalent to the comprehensive national framework provided by the UK's National Research Ethics Service. The composition of ethics committees is more tightly proscribed in the UK. Last but not least, the requirement for ethics committee review of research involving human participants and human tissues is more deeply embedded in UK law, although much of this legislation, such as the Human Tissue Act 2004 and the Mental Capacity Act 2005, is relatively recent.

### Statutory regulators

Both the UK and China have regulators overseeing application of requirements for medicinal drugs and devices. The UK has also established statutory regulators under many of the Acts detailed in the previous section and so a much broader range of research activity is subject to specialised statutory oversight. Thus the Human Fertilisation and Embryology Authority (HFEA) licenses and regulates embryo research and the Human Tissue Authority (HTA) licenses premises to store human tissue and regulates use of human tissue. There are also 'advisory groups' which must be consulted before certain types of research can be carried out, for example the Patient Information Advisory Group (PIAG) regulates access to patient health records where consent is not in place and the Gene Therapy Advisory Committee (GTAC) must approve research projects involving gene therapy. There are no equivalent regulatory or advisory bodies in China.

### Legal sanctions

In the UK, many statutes dealing with medical research have explicit sanctions. For example, certain breaches of the Human Fertilisation and Embryology or Human Tissue Acts constitute criminal offences with defined maximum penalties. The statutory regulators also have power to inspect premises and to withdraw licences as necessary. These powers are rarely used but their existence is well-known to researchers and adds considerable weight to the requirements imposed. Although the relevant Chinese guidelines do list potential sanctions for violations of research regulations, there is no clear specification of which sanctions would be applied for which type of violation. Moreover, the scope of the sanctions appears to be limited to the withdrawal of benefits and / or licences.

In the UK and in China, violations of laws could be dealt with through the Courts. We were told that this had happened in China when there was alleged harm resulting from participation in clinical trials. However, details of specific cases were not provided. In the UK, there is very little civil case law relating to clinical research although some principles can be extrapolated from rulings on consent and breach of duty of care in medical negligence cases.

### Ethics Committee review

Approval by a recognised ethics committee is a legal requirement for many types of project in both countries. For example, the UK Mental Capacity Act 2005 demands such approval for research involving adults who lack capacity. This is also the case for clinical trials of medicinal products and for use of human tissue in the UK. In China, ethical review is required by the regulations for clinical trials and embryo research and the 2007 guidelines for biomedical research

31 <http://www.aapec.org.uk/index.html>



involving human subjects (see Appendix) require that each institution conducting research has an IRB. However the requirement for ethical review is not as deeply embedded as it is in some aspects of UK law. Moreover, in the UK, there are separate Regulations detailing the nature of approved research ethics committees for some areas of research. In China, the 2007 guidelines do contain some guidance as to the composition of IRBs, but they do not control the composition of IRBs tightly enough to ensure their independence from the institutions that they review.

#### Key differences between China and the UK

- Role of statutory regulators
- Scope and detailed specification of legal sanctions
- Composition of ethics committees
- National Research Ethics Service

### III. RESEARCH ETHICS IN SPECIFIC AREAS OF RESEARCH

#### I. Stem cell science

Stem cell science research holds great promise for the future development of therapeutic and clinical applications<sup>32</sup> but it has given rise to controversy, much of it arising from the potential use of human embryos to provide pluripotent stem cell lines. The maintenance of high standards of research ethics is vital if the field is to continue to develop. China is making a major investment in stem cell science.<sup>33</sup> This is therefore an area of great potential for future China-UK collaboration. There are varying estimates of what has been achieved so far, but we were told that approximately 30 to 40 human embryonic stem cell (hESC) lines have been established and the research demonstrating this has been published in “good” journals, both domestic and international. China offers some attractive opportunities for collaboration in stem cell science, but the reputations of both partners will be jeopardised unless the highest standards of research ethics are practised.

In response to this concern and the intense UK interest in Chinese stem cell science, the CURE committee was asked to examine specifically the research ethics surrounding potential collaborations in stem cell science. We considered the following key questions:

1. What are the legal and regulatory frameworks for stem cell research in the UK and in China?
2. Are these frameworks compatible, such that collaborative projects would be acceptable in both countries?
3. What are the risks in conducting collaborative work in stem cell research?
4. Are there ways in which these risks could be mitigated?

Please refer to the Appendix for a detailed discussion of scientific terms used.

#### I. What are the legal and regulatory frameworks for stem cell research in the UK and in China?

##### UK REGULATIONS

###### Human embryo research:

The ethics of research involving embryos has been extensively debated in the UK since the first IVF baby was born in 1985. The 1984 Warnock Report formed the basis for the sections of the Human Fertilisation and Embryology Act 1990 relevant to embryo research. Some of the crucial points considered by the report and subsequent passage of the Act were whether an embryo had equivalent ‘rights’ to an adult; whether it had a ‘life’ of the same value and whether it should be accorded any special ‘status’ in law. The conclusion of the report was that the embryo did not have the legal or moral standing of a human after birth. However, the embryo should be accorded special respect due to its unique nature and potential to develop into a person. Thus, research should not continue beyond the appearance of the primitive streak (which will develop into the nervous system and brain). In order to draw a clear line, this point was taken to be at 14 days after conception. In addition, an embryo used for research must never be implanted into a woman. The following table summarises the relevant UK legislation. For further detail, please refer to the Appendix.

Human Fertilisation and Embryology Act 1990	This legislation established the Human Fertilisation and Embryology Authority (HFEA), which was given the power to grant licences in relation to embryos, including for specified research purposes and to inspect premises that are licensed. The unlicensed creation, storage or use of embryos was made illegal. In relation to research use: <ul style="list-style-type: none"><li>• No embryo may be kept beyond the appearance of the primitive streak which is deemed to be no later than 14 days.</li><li>• No embryo may be placed in an animal</li></ul>
Human Fertilisation and Embryology Act 2008*	This Act updates the 1990 Act. It prohibits reproductive cloning, defines ‘research purposes’ and allows creation and use of ‘human admixed embryos’ in research, under the same restrictions as human embryo creation and use for research*

\* <http://www.publications.parliament.uk/pa/ld200708/ldbills/006/08006.i-iv.html>

32 Some of the potential uses of stem cell research include the creation of disease-specific cell models, development of drug therapies and also derivation of cells or tissues for repair of damaged organs or cells. Please refer to Appendix for further discussion of stem cell science.

33 Chinese spending over the five years up to 2010 is projected to be between RMB 500 million (US \$63m) and RMB 2 billion (US \$250m). UK Stem Cell Initiative (2005). Report and recommendations. Department of Health, London. The MRC spent approximately £30m on stem cell research in 2006/7.

The UK system provides a strong system of national oversight of embryo research and derived stem cell lines (through the stem cell bank). UK legislation is explicit about the criminal nature of breaches and also the sanctions that may be imposed for such breaches. A licence is required in order to undertake research involving embryos and the HFEA inspects all premises where embryo research is conducted, reviews consent processes etc. Facilities or researchers that do not comply with the Code of Practice and standards set by the HFEA may have their licences removed. All IVF clinics where embryos are created for treatment purposes are inspected by the HFEA and by the Healthcare Commission.

### Other tissue used in research

The use of other tissues in the creation of stem cell lines is regulated in the UK (other than Scotland) by the Human Tissue Authority, which also licences and inspects premises which store tissues and cells for research purposes. The Human Tissue Act 2004 sets out the requirements for consent to store and use tissue from the living or the deceased in England, Wales or Northern Ireland. In Scotland, the Human Tissue Act (Scotland) 2006 makes similar provisions but only for tissue from the deceased.

### Stem cell therapies

In the UK, three statutory regulators share the responsibility for therapeutic applications of stem cells: the HFEA regulates uses of embryos, the HTA regulates cells for human application and the MHRA regulates products being used as therapies.

There are guidelines in the UK governing the introduction of innovative therapies in the NHS such that they must be used either within a research project with REC approval or as an innovative procedure with approval from the NHS Trust Clinical Governance Committee. Therapies could be used in the UK private sector outwith a clinical trial, but they would still require approval by the HTA and possibly also the MHRA.

In addition, before stem cell lines may be used for treatment purposes in the UK, they must satisfy additional regulatory processes relating to the human application of cell lines and to use of cell lines as therapeutic products. These are covered by two separate sets of regulations, both derived from European Union (EU) Directives. Each sets up a regulatory authority, as detailed in the following table.

Human Tissue (Quality and Safety for Human Application) Regulations 2007	These regulations give the Human Tissue Authority (HTA) power to license establishments to store, test, process or distribute cells for human application.*
Medicines for Human Use (Clinical trials) Regulations 2004	Authorise the Medicines and Healthcare Products Regulatory Agency (MHRA) as the UK regulator, to license clinical trials and therapeutic use of medicinal products and devices.**

\* These regulations transpose into UK law the 2006 European Union Tissue and Cells Directive.

\*\* These transpose the 2001 European Directive relating to medicines for human use. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use [www.europa.eu.int/eur-lex/lex/LexUriServ/LexUriServ.do?uri=CELEX:32001L0083:EN:HTML](http://www.europa.eu.int/eur-lex/lex/LexUriServ/LexUriServ.do?uri=CELEX:32001L0083:EN:HTML)

An additional EU protocol relating to Advanced Therapies deals with therapeutic uses of non-embryonic stem cells. This stipulates that stem cell therapies are to be regulated under the European Advance Therapies Directive and reviewed through a centralised European system by the European Medicines Agency (EMA). There are therefore several regulators involved in developing stem cell therapies for clinical use. An overview of how they will oversee has been provided and further discussions are underway to ensure this process is as streamlined as possible.<sup>34</sup>

Results of recent animal research suggests that it may be possible to 'reprogramme' adult somatic cells using various factors, and induce them to take on 'embryo-like' qualities, and become pluripotent. In that case, Government and regulators would need to determine if such induced pluripotent stem cells (iPS cells) should be treated as embryonic or adult tissue.

### UK Stem Cell Bank

The UK Stem Cell Bank, established in 2002, was the first in the world. It is based at the National Institute for Biological Standards and Control (NIBSC) and is funded jointly by the BBSRC and the MRC. The bank recently made available its first four research-grade stem cell lines. More will be available imminently. Good Manufacturing Practice (GMP) facilities are being constructed for the deposition and ultimate distribution of clinical-grade stem cell lines for transplantation. Confidence in the UK oversight arrangements has persuaded a number of overseas laboratories to deposit lines: of the 40 registered, some 20 are non-UK derived. It is a condition of funding by the MRC and BBSRC that any stem cell lines derived in research are deposited in the Bank, although this is not a requirement of an HFEA research licence.

The Steering Committee of the bank also acts as a non-statutory regulator of stem cell research. All research in the UK involving the use of hESC lines must comply with the Steering Committee's code of practice for the use of human stem cell lines.<sup>35</sup> This applies to hESC lines obtained from the UK stem cell bank, as well as those obtained from other sources. Approval is granted for individual projects.

### CHINA

#### Use of human embryos in stem cell research:

In China, hESC research is regulated at national level by ministerial guidelines, the "Ethical Guiding Principles on Human Embryonic Stem Cell Research",<sup>36</sup> which contain similar proscriptions to the UK legislation:

- embryos may not be developed beyond 14 days
- embryos used for research purposes cannot be implanted into a human or any other animal

However, the guidelines include no provision for national supervision to ensure their implementation. They are couched in relatively general terms and lack detailed codes or protocols for implementation. They merely require research institutions to formulate "detailed measures and regulatory rules" and to establish an ethics committee to supervise hESC research.<sup>37</sup>

The Chinese guidelines for hESC research prohibit the buying and selling of human eggs, sperm, embryos and fetal tissue and stipulate that all gametes and tissues must be voluntarily donated and that informed consent is required. In addition, the "supply side" of hESC research is governed in greater detail by the MOH's regulations on reproductive medicine. There is national oversight of these regulations through a licensing system for IVF centres.<sup>38</sup> The regulations on reproductive medicine forbid super-stimulation as opposed to therapeutic stimulation of the ovaries. Embryos can be created only for the purpose of procreation but, after treatment, supernumerary embryos may be donated for medical research. These guidelines state that informed consent must be obtained from the donor, but do not include specific detail of this procedure. In China, unlike in the UK, there is no requirement to separate the procedure for obtaining consent to donate from consent for treatment itself.

In the combination of human and animal material to create embryos, the Chinese regulations clearly prohibit the hybridisation of germ cells. However, we heard conflicting views about whether somatic cell nuclear transfer (SCNT) using animal eggs and human nuclei was currently permitted in China. Such work has been performed there in the past, prior to the promulgation of the national guidelines for hESC research.<sup>39</sup> An earlier set of guidelines, produced by the Ethics Committee of the Chinese National Human Genome Centre in Shanghai, had indicated that it would be permissible, subject to safeguards.<sup>40</sup> However, we were told by members of the MOH ethics committee that such work would not be permitted under the current national guidelines. However, this matter is, we believe, under consideration at the MOH. At present, the regulations state that it is prohibited to hybridise human germ cells with germ cells from any other species. It is, therefore, perhaps open to interpretation whether cytoplasmic hybrids may be created. Of course, it would be extremely unwise for a researcher to attempt such interpretation. The work would need to be discussed with the relevant institution and ministry before any collaboration could be considered. When considering research work in China, it is important to consult the most recent guidelines and to obtain an accurate translation, particularly in a field as complex and controversial as embryo research, where the detail of precisely which techniques are or are not permitted is all too easily lost in translation.

35 <http://www.mrc.ac.uk/PolicyGuidance/EthicsAndGovernance/StemCells/UsingTheUKStemCellBank/index.htm>

36 The guidelines were officially promulgated by MOST and MOH in January 2004.

37 The composition of the ethics review committee is discussed in the Guidelines and there is a requirement that it includes 'research and administrative experts in biology, medicine, law and sociology'. An official translation of the full text is provided in the Appendix.

38 Hepeng Jia "China cracks down on malpractice in fertility industry", SciDev.Net, 10 April 2006. Accessed on 21 March 2007.

39 See, for example, Y Chen et al, "Embryonic stem cells generated by nuclear transfer of human somatic nuclei into rabbit oocytes", Cell Research 13:4, 2004, 251-63.

40 Ethics Committee of the Chinese National Human Genome Center, "Ethical Guidelines for Human Embryonic Stem Cell Research", Kennedy Institute of Ethics Journal, 14, 2004, 47-54.

## Fetal Tissue

As with gametes and embryos, the sale of fetal tissue is prohibited in China. However, research on stem cell lines using tissue from spontaneous or induced abortions is permitted.

## Stem cell therapies

In China the regulation of innovative stem cell therapies, such as autologous stem cell transplants, appears to be under-developed. Although hESC are tightly controlled, adult stem cells are not. It is not clear which government body is responsible for policy in this area. There are already companies in China which offer a range of unregulated stem cell treatments for a wide range of diseases. Many of these have not been evaluated through full clinical trials. The SFDA indicated that cell line therapies, as biological products, would not come under their remit and would be overseen by the MOH. However, it appears that such therapies are the responsibility of one of SFDA's agencies, the National Institute for the Control of the Pharmaceutical and Biological Products (NICPBP) which covers the quality control of pharmaceutical and biological products in China. It was involved in what is, as far as we were able to discover, the only approved Phase I clinical trial of a stem cell therapy in China. The researchers involved, from the Centre of Excellence in Tissue Engineering (a collaboration between Peking University Medical College and the Chinese Academy of Medical Sciences) worked with NICPBP to create a quality control standard for the stem cells they are using in this trial.<sup>41</sup>

A recent document from the MOH in China relating to medical technology use includes autogenic and allogenic stem cell transplantation as Class III medical technologies<sup>42</sup>. The release from the Ministry states that heterogenic and cloned stem cells should not be used clinically at present. Institutions already using these technologies will be subject to a reporting and inspection regime that will be implemented by the MOH. Details of the review and inspection processes are not available at time of publication. It will be important for researchers in related areas to ensure that collaborations in China comply with these requirements.

## Stem cell banks in China

Over the next five years the Chinese Government is funding the development of five stem cell banks which will focus mainly (but not exclusively) on hESC lines. One bank, based in Shanghai, will have GMP facilities and will focus on achieving clinical grade lines.

## 2. Are these frameworks compatible, such that collaborative projects would be acceptable in both countries?

Overall, the Chinese guidelines have affinities with UK regulation. Both China and the UK prohibit research on embryos beyond 14 days, reproductive cloning and implantation of human embryos used in stem cell research. It is encouraging that both countries appear to have adopted very similar policies towards the creation of hESC lines and it would seem that the frameworks for research are, at present, largely compatible judged by their principles. We expect that the creation and use of human admixed embryos, including true hybrids, will become legal in the UK, subject to conditions and under a licensing system. At present it appears that such work may not be permitted in China. It remains to be seen whether work with entities such as cytoplasmic hybrids will proceed in China.

There are, however, important differences between the UK and China in how regulatory guidelines are implemented and enforced in practice. The Chinese guidelines contain no equivalent to the UK's licensing structure for facilities undertaking research on human embryos or oversight of work involving hESC lines. There is no national infrastructure for monitoring and inspection and; as in other areas of research ethics, compliance appears to depend on ethics committees created by individual institutions. As we have already discussed, there are reasons for concern about such committees, including the limited ethical expertise available at individual institutions. In the case of hESC research, the same committees deal with both scientific and ethical aspects of research, giving rise to potential conflicts of interest. Finally, there is no requirement for the independent or lay representation on review committees that is demanded in the UK. Since Chinese institutions are largely self-governing, potential collaborative partners should carefully scrutinise their ethical regulations and the institutions and procedures that have been put in place for ethics review.

Considerable interest in the UK system of regulation was expressed during both the visits to China and the visit of Chinese delegates to the UK. During the latter, delegates met representatives of the HFEA and discussed the processes for licensing research activity. Many of the stem cell scientists whom we met were supportive of some system of external regulation, partly to discourage less well governed facilities and also to provide increased reassurance for international collaborators and reviewers.

<sup>41</sup> The trial is testing the use of mesenchymal stem cells in co-transplantation of haemopoietic stem cells for leukaemia patients. Lianming Liao, Lingsong Li and Robert Chunhua Zhao, "Stem cell research in China", *Philosophical Transactions of the Royal Society B* (2007) 362 (special China issue), 1107–1112.

<sup>42</sup> The Management Methods on Clinical Application of Medical Technologies, Ministry of Health translated by RC-UK office Beijing. Full text in appendix



### 3. What are the risks in conducting collaborative work in stem cell research?

Risks to potential collaborations are posed by lack of implementation of the guidelines governing this research in Chinese research facilities and by the absence of an oversight system to give external assurance of compliance. Whereas in the UK, funders of research are able to rely to some extent on the regulatory authorities, such as the HFEA, to license and inspect research premises and to confirm that relevant legislation and guidelines are being adhered to, there is no equivalent national oversight in China. The MRC must therefore consider how to ensure that the requirements of both Chinese and UK law and guidance are being met.

In the specific case of embryonic stem cell research, two particular areas require careful thought when any proposal for collaborative work is considered:

#### a. The source of cells, gametes or embryos

Materials used in collaborative research should be obtained in accordance with guidelines and research ethics in both countries. Where these differ the stricter of the two requirements should apply. This will require careful attention in any collaboration with China: the rules regarding consent procedures are much less stringent than they are in the UK and the system of oversight is problematic.

**hESC research:** Although the Chinese guidelines governing IVF and hESC research state that informed consent must be obtained from the 'subject' of such research, the guidelines do not ensure a clear separation between the procedure for obtaining consent to donate embryonic material for use in research from consent by a potential patient for IVF treatment. Even in leading IVF clinics, consent to donate for research may be obtained simply by the patient's placing a mark in a check box on the consent form for the IVF treatment itself. Ethics committees reviewing the arrangements for consent have differing levels of training and may lack experience. The lack of independent and lay representatives on the committee could compromise the committee's judgement. There is no external audit or review of the consent process and so, even if the ethics committee is satisfied with the formal procedure, its application cannot readily be verified.

**Adult and fetal research:** as detailed above, the other tissues used in the creation of stem cell lines are regulated in the UK (other than Scotland) by the Human Tissue Authority. There is, as far as we were able to ascertain, no equivalent oversight of the use of adult and fetal tissue for research in China.

#### b. The creation of embryos and use of SCNT

Collaborative research projects should be limited to procedures that conform to guidelines and research ethics in both countries. This will require careful attention in any collaboration with China because the system of oversight is under-developed and also because the regulations may be less clear than they are in the UK, particularly concerning human-animal admixed embryos.

**Implementation:** In the UK this work clearly comes under the remit of the statutes described above (soon to be updated). In addition to this legislation and the external scrutiny that it established, the MRC and other funders require stem cell lines derived from funded research to be deposited in the UK Stem Cell Bank and researchers must declare the provenance of all cell lines. Although the guidelines in China place restrictions on the creation and use of embryos for research that are similar to those of the UK, there is no mechanism to verify whether they are adhered to, other than reliance on institutional review and governance and the actions of the individual research teams. This places much greater responsibility for governance on individual research teams and their supporting institution. A further check on governance is provided by scientific journals which will require confirmation of aspects of ethics and governance prior to publication.

**Human-animal admixed embryos:** One of the issues arising during the passage of the revised Human Fertilisation and Embryology legislation in the UK is how animal embryos containing human material should be regulated. We anticipate that the legislation will be revised to allow certain combinations of human and animal material, creating human admixed embryos. As discussed above, it is not clear whether any of this work would be permissible under current Chinese guidelines, although this matter is, we believe, under consideration at the MOH. It is important to continue to review this area to ensure that any collaboration undertaken in China is compatible with a legal framework in the UK that may become more permissive than current requirements in China. We expect the UK legislation, once enacted, to define which embryos will be accorded the status and respect of human embryos. Separate discussions between the Home Office and other regulators are expected to clarify governance arrangements for animal-human embryos that lie beyond the remit of the human legislation.

### c. Human application, clinical trials and therapeutic use

Chinese bioethicists are wary about the rapid push for translational research in China, concerned that the results of basic biomedical research may be applied too hastily in the clinic. The general situation regarding the regulation of clinical trials is discussed in detail in the next section, but translational research involving stem cell therapies poses specific challenges.

In the UK, the regulatory path for developing therapeutic applications of stem cells is relatively clear.<sup>43</sup> The HFEA regulates uses of embryos, the HTA regulates cells for human application and the MHRA regulates products being used as therapies. In China, however, it is not yet clear which, if any, government body is responsible for regulation. The problem is exacerbated by the lack of a framework or body to monitor the boundary between clinical trials and innovative treatment. Relatively few hospitals in China have clinical ethics committees: these are only required if the hospital provides assisted reproductive technology (ART) or organ transplantation. This is a particular problem in areas of uncertainty surrounding certain innovative therapies, such as autologous stem cell transplants where the regulatory situation is unclear. Researchers should be wary of getting involved in such work in China until the regulatory system has been clarified and developed to the point where it can provide the necessary levels of reassurance both bioethically and technically.

Given the current state of the Chinese healthcare system there are strong commercial incentives for hospitals to obscure boundaries between appropriately regulated clinical research and experimenting with highly profitable but unproven therapies. In China, some hospitals are involved in the commercial exploitation of what appear to be unproven stem cell treatments – for example, the Nanshan Hospital in Shenzhen claims to have treated “around 1000 patients” with stem cell preparations.<sup>44</sup> These treatments are not being formally evaluated through clinical trials, as would be required in the UK before general clinical use. It is not clear whether these treatments are reviewed and regulated. CURE was not able to explore this area further in the time of this project, but it deserves further attention.

### 4. Are there ways in which these risks could be mitigated?

When considering potential international collaboration in stem cell research, careful attention must be paid to ensure that tissue has been obtained in accordance with UK standards. This is to ensure that scientific and ethical integrity is maintained in areas outside UK regulation and to minimise the risks of the MRC being associated with poor science or ethics.

It is crucial to examine the composition and operation of the ethics review committee or IRB as these determine whether high ethical standards are applied in practice.

Since regulation and governance are relatively weak in China, the UK collaborators in any potential UK-China research partnership are responsible for assuring themselves that robust ethics review procedures are being complied with in their collaborating institution. This does not question the integrity of most Chinese researchers in this area. We were impressed by how seriously our Chinese colleagues addressed these issues, and by the internal procedures developed in many of the leading research institutions. However, despite the guidelines, implementation of ethical governance is currently underdeveloped and there are fewer external checks on the conduct of research in China than in the UK.

#### Issues in embryonic stem cell research

- Implementation of national and international guidelines
- Ethical review of research procedures
- Source of embryos and consent for use
- Regulation of human admixed embryos
- Translation of stem cell research into clinical practice

## 2. Clinical trials and vaccine research (emerging infections)

There are many reasons why UK researchers might seek to collaborate on clinical trials in China. Conditions, such as cancers and heart disease are prevalent in both countries. Collaborative studies have the potential greatly to increase the power of a trial and speed of recruitment. Other conditions, in particular emerging infections, such as avian ‘flu or SARS, are present in China, but do not yet exist in the UK. China provides the opportunity to assess vaccines and other strategies. China’s enormous population allows large scale trials to be conducted in one country. A large segment of the population is not taking Western medicines and can be regarded as ‘treatment naïve’, allowing accurate assessment of the benefits of trial medications.

43 [http://www.hta.gov.uk/search.cfm?FaAreaI=CustomWidgets.content\\_view\\_1&cit\\_id=349&useCache=false](http://www.hta.gov.uk/search.cfm?FaAreaI=CustomWidgets.content_view_1&cit_id=349&useCache=false)

44 See [www.nanshanhospital.com](http://www.nanshanhospital.com)

Conduct of clinical trials in a country different from that of the funding agency, sponsor or researcher raises issues, not necessarily unique to China. These include ethical review, treatment in placebo arms and post-trial benefits which have been considered at length in other publications. Although China is not a developing country in the usual sense, some parts of the country are and its regulatory regime is being developed. Thus, the policies guiding the conduct of trials in developing countries should apply. The MRC's policy is based on the report of the Nuffield Council on Bioethics: *The Ethics of Research Related to Healthcare in Developing Countries*<sup>45</sup>. It is set out in the document: *'Research Involving Human Participants in Developing Societies'*.<sup>46</sup> The following discussion below considers the structure of regulation and implementation in China, how this relates to the UK environment and whether the principles in the two documents referred to above are relevant.

## Regulation of Clinical Trials in China

The main regulatory documents are the 1999 Drug Clinical Trial Regulations produced by the State Food and Drug Agency (SFDA), the 2001 Drug Administration Law of the People's Republic of China (PRC) and the associated Regulations 2002. Separate regulations deal with medical devices. The 1999 Regulations were promulgated by the SFDA. Trials are required to undergo ethical review and to comply with the principles of the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) Guidelines. These include the requirements to provide information to participants and to obtain their informed consent. The research must be 'scientific and reliable'. The 2001 Law passed by the People's Congress makes provisions for clinical trials in articles 29 to 31 (see Appendix for text) which are expanded in the 2002 Regulations. The 2001 Law includes details of the information about safety and efficacy that must be submitted for review by the SFDA before clinical trials may begin. Adherence to GLP and GCP is required in pre-clinical and clinical drug trials. The details of the GCP and GLP standards are set by the SFDA. The Regulations contain slightly more detail than the law. They allow the SFDA to authorise provincial offices to conduct site inspections, review the documentation submitted and test drug samples.

The SFDA<sup>47</sup> is the regulator of medicinal products in China and, like the MHRA in the UK, is responsible for medical devices. Like the FDA in the US, it is also responsible for food safety and regulation. The SFDA has a central headquarters in Beijing with around 180 staff and each province has a provincial FDA with city or local FDAs for smaller areas. Altogether, over 40,000 staff are involved. It was not clear from our discussions with the SFDA how autonomous the provincial and local FDA offices were from the HQ or how they were monitored or inspected.

The SFDA reviews all proposals for clinical trials of medicines in China, including trials of new products and of products already licensed abroad. The set procedure for review of applications for approval of clinical trials<sup>48</sup> is set out as a flow chart in the Appendix. All clinical trials, including Phase I trials, must be conducted at certified centres. A licence may only give permission for trials of certain types of drugs (e.g. antibiotics) or for certain phases of trials. Nationwide, there are approximately 160 hospitals certified to conduct trials of various kinds. These are open to random inspections by the central SFDA while individual clinical trials are open to inspection by local FDA officials but, after our meeting with the central SFDA, we were uncertain how often such inspections occurred. Clinical trials are reviewed by the hospital IRB at the sites where the trial will occur. Serious Adverse Events (SAE) are reported to the local and central FDA office. The central SFDA office knew of no trial that had been stopped following a SAE.

Both in our discussions and in the regulations themselves, frequent reference was made to the principles of Good Clinical Practice (GCP)<sup>49</sup>. The SFDA cited these international standards as the standard which trials in China should meet and against which they are inspected. Adherence to standards of international GCP was also evident in the discussions held with Sinovac, a company conducting trials of vaccines. Trials conducted by companies such as this will be used as the basis for applications for drug marketing within China and internationally. The documentation seen during our brief visit was compatible with the requirements of GCP, whether in the UK or another jurisdiction.

Clinical trials in China may involve new products being developed in China - such as the vaccines from Sinovac - or they may be in support of applications to market in China products already licensed elsewhere. All the latter products, except generic HIV treatments, have to be tested again in Phase II and III trials before being licensed by the SFDA. Re-testing is justified by possible pharmacogenetic variations in drug metabolism in the Chinese population which might lead to potential differences in drug safety and efficacy. So, for example, Peking University Medical College (PUMC) does 6-7 trials a year for drugs already registered overseas. Each of these trials requires approval from the IRB.

45 <http://www.nuffieldbioethics.org/go/ourwork/developingcountries/introduction>

46 <http://www.mrc.ac.uk/Utilities/Documentrecord/index.htm?d=MRC002461>

47 <http://eng.sfda.gov.cn/eng/>

48 <http://eng.sfda.gov.cn/cmsweb/webportal/W45649089/A64002920.html>

49 <http://www.mhra.gov.uk/Howweregulate/Medicines/Inspectionandstandards/GoodClinicalPractice/index.htm>

Trials carried out by international companies in China may involve products already licensed abroad or they may be initial trials of a product. At one meeting, it was suggested that the latter would need to have been licensed overseas before trials in China, but this has not been confirmed. Some companies have established direct collaborations with Chinese hospitals for early drug development through direct liaison with the Principle Investigator in the hospital. These still require IRB review by the hospital concerned. More commonly, applications are made to the SFDA which then selects a host hospital for the trial.

There have been many reports about difficulties with the regulation of medicines in China<sup>50</sup> and specifically in 2007 the problems at the SFDA.<sup>51</sup> There were concerns about the pharmaceutical industry in China: quality of production, the large number of 'copy-cat' generic drugs and the transparency and independence of procedures for approving clinical trials and drug licensing. These concerns culminated in the arrest and execution of the Director of the SFDA, Zheng Xiaoyu, on corruption charges. We met officials of the SFDA several months later and were informed that the SFDA had been radically reformed. The impact of these changes can only be assessed through continuing dialogue with the SFDA. The MHRA in the UK is in contact with the SFDA and a bilateral agreement between the two agencies has recently been signed.

### Clinical Trials Relating to Emerging Infections

The China Center for Disease Prevention and Control (CDC) is a key body in research on communicable and infectious diseases, as well as 'public health management' and preparing for potential epidemics.<sup>52</sup> Like the SFDA, the CDC has a central office and a network of provincial offices, which are linked to the local provincial governments.

CDC has research centres and also sample and data collection outposts throughout the regions. There are a total of approx 2600 CDC surveillance centres throughout China. These have 40,000 computer terminals to collect the surveillance data, which are linked to hospitals. Central CDC has scientific and professional contact with these surveillance centres but they 'belong' to the local governments. Some of the surveillance data are available on MOH website, full data are accessible internally through the CDC website.

CDC has 18 different sub-centres for research with laboratories. Five of these research laboratories are for infectious disease. Others are for public health, hygiene etc. Those relating to infectious disease are:

- Institute for Viral Disease Control and Prevention
- National Institute for Parasitic Disease
- National Centre for AIDS / STD Control and Prevention
- National Centre for Tuberculosis Control and Prevention
- National Centre for Chronic and Noncommunicable Disease Control

CDC has strong interests in vaccine development and infectious disease treatment e.g. antiviral treatments such as cytokines and interferons.

Some clinical trials of relevant products are done in CDC clinics. For example, the vaccine study discussed with CURE members by Sinovac was conducted through local CDC centres. CDC does not design trial protocols – these are produced by the researchers whether commercial or academic (although we had the impression that in this field most are commercial) and are reviewed by SFDA and IRBs. The CDC role in these applications is to advise SFDA about the infectious disease and the appropriateness of the intervention to be studied. The SFDA decides the site of clinical trials, which could be a hospital or CDC site. Some of the latter are located within hospitals.

The US CDC has collaborative projects<sup>53</sup> with the China CDC and has joint programmes including an International Emerging Infections Program (IEIP) and influenza activities which are run through a joint office in Beijing.

### Regulation of clinical trials in the UK: similarities and differences

As discussed above, clinical trials in the UK are governed by the Medicines for Human Use (Clinical Trials) Regulations 2001. These implement the European Directive on clinical trials, which applies to all EU member countries. The regulations make adherence to the ICH standards of GCP mandatory. They also require ethical review and approval of a trial protocol before it starts. There are detailed requirements for maintaining trial documentation. Requirements in the UK and China are similar, for example, adherence to GCP and GLP. In the UK, the MHRA is the competent authority overseeing licensing of all clinical trials of medicinal products and devices.

The MHRA reviews pre-trial safety and efficacy data before licensing a drug for use in a clinical trial. It is responsible for marketing authorisations in the UK, post-marketing surveillance and inspection of clinical trial sites. In China, we did not review the process of inspecting trial sites in detail as this is carried out by provincial FDA offices.

50 Nature Biotechnology 2006 24: 10; 1182-3

51 Nature Bioechnology 2007 25: 8; 835 - 837

52 <http://www.chinacdc.net.cn/n272562/n275958/index.html>

53 <http://www.cdc.gov/ieip/china.html>

Adherence to the guidance on GCP and other international standards is only one aspect of good governance of clinical trials. Of even greater importance are the processes that are followed in practice to meet these standards. Relevant study documentation must be available and must be consistent with clinical records and other paperwork. However, from the point of view of ethical standards, how the trials are conducted 'on the ground' is of the greatest importance in China and the UK. Documentation should reflect appropriate procedures for recruitment, consent and conduct of the trial.

## Particular points to be considered for collaboration

### Protocol

When considering collaborative research in trials in China, it is important first to justify the need for such collaboration, for example because of the number of participants required, to the prevalence of the particular disease or the uniqueness of the condition to China. The benefits to the participating countries may be different, for example, improving the power of the trial, building research capacity or increasing knowledge. Both parties should benefit.

China's insistence on re-testing products already licensed abroad may raise ethical questions. For example, if such products have proved efficacious in other countries, should they be used in placebo-controlled trials in China? However, it is unlikely that UK research funders outside the commercial sector would need to undertake such trials. This is not an area with which MRC is directly concerned at present and so is not considered further in this report.

### Approval

In the UK, the 'gatekeepers' for conduct of a trial are the MHRA and the REC. In China the equivalents are the SFDA and the IRB of certified hospitals. As detailed above, there have been concerns about the integrity of SFDA procedures and some of its senior staff. These may have been addressed but it is too soon to assess the impact of the recent reforms. The differences between UK RECs and the Chinese IRBs have been discussed above. The present composition of Chinese IRBs does not provide adequate assurance of their independence.

### Recruitment

Clinical trials are conducted at hospitals or other certified trial sites, such as CDC centres. In any clinical trial, it is essential that participants are provided with full information and are recruited from an appropriate population. The risks and benefits of participation should also be clear to participants. It is of note in relation to risks that many, if not most, Phase I trials in China are not true 'first-in-human' but rather 'first-in China'.

### Reimbursement

In China, the high costs of healthcare and medicines, and the dependence on local providers means that particular attention must be given to potential inducements to participate in research. Collaboration with China may offer attractive opportunities for large-scale recruitment, but potential UK collaborators must be alert to the risk that unethical inducements may be offered to potential participants. As with UK trials, these inducements may include payments to volunteers and, as in the UK, the nature and rationale for such payments must be scrutinised. UK reviewers need to be aware of the 'real' value of such payments in the Chinese context. For example, given the high cost of accessing health care in China, a 'free health check' may be a relatively greater inducement than it would be deemed to be in the UK.

### Consent

An important issue, discussed on many occasions was 'informed consent' to participate in trials (or medical research more broadly). This is also discussed above. All our Chinese colleagues accepted the need for individual consent, but opinions varied on whether consent was also a matter for the wider family and community. In China, at present, consent for medical treatment is required from a family member, as well as from the patient. This may in part be due to the potential involvement of the family in paying for medical treatment and in care of the patient after treatment. There is also a long tradition of requiring family consent for a variety of decisions affecting the medical care of patients in China.

In the UK, family and friends will often be consulted by potential participants in research and it is important to recognise the important support given by these people. However, the concept of individual autonomy and voluntary participation in research – without coercion – is a fundamental, albeit relatively recent, tenet of consent in the UK. Collaborative research projects must balance these two positions and respect the importance of family to many people in China without sacrificing individual freedom to consent. We must recognise that many factors play a part in giving consent in any country, including the UK. Trust in the researcher or doctor, altruism and financial considerations (especially in healthy volunteer studies) are also involved.

Gaining informed consent in the fullest sense relies upon a participant's being able to understand the information provided. This may require a basic level of education and understanding of science or medicine. As in the UK, this



may be a challenge for researchers, particularly in rural areas where educational levels may be generally low. This was highlighted in some discussions about information sheets provided by Western pharmaceutical companies, which were excessively long and complex for Chinese participants to understand. Similar concerns have been raised about studies in the UK.

During the visit, we found that the Case Report Forms (CRFs) for a vaccine trial were up to international standards. However, a full site inspection was not part of the remit of this visit.

### Monitoring

Although we visited a trial site, we did not do so with any intention of evaluating compliance with GCP standards. The discussions with researchers and commercial organisations indicated that a high level of understanding of and compliance with GCP standards was expected in clinical trials. It was less clear to what extent ongoing trials were subject to GCP-type inspections. Collaborative ventures should clarify how such trials would be inspected and by whom.

Allegations about SFDA's integrity, substantiated at several meetings, raised the concern that review by the SFDA alone might not be sufficient to ensure appropriate trial design and conduct. SFDA is currently undergoing a programme of reform and it was not clear to CURE how SFDA monitored trial procedures. Perhaps international collaborators, such as the MRC, should consider further steps to review trial design and product safety, over and above SFDA review. However, the current reforms in SFDA operations should be explored further. More information could also be obtained from internal and external organisations currently conducting clinical trials in China.

### Post-trial benefits

As with trials in other countries, the issue of post-trial benefits must be considered in China. This is particularly relevant for treatments that may not be routinely available or which would be prohibitively expensive for participants to continue. This topic has been considered in detail by the Nuffield Council on Bioethics and the MRC in previous publications. The principles set out in those reports certainly apply to research in China.<sup>54</sup>

#### Considerations for research involving clinical trials

- Protocol
- Approval
- Recruitment
- Consent
- Monitoring
- Post-trial benefits

### Specific issues relating to research in emerging infections

Infectious diseases, including SARS, avian 'flu and rabies, are important current or potential causes of morbidity and mortality in China. The development of vaccines against both emerging and established infections is, therefore, a priority for China making this country an advantageous place for trials to be based. Researchers should be aware that when they apply to conduct a trial in this field, data held by China CDC are used to inform SFDA about the best location for vaccine or other infectious disease trials. The level of consent and anonymisation of the CDC surveillance data, collected locally but held on large central databases, was not clear to us during our visits. It seemed that much of this data is not anonymised. Given that reporting of disease incidence is often mandatory, consent may not be in place for research uses of the data. UK researchers involved in collaborative trials on infectious diseases should ensure that, if they receive CDC data, it is anonymised. They should also ensure that appropriate consent has been given where such consent would be required in the UK for the proposed use of the data.

Vaccine trials raise the same ethical issues as those described in the previous section on clinical trials. Of particular relevance are those of consent and post-trial benefits for participants and the wider population. There are also issues specific to vaccine trials, such as exposure of participants to live agents in certain products. Another issue raised is that induction of antibodies. For example, antibodies induced as a result of participation in hepatitis vaccine trials could be misinterpreted as evidence of past of chronic infectivity. Measures must be taken to ensure participants in such trials suffer no disadvantage from this.

A regulation was passed in China in 2006 allowing fast track approval for vaccine in the event of a 'flu pandemic. This would ensure that a new vaccine could be approved within three days of submission for license. Our Chinese colleagues commented that, faced by an emerging infection, the priority in China would be to treat and prevent an outbreak whereas UK 'first thinks and talks about ethics'. It is important that ethical issues raised by the immense

<sup>54</sup> <http://www.nuffieldbioethics.org/go/ourwork/developingcountries/introduction> <http://www.mrc.ac.uk/Utilities/Documentrecord/index.htm?d=MRC002461>

health implications of pandemic infections should be taken seriously when considering how vaccines against these infections should be developed and approved. In the UK, the need to control an epidemic would not override any of the usual requirements for ethical and regulatory approvals for research. However, a very slow approvals process could have a devastating effect on the health of the population. This balance needs to be weighed in assessing trials of products aimed at emerging infections.

Post-trial benefits are of particular relevance to trials of vaccines for emerging infections and particularly pandemic 'flu. In the event of a pandemic, a vaccine targeted at the specific viral strain responsible could take months to develop and evaluate. It was estimated by CNCBD that this would take several months and that it would then take six months for Chinese companies to produce one to two million doses. Even if the vaccine were effective, there would, inevitably, be restrictions on its global availability. Several of the Chinese organisations we met raised this issue, asking whether, in these circumstances, international companies would release vaccines which had been tested in China to vaccinate the Chinese population. It would be unjust for 10% of the world's population to hold 90% of the vaccine, but such a situation is not impossible to envisage. Current research that attempts to boost the immune response to a pandemic 'flu virus by vaccination against seasonal 'flu may decrease the difficulties in this area, as these vaccines are much more widely available. Our colleagues at China CDC envisaged a strategy by which an increase in the uptake of seasonal 'flu vaccine would stimulate commercial production capacity, which could if necessary be redirected to produce a pandemic vaccine in the future.

Conduct of such research in China will require MRC, National Institute for Health Research (NIHR) or other collaborators to consider how such products would then be licensed in other countries, for example, the UK. Trials should be conducted in a manner that would ensure compliance with the UK regulatory process; this may require discussion with MHRA and other regulators. MRC guidance on conduct of trials would apply, which implies that international standards of Good Clinical Practice (GCP) would be expected to be implemented to allow harmonisation of standards. The SFDA requires GCP to be observed. Funders and sponsors of such studies should discuss with MHRA and industrial companies how results for trials in China might meet the requirements of the UK regulatory system.

Vaccine trials differ from other clinical trials in that large numbers of participants may be involved. The MOH ethics committee pointed out that there was a challenge to ensure that ethical review was incorporated into such large-scale clinical trials. In China, the current system does not allow for multi-centre or regional review and each participating centre needs to conduct its own review of a project. This may be time-consuming and lead to conflicting views on trial conduct. A further problem is that China's IRBs are largely composed of members affiliated to the institution that the IRB reviews and, as trials attract funding to the institution, there may not be mechanisms to prevent institutional rivalries affecting the decisions.

### 3. Traditional Chinese Medicine (TCM)

TCM refers to a broad range of diagnostic and treatment modalities. The common theme in all these approaches is that the person is diagnosed and treated on an individual and holistic basis. Treatment is not aimed at one specific symptom or disease but at restoring a balance to the body, lack of which manifests itself in symptoms and signs of disease. Medicinal treatments are based on plants and herbs. In addition, treatments such as acupuncture are used.

TCM has been practised for thousands of years and has had an important role in treating symptoms for centuries before the development of modern health care systems and it is very deeply embedded in Chinese society. It was suggested to CURE that 20 to 30% of the drug market in China is for TCM. The Chinese Government has made the evaluation of TCM a priority. CNCBD has an Office dedicated to the internationalisation of TCM. Development of TCM would have an impact on Chinese economic growth, in addition to its potential impact on healthcare. TCM and other herbal medicines are already used outside China: in 1999 the US Centers for Disease Control and Prevention estimated that 10% of the US population ingested herbal medicines<sup>55</sup>. It seems likely that this figure will have increased in the last decade. Although difficulties have been identified in conducting research in this area,<sup>56</sup> it is important to remember the huge importance of TCM to healthcare in China and also the growing use of these approaches within UK healthcare. The relevance to the UK lies both in the potential for new remedies to be identified and in the proportion of the population using herbal medicines in what is currently a relatively unregulated environment. This report focuses on potential UK collaborations for medical research and therefore we will focus on issues in TCM that are relevant to such collaborations. The question to be considered is thus whether it would be possible for the MRC to fund or sponsor collaborative research involving TCM in China. If such collaborations were possible, what ethical issues would arise?

55 What's in the Bottle Straus SE. *N Eng J Med* 2002 327 (25) 1997-8

56 Research and Evaluation of Traditional Medicine. Chaudury RR WHO Geneva 2005

### Regulation of TCM (China)

In China, traditional medicines are not licensed by the SFDA but by the State Administration for TCM (SATCM). Derivatives from traditional medicines, such as plants or herbs that are purified and marketed as medicines, would fall under the remit of the SFDA. Such products would thus have to undergo clinical trials in the same way as other medicinal products. However, most traditional medicines are administered as plants or herbs and do not come under the SFDA requirements.

The laws and regulations relating to Drug Administration (see above) refer to traditional medicines, translated as 'Chinese crude drugs'. There are broad principles controlling how such products should be produced and sold. Clinical trials of TCMs appear to be exempt from the requirement for an approval number for clinical trials.

### Regulation of TCM (UK)

In the UK herbal medicines such as most traditional Chinese medicines fall under the remit of the MHRA, who have recently defined three categories of such herbal preparations<sup>57</sup>:

#### 1. Unlicensed herbal remedies.

These products do not have to meet specific standards of safety and quality and so standards can vary widely. As the MHRA considers that this does not help the public to make informed choice or offer effective protection against low-grade and dangerous products, by April 2011 all manufactured herbal medicines will be required to have either a traditional herbal registration or a product licence (see below).

#### 2. Registered traditional herbal medicines.

A simplified registration scheme, the Traditional Herbal Medicines Registration Scheme, began on 30 October 2005. Products are required to meet specific standards of safety and quality and be accompanied by agreed indications, based on traditional usage, and systematic patient information allowing the safe use of the product.

#### 3. Licensed herbal medicines.

Some herbal medicines in the UK hold a product licence or marketing authorisation just like any other medicine. These are required to demonstrate safety, quality and efficacy (or effectiveness) and be accompanied by the necessary information for safe usage. These products can be identified by a distinctive nine digit Product Licence (PL) number on the product container or packaging which is prefixed by the letters PL.

There is therefore a deadline of April 2011 for herbal medicines in the UK to be either registered or licensed. These two categories deal with two of the main issues for research in TCM. The first is that of safety and quality, and the second of efficacy in clinical trials.

### Issues about research involving TCM and herbal medicines

These issues have been summarised by Professor Warrell, Chair of this Committee thus:

'Although the use of plant products is common to both Western allopathic medicine and traditional herbal medicine, the way in which herbal ingredients are prepared and the evidence of their efficacy and safety are strikingly different. The West's scientific method, involving rigorous definitions and trial design, randomisation and blinding to minimise bias, is in marked contrast to the accumulation of experience of many generations without clear comparison or controls which has established belief in many traditional remedies and encouraged their use over millennia.'<sup>58</sup>

These differences will be briefly considered further under two headings – the product and the methodology of research.

#### 1. Product

A key issue in the medicinal use of TCM (as opposed to techniques such as acupuncture) is the composition and quality of the medicine administered. Traditional herbal medicines have mainly been administered as whole plants or herbs or extracts of them. These may contain single or multiple active ingredients acting individually or synergistically. The ethos of Chinese medicine suggests that such treatments act holistically rather than on individual organs or disease pathologies. However, much effort has been devoted to isolating and purifying individual active ingredients that could be used in clinical trials.

Research involving herbal medicines needs to address the consistency of the composition and quality of herb administered. This may differ between practitioners and dispensaries. At present, herbal medicines do not, in the UK or China, have to be produced to the same standards as other medicines. There have been many problems with the

<sup>57</sup> The extract was adapted from the MHRA website: <http://www.mhra.gov.uk/Howweregulate/Medicines/Herbalandhomoeopathicmedicines/Herbalmedicines/index.htm>

<sup>58</sup> Warrell DA. In search of safe and effective remedies.

safety of herbal medicines<sup>59</sup>. This may be due to intrinsic properties of the herbal treatment (as is the case with St John's wort, the active ingredient of which, *Hypericum perforatum*, alters the metabolism of some other medications) or to contamination of the herbal remedy with other drugs or toxins. Researchers therefore have particular responsibility to ensure the safety and quality of products used.

It is the case that some herbal remedies contain an active ingredient that can be isolated and subjected to normal research methods. An example of this is found in the successful assessment of qing hao su. This venerable Chinese traditional remedy for fevers contains artemisinin derivatives that have proved to be the drugs of choice for treating severe, multi-resistant *Plasmodium falciparum* malaria.

## 2. Methodology

The efficacy of TCM is broadly accepted in China, but its wider international acceptance requires further validation. The current model for such validation in the UK and other Western countries is the randomised controlled trial. But this would involve assessing TCM by methods based on a very different approach to treating diseases. The following difficulties arise:

1. TCM is an individualised holistic treatment incompatible with the concept of randomisation and control. For example, it could be argued that an appropriate control would have to be an exactly matched individual who would be difficult, if not impossible, to provide.
2. There are difficulties in purifying the relevant extracts to use in a RCT and determining whether each has an individual effect. A plant or mixture may contain many ingredients that may interact with each other.
3. The proportions of these compounds may vary between preparations of the same product and so standardisation may be difficult.
4. Using a control or placebo arm in China raises an ethical problem as both the doctor and patient may believe that the efficacy and safety of the product is already proven. This makes it ethically difficult to withhold a treatment that the doctor or patient believes to be efficacious and safe in order to conduct the trial.
5. Conversely, assessment of TCM as a treatment may require withholding a Western medicine that is known to be effective, for example, in HIV - AIDS management.

In China there are at least twelve sites approved by the SFDA for TCM clinical trials – including the Academy of TCM in Beijing. Trials of some aspects of TCM have been reported in international journals. For example, there have been several studies on the efficacy of acupuncture in women undergoing IVF treatment – with varying results.<sup>60, 61</sup> The example of qing hao su has also been referred to above. So it is possible to assess aspects of TCM and herbal medicines using the methodologies required by UK regulators and researchers. However, the considerations above need to be addressed in order for such work to be undertaken. There also could be further discussion as to whether the RCT is necessarily the only methodology for assessment of TCM.

In summary TCM, including use of herbal medicines is a very widely accepted system of treatment in China. It is also used in many countries outside China, including the UK. However, as Straus commented in the New England Journal of Medicine in 2002

'both the quality of the data and the quality of the herbal products themselves must improve greatly if herbal medicines are to assume a respected place in the contemporary healthcare armamentarium'.<sup>62</sup>

In order to integrate Chinese medicines with Western healthcare systems evidence of safety and efficacy is required as are methods to standardise the treatments. In the UK such evidence, at least of safety and quality, will be mandatory by April 2011. There are difficulties in applying Western methodologies, in particular the RCT, to Chinese traditional medicines. These may be overcome, particularly if a single active ingredient can be isolated and purified from the TCM. Where this is not the case, however, researchers will need to consider whether it is possible to assess an individualised and often variable treatment within the frameworks imposed by Western regulators and scientific understanding.

### Considerations for research involving TCM

- Quality, purity and standardisation of product to be used
- Selection of participants – comparable groups
- Use of placebo and control groups
- Concurrent traditional or Western treatments being taken by participants

59 de Smet PAGM Health Risks of Herbal Remedies: an update Clin Pharm Ther 2004 76(1) 1 - 17

60 Effect of acupuncture on the outcome of in vitro fertilization and intracytoplasmic sperm injection: a randomized, prospective, controlled clinical study. Dieterle S, Ying G, Hatzmann W, Neuer A. : Fertil Steril. 2006 May;85(5):1347-51

61 A matched controlled study to evaluate the efficacy of acupuncture for improving pregnancy rates following in vitro fertilization-embryo transfer. Wang W, Check JH, Liss JR, Choe JK. Clin Exp Obstet Gynecol. 2007;34(3):137-8.

62 Straus SE Herbal medicines- What's in the bottle? N Eng J Med 2002; 347:1997-8.

## IV. SUMMARY AND RECOMMENDATIONS

CURE was asked to make recommendations for the management of China-UK research collaborations and the further development of mutual understanding in the area of research ethics, including suggestions for ways to maintain the communication and exchange of experience between China and the UK. These are discussed in this section, which comprises a summary of findings and two sets of recommendations for future policy. The first set of recommendations is directed towards the management of collaborative projects. The second set of recommendations raises strategic issues regarding the future direction of funding and policy of international collaborations with China.

### I. Summary of findings

This project has provided an overview of the current regulations and guidance in China relating to medical research. Chinese laws and guidelines cover many aspects of medical research as the regulation of research is rapidly evolving in China, many of these guidelines and regulations have been produced over the past decade. Ongoing review of the regulatory situation in China (and indeed the UK), is required to ensure that collaborations are governed appropriately, in accordance with the regulatory systems of both countries.

The more recently introduced guidelines in China frequently transpose international guidance, such as the ICH's GCP guidelines, into Chinese regulations. In many cases, Chinese regulations are particularly similar to UK regulations, for example for the conduct of clinical trials and embryonic stem cell research. The principles underpinning the standards governing the conduct of medical research in China are broadly compatible with those in the UK. There are, however, some aspects of medical research that are much more closely regulated in the UK than in China, such as uses of human tissues and data.

Moreover, the procedures for implementation of these principles, differs widely between the two countries. This is the key area of difference and the reason why close review of potential collaborations is recommended. The elite scientists and institutions we visited were clearly committed to adhering to international requirements, but the situation elsewhere remains unclear and it appears that the implementation and enforcement of the regulations is not as consistent as it is in the UK.

One area in which the differences between China and the UK are most marked is in ethical review of projects. Ethical review has followed the US model of institutional review boards (IRBs) but Chinese IRBs are largely composed of professionals associated with the institution and are often chaired by the director or a senior member of the research staff of that institution. We have described in detail the differences between review committees in the UK and China. For example, there is a clear requirement in the UK that RECs include members who are independent of the research teams, but this is not the case in China.

Another area of difference is the extent to which there is oversight of the conduct of research by regulatory agencies. The SFDA performs a similar role to the MHRA in reviewing applications for clinical trials, but the MHRA has a system of inspection that is more transparent and covers a greater proportion of clinical trial sites than we believe to be the case in China. In addition, given recent difficulties at the SFDA, further review will be required to determine if the current programme of reforms have fully addressed the problems.

China lacks national oversight of regulatory compliance for medical research. There is little inspection or review of compliance with the guidelines and it was not always clear what sanctions would be applied in cases of non-compliance. Adherence to guidelines therefore relies on the integrity of the institution and individual staff. In contrast, the UK has many agencies overseeing and, in some cases, licensing and inspecting aspects of research – including uses of human tissue and embryos. There are separate regulatory processes for gene therapy research and some research involving patient data. These added layers of oversight are often viewed as a burden by the UK research community, but they provide considerable assurance of appropriate conduct of research. This does not mean that research is conducted inappropriately in China, but it does place the onus on individual institutions to ensure compliance with regulations and good governance.

Particular issues were raised about the three areas in which CURE has taken a special interest: stem cells, clinical trials and traditional Chinese medicine. With respect to collaborations in embryonic stem cell research, particular attention should be paid to the source of embryos and procedures for obtaining consent for the use of embryonic material, which should be compatible with the regulatory requirements in place in both China and the UK. The situation in China regarding the regulation of human admixed embryos is unclear and needs to be monitored carefully. Any proposal involving the translation of stem cell research into clinical practice needs to be reviewed with great care,



as the regulatory situation in China lacks clarity and it is important to ensure that this is not exploited, intentionally or not. Research involving clinical trials should be reviewed carefully, including the protocol, procedures for approval, recruitment and consent, and the issue of post-trial benefits. It is important to ensure that there are monitoring mechanisms in place. For research involving TCM, attention needs to be paid to the quality, purity and standardisation of product to be used, the selection of participants and the use of placebo and control groups. Consideration should be given to the issue of concurrent traditional or Western treatments being taken by participants.

In addition to these particular concerns, another challenge, which has resonance across the spectrum of medical research in China is that of obtaining individual informed consent in a culture that places high value on family and 'filial piety' as well as the need for the individual to contribute to the wider community.

## **2. Recommendations: managing China-UK collaborative projects**

These recommendations are specifically addressed to the MRC. However, they may also be of relevance to other UK research funders, as well as clinicians and scientists involved in work in China.

The MRC must ensure the highest possible standards of governance of future China-UK collaborations. The Committee was in clear agreement that MRC-funded collaborations with China should never, under any circumstances, involve any abrogation of research ethics. To do so would risk undermining the integrity of research itself, as well as damaging public confidence in the research and support for international collaboration. If the UK, or specifically the MRC, is perceived to have been involved in unethical research, the negative effects on the reputation of the MRC and on future China-UK collaborations could be considerable.

It is clear that the maintenance of research ethics in China-UK collaborations will depend on the nature of the Chinese institution with which collaboration is proposed. Our current hypothesis is that any potential collaborative research needs careful discussion with the host institution in China and some review of the procedures undertaken there. The depth of this review will depend on the existing structures and procedures at the proposed partner institution. It may be appropriate to include some ethics components in the research protocol to gain further information into procedures in China, such as informed consent and IRB review.

We recommend that the MRC should focus on established centres of excellence when funding collaborations with China and seek to build durable relationships with these centres. There are a number of such centres emerging in China, characterised by good institutional governance as well as concentrations of investigators with international reputations and, in many cases, training and research gained outside China. In evaluating potential collaborations, we recommend that the MRC should look for both an international reputation in research, indicated by publications in international journals and funding from overseas funding agencies known to require tight ethical regulation, and for markers of good institutional governance. These include an international scientific review committee and well-constructed Institutional Review Boards with an appropriate proportion of independent members recruited from outside the institution.

Outside these established centres of excellence, the MRC will need to take proactive measures in all stages of planned collaborations to ensure that high standards of research ethics are maintained. In the following sections we outline some special measures that would help to ensure high standards of research governance.

We recommend that the MRC continues to discuss research ethics with Chinese counterparts and maintains the lines of communication developed through the CURE project – those Chinese colleagues with whom we discussed these issues universally welcomed the idea of such collaboration.

Furthermore, we recommend that, where the MRC cannot be confident that the monitoring and inspection procedures in China are robust, the MRC should take steps to remedy this by studying the situation and, where necessary, engaging with researchers and policy-makers to improve capacity. To this end, MRC should consider making provision for additional research to take place alongside international scientific collaborations, collaborating with appropriate experts to examine and analyse the approvals and research process, relating to the specific project and / or the general procedures in place at the collaborating institution. This could also include development or improvement of processes for ethics review or research governance. Such research would provide data on the rapidly evolving situation in China and allow the MRC to build relationships and develop confidence in an increasing number of institutions.

With regard to individual projects, the MRC and ethics committees need to satisfy themselves that appropriate mechanisms for consent are present. If there is any lack of clarity or confidence in this area, a research proposal could seek to remedy this uncertainty by incorporating elements such as the review of consent procedures, with the approval of the ethics committees.

On a broader scale, the MRC could consider funding research to develop knowledge of institutional governance and matters relating to research ethics in China. This increased depth of understanding could facilitate future collaborations. Clinical research programmes run in collaboration with the UK could provide the opportunity to act as platforms for such work.

### Ethics review

The process of ethics review and surveillance needs to be at least as rigorous when international researchers are working overseas, in countries such as China as well as less developed countries, as when research is conducted in the UK. All proposed collaborations should be fully scrutinised by both countries, following the relevant Chinese and UK procedures. There is precedent for this requirement in other bilateral relationships: for example, the US National Institute of Health (NIH) does not accept UK ethics review of collaborative projects between the UK and US without separate US review.

Under no circumstances should the MRC fund research that has not been judged acceptable by a UK ethics committee. We therefore recommend that, when considering the funding of international research collaborations, adequate ethics review should be a requirement for both sides of the collaboration. Where the collaborating partner lacks the requisite governance structures to perform such a review, the MRC should not merely ensure that its own review addresses the ethical adequacy of arrangements in China, but also should stimulate the development of appropriate structures. It is also important to encourage dialogue between the UK REC and Chinese IRB.

It is important for the MRC and research ethics committees to review the whole programme of research, including related projects as well as the specific piece of research for which funding and or ethics approval is sought. For example, where the proposed collaboration involves analysis of samples or data that have already been collected in the course of a clinical trial, the trial itself should be reviewed to ensure that it is being conducted in accordance with internationally acceptable guidelines. Our experience in China demonstrated that, even where MRC may not be involved in the conduct of the trial itself, its participation in a spin-off or secondary aspect of the trial is likely to be presented as an endorsement of that trial.

We recommend, therefore, that even where the MRC is only secondarily involved, the relevant UK RECs should require full information on, for example, the recruitment and treatment (including compensation) of participants in the trial and weigh such issues as the availability of post-trial benefits.

### Licensing and legal obligations

All research must comply with relevant Chinese as well as UK guidelines and legislation. The picture is complicated by the existence of regulatory pluralism in China, such as the differences between the national guidelines and the Shanghai recommendations on hESC research, and also by the differences in approach between different Chinese Ministries.

We recommend that the MRC ensures that all participating institutions and researchers have the required Chinese licences from all appropriate bodies to undertake their proposed programme of research. In the case of clinical trials, we note that, in China, an institution must have a licence (issued by the SFDA) to undertake such trials. Special approval is required to undertake Phase I trials: these licences may be limited to particular types of therapy. For example, a hospital may have a licence to conduct Phase I trials only for antibiotics and, if this is the case, that hospital cannot legally conduct any other type of Phase I trial.

Further, it is important to note that clinically active researchers must have the appropriate licences for the countries where they are undertaking clinical work. In the Chinese situation, according to the law governing medical liability in China, UK researchers must obtain a Chinese licence to practise before they may undertake clinical work in China.

It is also important for the MRC to be aware that researchers must ensure that all necessary permissions are in place on the Chinese side for international collaboration. In the past, foreign researchers who wished to undertake research in China had to seek approval from the MOH in China, as well as the appropriate organisations in their own country. The most recent MOH guidelines on biomedical research involving human subjects make it clear that foreign researchers must get permission from a Chinese IRB, as well as from an ethics committee in their own country.<sup>63</sup>

For the development of future co-operation, we recommend that the MRC seeks to build on the ties that CURE has established with members of the MOH Ethics Committee. Proposed collaborations can then be discussed with these members and their view sought at an early stage in planning such projects.

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63 “[Article 26] If any foreign institution or individual wants to carry out biomedical research involving human subjects in China, its/his research plans shall also be submitted to IRBs set up in China ...after they are examined by IRBs of the country or region where it/he lies.” “Measures for Ethical Review of Biomedical Research Involving Human Subjects”. See Appendix.

### Cultural and social context

For research involving human participants, the procedures specified in the protocol should be reviewed to ensure that they are sensitive to cultural differences and social context. For example: Does the protocol allow time for potential trial participants to discuss their proposed participation with their families if they wish? Is information provided in an accessible form? Careful attention must be paid to the wording of the consent form, bearing in mind the cultural (role of the family) and social context (poverty and lack of access to healthcare). We recommend that the consent procedure be reviewed with these issues in mind, and further, that information and consent forms are reviewed by native speakers familiar with the local context of the trial participants. Research designs should ensure that adequate time is set aside for oral discussion and explanations, particularly in areas where literacy levels are low.

The Committee agreed a strong commitment to improving the understanding of participants in research, whether in the UK or China, and recommends that the MRC should endorse this commitment.

Concerning incentives and inducements, MRC and funded researchers need to be aware of the different contexts that confront many potential trial participants in China, including poverty and problems with the healthcare system. Awareness of local (not national) context regarding salaries and the state of the healthcare system is important and should be taken into account in the evaluation of incentives and inducements to participate in a trial. They need also to be aware that there may be financial inducements for the hospital as well as for the clinicians and patients involved in a trial. We recommend that MRC reviews the level of payments or nature of inducements in any collaborative projects to ensure that they conform to current MRC policy and are not 'undue' inducements. In the UK this balance would need to be approved by the Ethics Committee: for China-UK collaborations it should be submitted for approval to relevant research ethics committees in both the UK and China.

### Mutual benefit

Mutual benefit sharing is very important, as well as respect for each other's guidelines, regulations and laws. There is a widespread perception of problematic attitudes and inappropriate actions by foreign researchers working in China. Concerns about the potentially exploitative nature of Western medical and pharmaceutical interest in China were voiced to us by a wide range of interlocutors, including scientists, bioethicists and policymakers. Chinese bioethicists emphasize that collaborative projects should meet Chinese needs as well as those of the sponsor and there should be a commitment to capacity building in China. In practice, Chinese partners may seek: 'collaborative research contracts that require that a certain proportion of the value-added research work be done in China, that research equipment be provided to help upgrade Chinese research capacity, and that the Chinese side have a share in any resulting intellectual property rights.'<sup>64</sup>

In order to avoid exploitation or accusations of exploitation it is important that the MRC seeks clarity, from the outset, regarding the reasons to seek collaboration on both sides of a proposed collaboration and an understanding about benefit-sharing. It should not necessarily create difficulty if part of this justification includes reference to the lower cost of carrying out the research in China, but if this is a motive, it must be balanced by specific mechanisms to ensure benefit to those Chinese researchers and subjects involved in the research. It would not, however, be permissible for any proposed collaboration, implicitly or explicitly, to seek to benefit from perceived or real less rigorous regulatory standards in China or from the greater permissiveness towards some kinds of research or translation to the clinic.

The MRC should be aware of the interests of Chinese collaborators. These may be entirely appropriate, such as the wish for international publication and recognition. However, they may also relate to the financial benefits associated with the collaboration, and the ethical implications of such inducements must be carefully assessed.

It is important to be clear about intellectual property issues before undertaking translational research, in the case of MRC-funded research, MRC Technology (MRCT) should be involved in these discussions.

### Ethics review and governance procedures

If the MRC is to ensure that acceptable standards of research ethics are maintained in China-UK collaborations, it must develop a good understanding of how ethical and scientific review is implemented in practice. However, the constitution of review committees and procedures varies considerably between different institutions in China. How can the MRC ensure that collaborations are well governed? The committee has given this matter much consideration and we would recommend a phased approach to funding for China-UK collaborations, as outlined below (see "Phase Zero").

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64 US Embassy, "Human Research Subject Protection in China: Implications for US Collaborators" 2000. Available at <http://www.usembassy-china.org.cn/sandt/humanresearchsubjectprotection.htm> accessed 20 August 2007.

We also recommend that the MRC introduces an extra stage in the pre-funding review process for China-UK collaborations, whereby the proposal would be scrutinised by one or two experts with experience and knowledge of Chinese regulation and science. It may be that MRC would wish this group to report to the Ethics, Regulation and Public Involvement Committee (ERPIC) of the MRC. In addition, the MRC should consider whether additional support and resources should be made available to enable those involved in evaluating the research ethics of proposals to determine, to their own satisfaction, whether adequate institutions and procedures are in place to ensure the maintenance of a high standard of research ethics. Site visits would be impracticable, in light of the burden they would place on reviewers and the competing demands on the time of REC members, but they may wish to bring in expert advice on China to aid them in their deliberations. REC members may wish to meet the scientists who would be involved with the collaboration in the UK and in China. Funds should be made available to ensure that travel expenses can be reimbursed.

As we discuss in the next section, the MRC should encourage the integration of ethics training into the training for Chinese clinicians, scientists, social scientists and associate professions. In the context of a specific proposal for collaboration, this could include, for example, providing funding for workshops or training for the proposed collaborative partners in China. In the light of some concerns about the operation of China's IRB system, the MRC should consider support for capacity building in research ethics review and governance in the hospitals and other research sites. We recommend that the MRC should accept only those Chinese IRBs that fulfil the criteria for RECs in the UK, including lay and patient representatives who are independent of the hospital. It would also be desirable if Chinese IRBs followed UK convention by selecting the chair from amongst the lay representatives.

The MRC may wish to follow the model suggested by its Ethics Regulation and Public Involvement Committee (ERPIC) for the egg-sharing project in Newcastle and commission social science studies of particularly sensitive projects. Such work could draw on existing expert knowledge regarding research regulation in China.

#### “Phase Zero”

The Committee recommends that potential MRC-funded collaborators should be able to apply to MRC for funding for an initial “Phase Zero”, lasting six to twelve months. Phase Zero funding would provide a way forward for potential collaborations between China and the UK in circumstances where relationships between the would-be collaborators need to be developed further to ensure the success of their collaboration, for example, by providing the resources to resolve any uncertainty about governance issues. This initial phase would be conceived as a period during which relationships and institutional developments might evolve before start of the research itself. It could provide knowledge relating to governance or ethics of the proposed project or allow for a period of capacity-building within the proposed team. Although further funding for later phases of the research could be allocated to the project at the same time, we suggest that this further funding should remain conditional on the satisfactory completion of Phase Zero.

The aim of Phase Zero funding is to develop the teams: lab exchanges could familiarise the researchers with the science and with each other; building the relationship between Chinese and UK participants. These exchanges should help to satisfy the MRC that institutions on both sides have appropriate structures in place to ensure the research is well governed and to develop the regulatory knowledge base and capacity amongst the researchers. It is important that collaborators in both countries should understand the laws, regulations and potential issues in both one another's countries. Trust and relationships, important in any scientific collaboration, are crucial in China.

This phase could involve exchange visits and fellowships, for example funding students and junior researchers from China to spend time developing their skills in the UK, either through further study or by working with a UK group. In addition to building the foundations for the collaborative project, such exchanges would provide the opportunity for professional development, contributing towards capacity-building goals and providing clear benefits for Chinese participants in collaborative research. This capacity-building could be focused on scientific or ethics topics – or both.

Where collaboration is already established, the MRC would not necessarily require the researchers to complete a Phase Zero, but funding should still be made available if the MRC considers that it would provide assurance of governance or be of benefit to the project or researchers.

In addition, for larger projects or research in areas of particular concern or sensitivity, the MRC should provide funding for expert evaluation of the research governance structures. Such evaluations should take full advantage of existing experience of research regulation in China, drawing on the knowledge of UK research centres with such experience.

#### Scope of additional procedures: which proposals should be scrutinised?

Some members of the committee suggested that additional review, restrictions and requirements should apply only to certain areas of research that were particularly sensitive or perceived as raising especially difficult issues of research ethics. However, our considered view was that it would not be possible to specify in advance which areas of research were likely to prove difficult and that such an approach might prove unduly restrictive given the rapid development of biomedical research and regulation in China.

The committee also discussed whether collaborations with other countries, apart from China, should be considered for this type of special review. We recommend that the MRC should carry out an initial review of governance procedures in each country where potential collaborative research might take place, and establish a list of those countries where special review procedures as described above should be required.

### 3. Strategic issues

In order to implement many of the recommendation above, the CURE committee recommends the following policy issues for further consideration by the MRC, bearing in mind the MRC's long term strategy and goals:

- Strategic issues in the funding of collaborative research
- Support for ethics review capacity building in China-UK collaborations

#### (a) Strategic issues in the funding of collaborative research

The development of biomedical research in China has excited international attention. Other countries have established joint research centres in China, working with partners such as the Chinese Academy of Science and the NSFC (see box). Such long term relationships can be developed gradually and can offer considerable benefits for both sides. Benefits for the MRC could include the facilitation of China-UK collaboration by improving the visibility of UK biomedical research in China and the opportunity to disseminate UK research and research ethics practice in China. The MRC should consider the examples provided by other countries that are building up collaborations by working with trusted partners in China.

A further potential benefit for UK researchers could be improved access to Chinese data and samples. China is not only an emerging science power but also an important site for research on global health, particularly on emerging infections. In relation to this area, the US CDC is collaborating with China CDC on an International Emerging Infections Program (IEIP) and has opened a Program Office in 2006 inside the offices of China CDC.<sup>65</sup>

#### Examples of International co-operation with China

##### France

France collaborated with CAS and the Shanghai municipal government to establish “Institut Pasteur of Shanghai, Chinese Academy of Sciences”. The institute has French and Chinese funding, and is focused on infectious diseases under the supervision of a French general director and a Chinese co-director.

##### Germany

The Max Planck Society (MPG) worked with CAS to establish the “CAS-MPG Partner Institute for Computational Biology”, with German and Chinese directors, also located in Shanghai. German funding also contributed to the establishment of the Shanghai Institute of Advanced Studies on the SIBS campus.

##### Canada

The Canadian Institutes of Health Research (CIHR) has chosen to partner with the National Natural Science Foundation of China (NSFC) to establish the “China-Canada Joint Health Research Initiative - Grants Program”. Established in 2005, the programme is jointly managed and funded by CIHR and NSFC with the aim of promoting the development of Canadian-Chinese scientific co-operation between universities, hospitals, research institutes or affiliated research organisations in Canada and China through the support of collaborative research grants.

##### US

US funding and support for capacity building in China has fostered a close relationship between China and key US institutions in the field of emerging infections. The US Department of Health and Human Services provides considerable technical assistance to China, including funding for a number of US researchers working full time in China, e.g. coordinating a Field Epidemiology Training Program.

References for textbox: France<sup>66</sup> Germany<sup>67</sup> German funding for SIBS campus.<sup>68</sup> Canada<sup>69</sup>

65 [www.cdc.gov/ieip/china.html](http://www.cdc.gov/ieip/china.html)

66 See [www.pasteur.fr/pasteur/international/Dai\\_en/shanghai\\_en.html](http://www.pasteur.fr/pasteur/international/Dai_en/shanghai_en.html)

67 See [www.picb.ac.cn/introduction.htm](http://www.picb.ac.cn/introduction.htm)

68 See [www.sias.ac.cn/pl.html](http://www.sias.ac.cn/pl.html)

69 See [www.cihir-irsc.gc.ca/e/35047.html](http://www.cihir-irsc.gc.ca/e/35047.html)



One model for developing mutual confidence in research governance could be the establishment of a research centre in China. This would have to be based on a need for scientific co-operation. Such a centre could benefit other researchers, in addition to its own staff, by providing advice and support as well as functioning as a model for China-UK collaborations. Moreover, the establishment of such a centre could boost the profile of the MRC and of UK medical research in China. The Chinese partner would need to be carefully selected.

In our discussions with members of the CNCBD delegation, it was suggested that joint workshops would be a useful step towards developing China-UK collaboration. There is the prospect of funding from the Chinese side: they are keen to be seen as equal partners in future joint enterprises. These would help to build understanding between the Chinese and UK research communities and would enable collaborators to identify promising potential collaborations. In the medium to long term, China-UK cooperation could be developed in a science-led fashion by focusing on a few special projects with top scientists, possibly through the establishment of a joint laboratory or research centre. Encouraging exchanges between young researchers would be a good way to invest in future collaboration, perhaps via a funding programme designed to support exchanges between researchers from the top groups in China and the UK.

#### (b) Ethics capacity-building

The Committee feels that there is a strong case for working with Chinese bioethicists to help them to continue to develop the system and build up the capacity for ethics review and regulation in China.

Research governance, including ethics review, is evolving in China. During the meetings held with bioethicists and policy-makers, as well as researchers, there was much interest in the regulatory framework and review processes in the UK and their effectiveness. We were assured that those involved in developing Chinese bioethics and bioethics policy would welcome help with capacity-building and they seemed eager to gather information and models to help them develop their own practice. There is clearly scope for continued dialogue with these groups as to how structures and processes could evolve in China. There are several ways in which the MRC could contribute to this evolution.

First, there will be a continued need for discussions between all parties with an interest in this area. There are already some mechanisms by which this will occur, for example, the BIONET collaboration, which brings together Chinese and European researchers and ethicists will continue for at least a further two years. In 2008 and 2009 it will have two further workshops in China, on the ethical governance of clinical trials, and on the ethical governance of genomic research, followed by a conference, and in addition it will develop a set of guidelines and recommendations for good ethical and governance practice in EU-China research collaborations. In addition, other international collaborations, such as the International Stem Cell Forum, involve Chinese participants and will contribute to development of policy and reciprocal knowledge. It may not be necessary for the MRC to undertake more specific work in this area, but continued engagement with developments will be essential to ensure up-to-date knowledge is used in assessing possible collaborations.

Secondly, there are continuing discussions within China about the model that should be followed for ethics review and governance structures. The UK model for reviewing research ethics differs from the US IRB model followed in China: for example, UK requirements for patient representation and independence from the institution under scrutiny are stricter. We found that there was considerable interest in the UK model of non-institutional ethics committees and the use of MRECs. There was also some interest in the value of a national regulator in areas such as embryo and stem cell research. Involvement in these discussions by the MRC or other UK organisations, such as NRES or HFEA, would be of value, both in providing experience of the different structures and possibly also in training or capacity-building. A continuing exchange of information would help to build mutual understanding of each other's regulatory system and thus smooth the path of future China-UK research collaborations.

One possible route to improve research ethics or provide some assurance about standards in this area could be voluntary standards, with appropriate processes for independent verification, accreditation and monitoring. The elite Chinese scientists whom we met appeared strongly motivated to develop China's regulatory capacity. They indicated a willingness to develop some form of accreditation for their research groups. There are a small number of elite hospitals in China that have gained international accreditation through organisations such as the College of American Pathologists (for laboratories) or the Joint Commission International (for the whole hospital).<sup>70</sup> The latter, in particular, involves an extensive list of standards that have to be verified by an independent assessor. Voluntary standards could be a promising route to facilitate China-UK collaboration in areas where there are complementary strengths: stem cell research might be one such area. However, we were informed that at present external accreditation is not accepted by the Chinese Government.

<sup>70</sup> Information on these accreditation programmes is available from their websites: <http://www.cap.org> and <http://www.jointcommissioninternational.org/22758/>

For future engagement, we would strongly recommend that the MRC should seek to involve China in discussions about how to manage ‘first-in-human’ trials for innovative therapies. This is an area where there is already some discussion taking place within the MOH, but it is a global problem and both China and the UK could benefit from maintaining a continuing dialogue. Measures towards this goal could include developing a continuing relationship with CNCBD, maintaining the contacts that CURE has made with that organisation. The MRC could also continue to engage bioethicists and, critically, the key scientists who, in the Chinese system, play an extremely important role in developing regulation. CURE has identified a number of such figures in the field of stem cell research.

## CONCLUSION

China's approach to the regulation of research ethics is developing rapidly. The underlying principles and formal content of Chinese guidelines is largely compatible with UK regulation. However, significant differences remain in terms of the procedures that are in place to implement regulation and monitor compliance. There is also variation within China, where a diverse range of research institutions have taken different approaches to ethical review. The CURE Committee recommends that the MRC seeks to establish relationships with centres of excellence in China. The MRC should also undertake close scrutiny of institutional governance and ethical review procedures in potential collaborative partners. In a rapidly evolving field, it is important to monitor future changes in Chinese regulation and research ethics. The MRC should also seek to engage Chinese partners in discussions about topics of mutual concern, building on the relationships that have been established by CURE.

## ABBREVIATIONS

AMS = Academy of Medical Sciences, UK  
AAPEC = Appointing Authority for Phase I Ethics Committees, UK  
BBSRC = Biotechnology and Biological Sciences Research Council, UK  
CAS = Chinese Academy of Sciences  
CAMS = Chinese Academy of Medical Sciences  
CDC = China Centre for Disease Control and Prevention, PRC  
CIOMS = Council for International Organizations of Medical Sciences  
CNCBD = China National Centre for Biotechnology Development, PRC  
CRF = Case Report Form  
CURE = China-UK Research Ethics committee, UK  
EU = European Union  
EUTCD = European Union Tissue and Cells Directive  
GCP = Good clinical practice  
GLP = Good laboratory practice  
GMP = Good manufacturing practice  
hESC = Human embryonic stem cell\*  
HFEA = Human Fertilisation and Embryology Authority, UK  
HTA = Human Tissue Authority, UK  
ICH = International Committee on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use  
IEC = Independent Ethics Committee  
iPS cells = Induced Pluripotent stem cells\*  
IRB = Institutional Review Board  
LREC = Local Research Ethics Committee  
MHRA = Medicines and Healthcare Products Regulatory Agency, UK  
MOH = Ministry of (Public) Health, PRC  
MOST = Ministry of Science and Technology, PRC  
MREC = Multi-centre Research Ethics Committee  
MRC = Medical Research Council, UK  
NICBPB = National Institute for the Control of Pharmaceutical and Biological Products, PRC  
NIH = National Institutes of Health, US  
NIHR = National Institute for Health Research, UK  
NHS = National Health Service, UK  
NRES = National Research Ethics Service, UK (previously COREC)  
NSFC = National Natural Science Foundation of China, PRC  
PRC = People's Republic of China (for ease of reading, 'China' is used in the text).  
PUMC = Peking Union Medical College, PRC  
RCT = Randomised Control Trial  
REC = Research Ethics Committee  
SAE = Serious Adverse Event  
SCNT = Somatic cell nuclear transfer\*  
SATCM = State Authority for Traditional Chinese Medicine, PRC  
SFDA = State Food and Drug Administration, PRC  
TCM = Traditional Chinese Medicine  
UK = United Kingdom

\*Please refer to the Appendix for discussion of scientific terms

# CHECKLIST FOR UK RESEARCHERS

## How to approach a potential collaboration with Chinese researchers.

### General for all research involving human participants

- Need clear reasons why collaboration with China would be mutually beneficial
- Need to know which UK and Chinese regulations and guidelines apply
- Clarify which guidelines are relevant
- Ensure most recent versions are used
- Consider each aspect of the research to ensure compliance with UK and China expectations, including:
  - Sources of human tissue or data to be used
  - Consent procedures, materials and recording
  - Direct and indirect inducements to participation and whether they may give rise to undue pressure
- Ethics review of the research. This needs to occur in the UK and in China. In relation to the review in China researchers should consider:
  - The composition of the Institutional Review Board
  - Whether any patient or lay views will be sought
  - Whether any further review is necessary
- Capacity-building: researchers and funders should consider whether the proposed collaboration gives rise to increasing capacity in ethics review or mutual understanding of ethical issues.
- Arrangements for monitoring compliance with relevant regulations, guidelines and agreed protocol

### Stem cell research (section III. 1)

- Compliance with both UK and Chinese guidelines, with particular regard to:
  - Source of embryos or gametes if used
  - Consent for use of tissue in stem cell research
  - Restrictions on keeping embryos beyond 14 days or implantation of research embryos
  - Combinations of human embryos and animal material and vice versa.
- Integrity of governance procedures in the collaborating Institution. As there is no external regulator of embryonic research in China, collaborators must have confidence that the institution will be able to ensure good governance.
- Human treatment with stem cells should be in accordance with standards expected in the UK. As with any innovative therapy, this should only be introduced in the context of an appropriately designed clinical trial. Such application should only be considered once all necessary safety and quality testing has been completed. This should be consistent with the requirements in the UK transposed from the EU Tissue and Cells Directive. It would not be acceptable to expose Chinese patients to risks that could not be undergone by patients in the UK.

### Clinical Trials (section III.2)

- Guidance relating to research in other countries should be adhered to, including that of the MRC.
- Researchers should be aware that the SFDA has had some problems in recent years. They must be confident that trials will be conducted to the same standards as would be expected in the UK.
- Issues relating to recruitment and consent are particularly pertinent in this area. Researchers need to be confident that appropriate methods are in place and also that these are applied in practice.
- There are cultural and social differences between the UK and China. Researchers in the UK must be conscious of these and respect Chinese practices. They should not collaborate in any projects that could exploit Chinese participants.
- It must be clear as to what regulatory procedures would be adhered to and whether the trial would be subject to inspection other than that potentially occurring under the SFDA.

### Emerging Infections (section III.2)

- Particular consideration must be given to the participants in research in this area. What will be the benefits and risks from participation?
- Researchers (and funders) must consider whether and how potentially beneficial treatments will be made available after research. This must be considered in all research, but of particular relevance is the management of pandemic global infections.



### Traditional Chinese Medicine (section III.3)

- The quality of any medicinal product to be tested must be assured. It needs to be free from contamination and also be consistent across participants (unless the trial design allows for variations in the latter).
- Researchers must be confident that the safety profile of the medicine to be administered is satisfactory to allow use in clinical research.
- The protocol must be reviewed to ensure adequate procedures are in place to monitor efficacy and safety outcomes.
- The appropriate control arm must be considered.
- The possibility that participants may be using other Western or Chinese medicines concurrently with the trial treatment or control must be specifically considered in the protocol

## APPENDICES

Appendix 1: Chinese guidelines and regulations (translated texts)

Appendix 2: Institutions – who's who in research in China

Appendix 3: UK legislation relating to stem cell research

Appendix 4: Stem cell science

Appendix 5: Site visits

### Appendix 1: Chinese guidelines and regulations

Regulations are listed in chronological order, according to the date each regulation was first promulgated and entered into force.

[1] Official translation published by the Ministry of Science and Technology (MOST) / China National Centre for Biotechnology Development (CNCBD).

[2] Unofficial translation provided by Professor Xiaomei Zhai.

[3] Unofficial translation provided by UK Foreign Office Science and Innovation Network, Beijing office.

[4] Unofficial translation published by the website of the Chinese bioethics network, sponsored by the Chinese Society for Philosophy of Science: [www.chinaphs.org/bioethics/regulations\\_&\\_laws.htm](http://www.chinaphs.org/bioethics/regulations_&_laws.htm).

[5] Unofficial version provided by the Research Councils UK (RCUK) Beijing Office.

#### Regulation on the Governance of Medical Institutions [2]

State Council, 1994

“When a surgical operation, special examination or special treatment is performed, informed consent must be obtained from the patient him/herself and from his/her family member or relative with his/her signature; in the case that it is impossible to get the patient's opinion and there is no family member or relative present, it can be performed after the treatment protocol is proposed by the physician and approved by the responsible person of the institution or by an authorized person.”

#### Interim Measures for the Administration of Human Genetic Resources [2]

MOST and MOH, 1998

Includes provisions regarding: license system; mutual respect; benefit-sharing; informed consent; ethical review

Article 13: No approval of the application in which no evidence to confirm the informed consent being obtained from the donor of human genetic sample and her/his family member.

#### Law on Practicing Doctors [2]

National People's Congress, legislation entered into force 1999

If a doctor conducts experimental clinical treatment without the consent from the patient or her/his family member (Article 8) and discloses patient's privacy and cause serious consequences (Article 9), he/she “has to bear the legal accountabilities”.

#### Drug Clinical Trial Guidelines [4]

State Food and Drug Administration (SFDA), 1999 / 2000

##### Chapter 1: General Provisions

Article 1: In order to guarantee the standardization of drug clinical trials, to make the results scientific and reliable, and to protect the rights and interests of human subjects and safeguard their safety, stipulated the Regulations according to the Law of Drug Regulation of the People's Republic of China and with reference to international accepted principles.

##### Chapter 2: Preparation before Clinical Trial and Necessary Conditions

Article 4: All researches involving human subjects must comply to ethical principles in Helsinki Declaration and CIOMS' International Ethical Guidelines on Biomedical Research Involving Human Subjects, i.e. justice, respect, maximum benefits to human subjects, and avoidance of harms as far as possible.

### Chapter 3: Guarantee the Rights and Interests of Human Subjects

*Article 8:* In the process of drug clinical trials the individual rights and interests of human subjects must be safeguarded, and the research must be scientific and reliable as well. Ethics Committee and informed consent are major measures to guarantee human subjects' rights and interests.

*Article 9:* In order to guarantee human subjects' rights and interests Ethics Committee shall be set up in the medical institutions conducting clinical trials. Ethics Committee shall have its members from non-medical profession, law and other institutions. The number of members is five at least with different genders. The composition and work of Ethics Committee shall be relatively independent from and not be intervened by any researcher.

*Article 10:* Before the clinical trials the protocol shall be reviewed, and approved by Ethics Committee with signatures, and then it can be conducted. In the period of trial any change of the protocol shall be approved by Ethics Committee, and then it can be conducted. Any serious adverse event in the trial shall be reported to Ethics Committee.

*Article 12:* Ethics Committee shall strictly review the following points of the protocol from the perspectives of safeguarding the rights and interests of human subjects:

1. Qualifications and experiences of researchers, whether they have sufficient time to conduct clinical trial in question, whether the personnel and equipments conform to the requirements.
2. Whether the protocol is appropriate, including purpose, possible harm/risks and benefits to human subjects and others, and whether the design of trial is scientific.
3. Whether the procedure of human subjects' enrolment is appropriate, the procedure of providing information to human subjects or her/his family member, or her/his guardian or legal proxy is complete and understandable, and the procedure of obtaining her/his written informed consent is appropriate.
4. Providing treatment and giving compensation when human subjects are injured or died because of their participation in the trial.
5. The acceptability of the revision of the protocol.
6. Regularly review the risks to human subjects during the process of clinical trials.

*Article 14:* Researcher or her/his designated representative must explain the relevant information on clinical trial to human subjects:

1. The participation of human subject in clinical trial is voluntary, and at any stage of trial, human subject has right to withdraw without discrimination or retaliation, her/his medical treatment and rights/interests shall not be affected.
2. Must make human subject understand her/his individual materials about her/his participation, and obtained in the trial are confidential. Ethics Committee, Drug Regulation Administration and researchers can get access to these materials when necessary according to the regulations.
3. Purpose, process and period of the trial, procedures of examination, expected possible harm/risks, inconveniences and benefits to human subject, and the possibility of her/his assigned to different groups in the trial.
4. Human subject can get access to the relevant information at any time. Must give sufficient time to human subject to consider her/himself whether to participate in the trial. For incompetent human subject, information shall be provided to her/his legal proxy. In the process of informed consent shall be used the language and words that are understandable to human subject.
5. When there is injury relevant to the trial, treatment and appropriate compensation shall be provided to human subject.

*Article 15:* The written informed consent form shall be obtained after complete and detailed explanation of the trial.

1. The written informed consent form shall be signed and dated by human subject or her/his legal proxy, and by the researcher or her/his representative too.
2. In the case that the human subject or her/his legal proxy is illiterate, there shall be one witness who is present in the all process of informed consent. After detailed explanation of the written informed consent form, human subject or her/his legal proxy expresses the consent orally, it shall be signed and dated by the witness.
3. If Ethics Committee agrees in principle with researcher who judges that the participation of incompetent human subjects in the trial will be in their interests, these patients are permitted to enter into the trial, and the informed consent form shall be signed and dated by their legal proxy.
4. If the informed consent is not obtained from human subject, witness or guardian, researcher must record this situation and the detailed reasons of why the consent is not obtained in the file and sign on it.
5. If new important materials relevant to drug in trial are found, the informed consent form must be revised and submitted to Ethics Committee for approval, and be got consent from human subject again.

## Drug Administration Law of the PRC<sup>1</sup>

National People's Congress, revised version promulgated 2001

### Chapter V: Control over Drugs

*Article 29:* The dossier on a new drug research and development including the manufacturing process, quality specifications, results of pharmacological and toxicological study, and the related data and the samples shall, in accordance with the regulations of the drug regulatory department under the State Council, be truthfully submitted to the said department for approval, before clinical trial is conducted. Measures for verifying the qualifications of clinical study institutions for drugs shall be formulated jointly by the drug regulatory department and the administrative department for health under the State Council.

When a new drug has gone through clinical trials and passed the evaluation, a New Drug Certificate shall be issued upon approval by the drug regulatory department under the State Council.

*Article 30:* The institutions for non-clinical safety evaluation and study and clinical study institutions shall respectively implement the Good Laboratory Practice for Non-Clinical Laboratory Studies (GLP) and Good Clinical Practice (GCP). The GLP and GCP shall be formulated by the department designated by the State Council.

*Article 31:* Production of a new drug or a drug admitted by national drug standards shall be subject to approval by the drug regulatory department under the State Council, and a drug approval number shall be issued for it, which the exception of the Chinese crude drugs and the prepared slices of Chinese crude drugs which where no control by approval number is exercised. The list of the Chinese crude drugs and the prepared slices of the Chinese crude drugs to be controlled by the approval number shall be compiled by the drug regulatory department under the State Council, in conjunction with the administrative department for traditional Chinese medicine under the State Council. A drug manufacturer may produce the drug only after an approval number is granted to it.

## Regulations for Implementation of the Drug Administration Law of the People's Republic of China<sup>2</sup>

State Council, 2002

### Chapter V: Control over Drugs

*Article 28:* Institutions for non-clinical safety evaluation and study of drugs shall implement the Good Laboratory Practice for Non-Clinical Laboratory Studies (GLP) and institutions for drug clinical trial shall implement the Good Clinical Practice (GCP). The GLP and GCP shall be formulated by the drug regulatory department under the State Council through respective consultation with the science and technology administrative department under the State Council and the health administrative department under the State Council.

*Article 29:* Clinical trials, manufacturing or importation of drugs shall be in conformity with the provisions in the Drug Administration Law and in the Regulations, and shall be reviewed and approved by the drug regulatory department under the State Council. The drug regulatory department under the State Council may authorize the drug regulatory department of the people's government of the province, autonomous region or municipality directly under the Central Government to conduct site inspection of research and development conditions of the drugs being applied, to conduct preliminary review of the submitted dossier, and to test the pilot samples. The specific measures therefore shall be formulated by the drug regulatory department under the State Council.

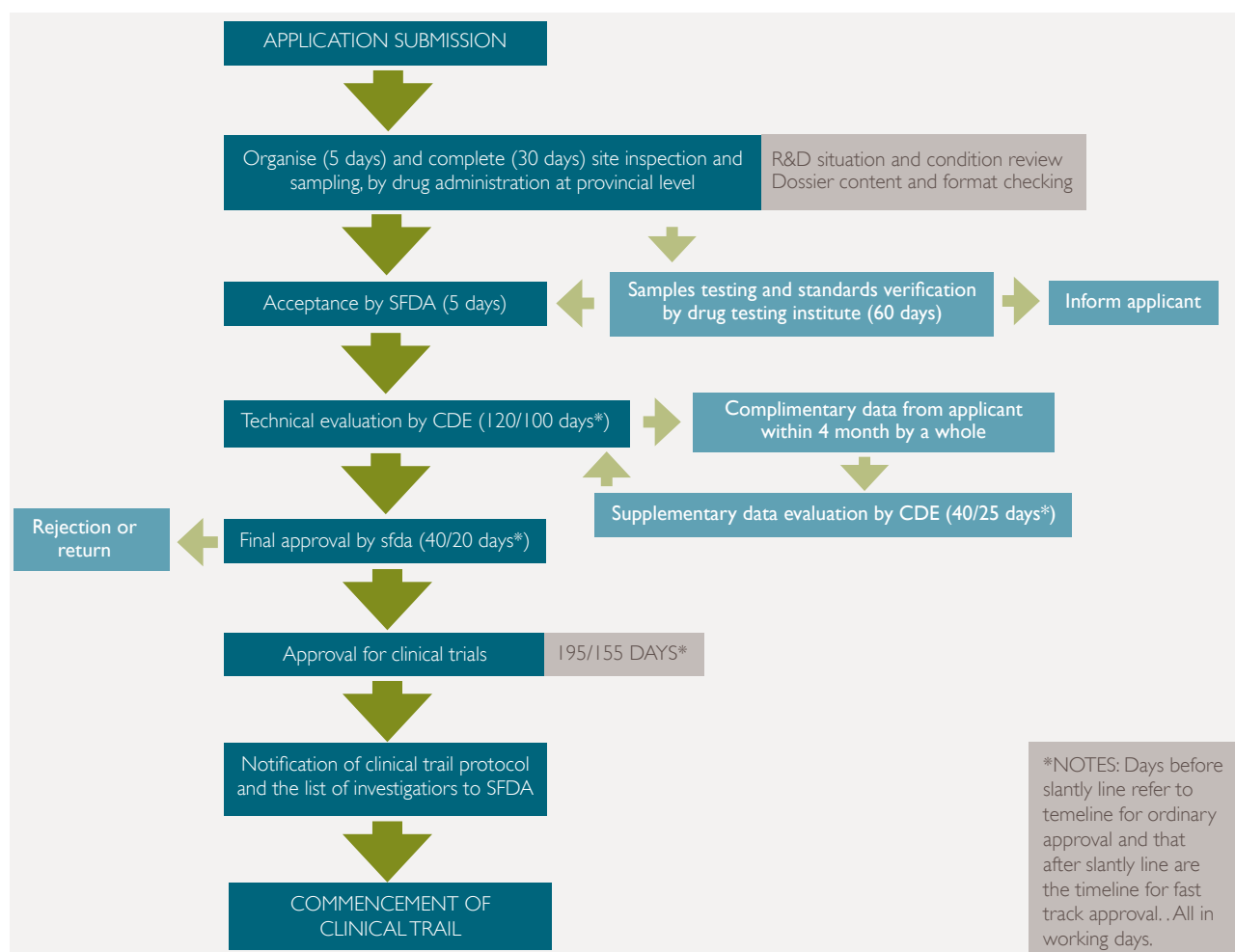
*Article 30:* Any clinical trial to be conducted for research and development of a new drug shall be subject to the approval by the drug regulatory department under the State Council in accordance with the provisions in Article 29 of the Drug Administration Law. When an application for conducting clinical trials is approved by the drug regulatory department under the State Council, the applicant shall select institutions for clinical trials from the lawfully certified ones to conduct the trials, and make a report thereof to the drug regulatory department and health administrative department under the State Council for the record. Prior to the drug clinical trial, the institution for drug clinical trial shall provide the subjects or their guardians with the truthful information on the trial, and obtain a written informed consent.

*Article 31:* For production of a drug admitted by national drug standards, an application shall, in accordance with the provisions of the drug regulatory department under the State Council, be submitted to the drug regulatory department of the people's government of the province, autonomous region or municipality directly under the Central Government or to the drug regulatory department under the State Council, and the relevant technical data and supporting documents shall be provided. The drug regulatory department of the people's government of the province, autonomous region or municipality directly under the Central Government shall, within 30 working days from the date it receives the application, review and make comments, and report the matter to the drug regulatory department under the State Council for review while notifying the applicant of its comments. If all the requirements are fulfilled upon review, a drug approval number shall be issued by the drug regulatory department under the State Council.

<sup>1</sup> <http://eng.sfda.gov.cn/cmsweb/webportal/WV45649037/A48335975.html>

<sup>2</sup> <http://eng.sfda.gov.cn/cmsweb/webportal/WV45649038/A48335997.html>

## Summary of SFDA application and approval procedure for clinical trials <sup>3</sup>



## Ethical Principles and Conduct Norms of Human Assisted Reproductive Technologies [2]

MoH, promulgated 2001, revised 2003

### Ethical Principles of Human Assisted Reproductive Technologies

- Benefit to patient
- Informed consent
- Protecting children
- Social good
- Privacy and confidentiality
- Non-commercialization
- Ethical review and surveillance

### Guidelines for Practitioners

- Must strictly observe the voluntary principle of informed consent or informed choice;
- Must respect the patient's privacy;
- Prohibit sex selection without medical indications;
- Prohibit surrogate motherhood technology;
- Prohibit the donation of human embryo;
- Prohibit the human egg plasma and nucleus transfer technology for the purpose of reproduction;
- Prohibit the hybrid between human gamete and gamete from of species; prohibit to implant gamete, zygote and embryo of other species into human body; and prohibit to implant human gamete, zygote or embryo into the body of other species;
- Prohibit the manipulation the gene in human gamete, zygote or embryo for the purpose of reproduction;
- Prohibit the coagulation between sperm and egg of close relatives;
- In the same period of treatment the gamete or zygote must be derived from same male and female;
- Prohibit to transfer the gamete, zygote or embryo to other people or to do research without the patient informed and free consent;
- Prohibit to do the study on human chimera embryo;
- Prohibit human reproductive cloning.



## Ethical Guiding Principles for Research on Human Embryonic Stem Cells [1] MOST and MoH, 2003

1. The Ethical Guiding Principles for Research on Human Embryonic Stem Cells (hereinafter referred to as the Guiding Principles) are formulated for the purpose of bringing human embryonic stem cell research in biomedical domains conducted in the People's Republic of China to accord with bioethical norms, to ensure internationally recognized bioethical guidelines and domestic related regulations to be respected and complied with, and to promote a healthy development of human embryonic stem cell research.
2. Human embryonic stem cells described in the Guiding Principles include stem cells derived from donated human embryos, those originated from germ cells and those obtained from somatic cell nuclear transfer technology.
3. Any research activity related to human embryonic stem cells conducted in the territory of the People's Republic of China shall abide by the Guiding Principles.
4. Any research aiming at human reproductive cloning shall be prohibited in the People's Republic of China.
5. Human embryonic stem cells used for research purpose can only be derived from the following means with voluntary agreement.
  - i. Sperm or oocyte after in vitro fertilization (IVF);
  - ii. Fetal cells from accidental spontaneous or voluntarily selected abortions;
  - iii. Embryos obtained by somatic cell nuclear transfer technology or parthenogenetic split embryos;
  - iv. Germ cells voluntarily donated.
6. All research activities related to human embryonic stem cells shall comply with the following norms.
  - i. Embryos obtained from IVF, human somatic cell nuclear transfer, parthenogenesis or genetic modification techniques, its in vitro culture period shall not exceed 14 days starting from the day when fertilization or nuclear transfer is performed.
  - ii. It shall be prohibited to implant embryos created by means described above into the genital organ of human beings or any other species.
  - iii. It shall be prohibited to hybridize human germ cells with germ cells of any other species.
7. It shall be prohibited to buy or sell human gametes, fertilized eggs, embryos and fetal tissues.
8. The principle of informed consent and informed choice shall be complied with, the form of informed consent shall be signed, and subjects' privacy shall be protected in all research activities related to human embryonic stem cells. The informed consent and informed choice mentioned above refer to that the researchers shall use accurate, clear and popular expressions to tell the subjects the expected aim of the experiment as well as the potential consequences and risks and to obtain their consent by signing on a form of informed consent.
9. Research institutions engaged in human embryonic stem cells shall establish an ethical committee, which consists of research and administrative experts in biology, medicine, law and sociology with the responsibilities for providing scientific and ethical review, consultation and supervision of the research activities related to human embryonic stem cells.
10. Research institutions engaged in research related to human embryonic stem cells shall formulate corresponding detailed measures and regulatory rules in compliance with the Guiding Principles.
11. The Ministry of Science & Technology and the Ministry of Health of the People's Republic of China shall be responsible for the interpretation of the Guiding Principles.
12. The Guiding Principles shall go into effect as of the date of its promulgation. [24 December 2003]

## Measures on Ethical Review over Biomedical Research Involving Human Subjects (Implemented for an initial trial period) [5]

Promulgated by Ministry of Health on January 11, 2007

### Chapter I: General Provisions

**Article 1:** These Measures are formulated in accordance with relevant provisions of the Law on Licensed Doctors of the People's Republic of China and the Regulations on the Administration of Medical Institutions, and for the purposes of standardizing the biomedical research involving human subjects and the application of relevant technologies, protecting human life and health, safeguarding human dignity, respecting and protecting the legal rights and interests of human subjects.

**Article 2:** The ethical review of biomedical research involving human subjects shall be organized and implemented in accordance with these Measures.

**Article 3:** Biomedical research involving human subjects and the application of relevant technologies referred to in these Measures shall include the following activities.

Research activities on human physiological and pathological phenomena and the diagnosis, treatment and prevention of diseases by adopting modern physical, chemical and biological methods.

Experimental application activities of medical and health technologies or products formed in the biomedical research on human subjects. The technologies which have been applied in the clinic for more than two years or have been approved by administrative departments for health to be applied in the clinic before the implementation of these Measures shall be excluded from the scope of the review stipulated in these Measures.

*Article 4:* The provisions of the laws, regulations and rules of the State and recognized principles of bioethics shall be followed in the ethical review and the process of the ethical review shall be independent, objective, just and transparent.

## Chapter II: Ethical Committees

*Article 5:* Ministry of Health shall set up a Medical Ethical Committee. Administrative departments for health at the provincial level shall set up the guidance and consultation organizations on ethical review within their respective administrative regions. The committees set up by Ministry of Health and administrative departments for health at the provincial level are expert consultation organizations on medical ethics, they mainly carry out researches and discussions on major ethical issues and put forward their consultative opinions on the policies, if necessary, they may organize the ethical review over major research projects; and may guide and supervise the ethical review by the institutional review boards (IRBs) under their jurisdiction. The Articles of Association for the expert ethical committees set up by Ministry of Health and administrative departments for health at the provincial level shall be made separately.

*Article 6:* Institutions implementing biomedical research involving human subjects and application of relevant technologies, including the institutions for medical and health, research, prevention and control of diseases, and healthcare of women and children, shall set up IRBs. IRBs shall mainly undertake the ethical review and carry out the ethical review and supervision over biomedical research involving human subjects and application of relevant technologies by the institutions themselves and those subordinating to them and may accept the entrusted review as to the demand of the society; they may also organize and carry out relevant ethical trainings.

*Article 7:* Members of IRBs shall be elected by the departments or institutions setting them up from the experts in such social science fields as biomedical, management, ethics, law and sociology after extensively soliciting opinions, the members of each IRB shall not be less than 5 and shall include both male and female. IRBs in minority regions shall consider including minority members.

*Article 8:* The term of office of IRB members shall be 5 years, which is renewable upon re-election. Each IRB shall have one Director and several Deputy Directors, who shall be elected and may be re-elected by IRB members. The departments or institutions setting up IRBs shall grant proper remuneration to IRB members according to their work.

*Article 9:* Duties of IRBs: reviewing research plans and safeguarding the dignity, rights and interests of the subjects; ensuring the subjects will not be disposed to unreasonable dangers in the research; supervising and inspecting the approved research and timely disposing of the complaints of the subjects and adverse events.

*Article 10:* IRBs may execute the following powers.

1. Requiring the researchers to provide the Informed Consent Form, or approving the exemption of the informed consent procedure according to the request of the researchers.
2. Requiring the researchers to revise the research plans.
3. Requiring the researchers to suspend or terminate the research activities.
4. Making such decisions as approval, disapproval or reconsideration after modification to the research plans.

*Article 11:* IRBs shall keep the research projects for ethical review in secret.

*Article 12:* IRBs shall make their own decisions in accordance with ethical principles and shall not be interfered with; the review results shall be timely conveyed or promulgated.

*Article 13:* IRBs shall accept the supervision and administration of the administrative departments for health of the administrative regions or the State.

## Chapter III: Review Procedures

*Article 14:* The principles on ethical review over biomedical research involving human subjects are:

1. The right of the subjects in making their own decisions on agreement or disagreement of the experiment shall be respected and safeguarded, the informed consent procedure shall be strictly executed, the subjects shall not be made to agree the experiment by such improper measures as cheat, lure and force, the subjects shall be allowed to withdraw from the experiment in any phase.

2. The consideration on the safety, health, interests and rights of the subjects must be higher than the consideration on the scientific and social benefits, the subjects shall be made to be benefited to the largest extent and harmless as far as possible.
3. The economic burdens shouldered by the subjects during the experiment due to the benefits they get shall be alleviated or exempted.
4. The privacy of the subjects shall be respected and safeguarded, the conditions on the keeping and use and the confidential measures related to the private information of the subjects shall be notified to the subjects as to the facts, no material or information related to the privacy of the subjects shall be disclosed to irrelevant third parties or media.
5. It shall be ensured that the subjects may get timely and free treatment and corresponding compensation if injured in the experiment.
6. Special protection shall be given to the subjects having no or insufficient capacity to safeguard their rights and interests (vulnerable groups), including children, pregnant women, persons suffering from mental retardation or mental illnesses, prisoners and persons with bad economic conditions or little knowledge.

*Article 15:* The following materials shall be submitted to IRBs on the research projects for ethical review:

1. Ethical Review Application Form;
2. Research plans of plans for application of relevant technologies;
3. Informed Consent Forms of the subjects.

*Article 16:* The applicants of the projects must acquire the voluntary informed consent of the subjects beforehand. If it is impossible to the informed consent, they shall first acquire the oral informed consent of the subjects and submit the evidential materials on acquiring the oral informed consent. As to the subjects who have no capacity for act or unable to make decisions by themselves, the written informed consent of their guardians or agents must be acquired.

*Article 17:* When acquiring the informed consent of the subjects, the applicants must provide the subjects with complete, easily understandable and necessary information, the Informed Consent Form shall be written with easily understandable words and the Informed Consent Form in the minority regions may be written with minority characters, the subjects shall understand the words in the Informed Consent Form and shall be given sufficient time to consider whether to agree the experiment.

*Article 18:* If there is any change to the implementation procedures or conditions of the projects, the informed consent of the subjects must be acquired anew, and the applications for ethical review shall be submitted to IRBs anew.

*Article 19:* IRBs shall not accept the applications for ethical review of research projects in violation of laws and regulations of the State. If there is any interest conflict between any IRB member and the applied project, the member shall proactively adopt avoidance. If avoidance is impossible, the interest shall be made public to the applicant.

*Article 20:* IRBs shall carry out the following examinations on the project applied for ethical review. Whether the qualifications and experiences of the researches measure up to the requirements of the experiment.

1. Whether the research plan measure up to the requirements of the scientific and ethical principles.
2. Whether the extent of the risk may be suffered by the subjects is appropriate compared with their expected benefits in the research.
3. Whether relevant information and materials provided to the subjects (or their family members, guardians and legal agents) during the informed consent procedure are complete and pellucid, whether the methods to acquire the informed consent are proper.
4. Where confidential measures are taken to the materials of the subjects.
5. Whether the standards for the election and failure of the subjects are proper and just.
6. Where the subjects are clearly notified their due rights and interests, including the right to withdraw from the experiment during the research process without giving any reason or being discriminated.
7. Where the subjects get reasonable compensation for participating in the research, whether the treatment and compensation measures given to the subjects are proper if they suffer damages of death for participating in the research.
8. Whether there are special staff in the researchers to be responsible for dealing with the informed consent and safety of the subjects.
9. Whether protection measures are taken against the risks may be suffered by the subjects in the research.
10. Whether there is any interest conflict between the researchers and the subjects.

*Article 21:* IRBs may make such decisions as approval, disapproval or reconsideration after necessary modification after their examinations. The decisions of the IRB shall be passed by two thirds of members of the IRB. IRBs shall explain the reasons for their decisions. As to the projects in which the probability and extent of the expected damage or inconvenience of the subjects does not exceed the probability and extent of the expected damage or inconvenience of the subjects in their daily life or regular treatment (i.e. projects whose risks are less than the minimum risks), Chairman of the IRB or one or more members appointed by Chairman may carry out the examination.

*Article 22:* If the applied projects need to be modified in the implementation after they are examined and approved by IRBs, the modification shall be reported to IRBs for examination and approval. If any serious adverse reactions or adverse event happens during the implementation process, it shall be timely reported to IRBs.

*Article 23:* If the applied projects are not approved by IRBs, the projects shall not be initiated.

#### Chapter IV: Supervision & Administration

*Article 24:* The supervision and administration of ethical review over biomedical research involving human subjects shall be included in the scope of the administration of scientific researches by the administrative departments for health at all levels. The contents of the supervision and administration shall include:

1. Whether the institutions implementing biomedical research involving human subjects have set up IRBs as required.
2. Whether IRBs of the institutions have implemented ethical review in accordance with the principles on ethical review.
3. Whether the contents and procedures of ethical review measure up to the requirements.
4. Implementation of ethical review results and whether there is any dispute.

*Article 25:* Ministry of Health shall carry out the macro administration of IRBs all over the country, shall set up and perfect the rules and systems on ethical review and shall consider and make relevant policies. Administrative departments for health at the provincial level shall be responsible for the supervision and administration of ethical review by IRBs within their respective administrative regions.

*Article 26:* If any foreign institution or individual wants to carry out biomedical research involving human subjects in China, its/his research plans shall also be applied to IRBs set up in China in accordance with these Measures after they are examined by IRBs of the country or region where it/he lies.

*Article 27:* Upon the acceptance after the completion of biomedical research involving human subjects, the principals of the projects shall be required to show the evidences on the fact that the project has passed the examination by the corresponding IRB. When the results of biomedical research involving human subjects are published on academic magazines, the researchers shall show the evidences on the fact that the project has been examined and approved by the corresponding IRB.

*Article 28:* Any individual or unit shall have the right and obligation to report the rule-breaking acts or misdeeds in biomedical research involving human subjects.

*Article 29:* If any researcher violates the ethical principles, the unit of the principal of the research project or the competent administrative department for health shall have the right to impose corresponding punishments, make public criticism and cancel his qualification for reward-winning; the implementation of the research project shall be suspended according to the seriousness of the circumstances, and the case shall be transferred to the judicial organs if laws of the State are violated.

#### Chapter V: Supplementary Provisions

*Article 30:* These Measures shall be effective as of the date of promulgation.

#### Management Methods on Clinical Application of Medical Technologies

Recently, the Ministry of Health has released and distributed the Management Methods on Clinical Application of Medical Technologies, clarifying that the state shall set up regulations on entry and management of clinical application of medical technologies so as to manage the medical technologies by classes and grades. The Ministry of Health shall be responsible for the approval and clinical application management of Class III medical technologies with high risks, as well as formulation and adjustment of the Content of Class III Medical Technologies. The Methods will be implemented from May 1.

The gene cloning technology will not be applied clinically for the time being.

The heterogenic stem cell treatment technology, xenogeneic treatment technology, human body cell cloning technology and the like shall not be applied clinically for the time being. In addition, as for the Class III medical technologies that have been put into in clinical application before the Methods is promulgated, the medical institutions shall submit an inspection application to technology inspection and approval authority within 6 months after the Methods is promulgated. If any medical institution fails to do so or the health administrative authority determines not to register such medical technologies under the diagnosis and treatment items, the clinical application of all Class III medical technologies shall be stopped.

Before Class III medical technologies are clinically applied for the first time, they shall pass through the safety demonstration and ethical inspection organized by the Ministry of Health. Before Class II and Class III medical technologies are clinically applied, they shall pass through the technical inspection made by the third party. When the medical workers clinically apply Class I medical technologies, the medical institution can inspect such technologies by itself or comply with the regulations stipulated by health administrative authority at provincial level. The technology inspection authority designated or established by the Ministry of Health or health administrative authority at provincial level shall be respectively responsible for inspecting the clinical application capability of Class III and Class II medical technologies. The Ministry of Health can also appoint the health administrative authority at provincial level to inspect the designated Class III medical technologies.

The technology inspection authority shall establish expert database in line with actual needs. The inspection work system, procedure and list of the expert database shall be submitted to health administrative authority that appoints it to do the inspection for file. Members of the technical inspection expert database shall include experts in the fields of medicine, law, ethics, management, etc. Employment of such experts by the inspection authority will not be restricted by administrative regions. When members of the expert database inspect technologies, the Avoidance System and Responsibility Seeking System shall be implemented.

#### Class III medical technologies

Medical technologies involving significant ethical problems with safety and validity needing further demonstration by standard clinical tests and studies: Cloning treatment technology, autogeneic stem cell and immunocyte treatment technology, gene treatment technology, treatment of drug addiction by operation in central nervous system, technology on treating insanity by stereotactic surgery, allogenic stem cell transplantation technology, tumor vaccine treatment technology, etc.

Medical technologies involving significant ethical problems, but with ensured safety and validity: homorganic transplantation, transsexual operation, etc.

Medical technologies involving high risks with safety and validity either needing further demonstration or already ensured: technology of ablation treatment by large-sized instrument and equipment such as particle generator, treatment technology of radioactive particle implantation, tumor hyperthermia technology, tumor cryotherapy technology, tissue and cell transplantation technology, artificial heart implantation technology, technology of auxiliary diagnosis and treatment by artificial intelligence, etc.

Other medical technologies that need special management: gene chip diagnosis and treatment technology, distraction osteogenesis treatment technology, xenogeneic organic transplantation technology, etc.

## Appendix 2: Institutions – who's who in research in China

This part of the appendix contains further details and background information on the following government bodies in China. A brief overview and diagram of the relationship between these bodies may be found at figure 1 of the report.

1. Ministry of Science and Technology (MOST) / China National Centre for Biotechnology Development (CNCBD)
2. Chinese Academy of Sciences (CAS)
3. The National Natural Science Foundation of China (NSFC)
4. Ministry of Health (MOH) and MOH ethics committee
5. Chinese Academy of Medical Sciences (CAMS) / Peking Union Medical College (PUMC)
6. State Food and Drug Administration (SFDA)
7. China Centre for Disease Control and Prevention (CDC)
8. National Institute for the Control of Pharmaceutical and Biological Products (NICBP)

### 1. Ministry of Science and Technology (MOST) / China National Centre for Biotechnology Development (CNCBD)

The Ministry of Science and Technology (MOST) makes, manages and administers national policy for all aspects of science and technology, with a strong emphasis on commercialisation and the industrial application of new technologies. It was created in 1998, reflecting the importance placed on science and technology by the administration of the then Premier, Zhu Rongji. MOST is primarily concerned with the development of high technology and economic returns: its major concerns in the area of research governance are the targeting of funds and scientific integrity.

MOST controls a number of important science programmes, including the 973 programme, which is the major source of funding for basic science in China. Although focused on basic research, the programme still emphasizes applications and “strategic research”. Another funding programme is the 863 programme, which funds research in high technology. The 863 programme is the source of funding for many of China's stem cell projects.<sup>4</sup> Bioscience and biotechnology funding under the 863 programme are managed by the China National Centre for Biotechnology Development (CNCBD) – an affiliated agency of MOST. CNCBD comprises eleven divisions including four dealing with medical biotechnology: Biomedical, Chemical, Public health and Traditional Chinese Medicine (TCM). Other departments that also deal with related matters include: International cooperation, Industry and Biomedical resources.

The Project Administration infrastructure at MOST includes Offices for Internationalisation of TCM, a National Office for new drug development (these areas are both national priority projects) and an Office for Commercialisation of Biotechnology. It also deals with Bioresources and Safety and the latter includes ethics.

On the website for CNCBD<sup>5</sup> its mission is summarized as:

- To develop biotechnology, cultivate new bio-industry, promote bio-economy.
- To study biotechnology and bio-industry strategies, policies and measures home and abroad.
- To take the responsibility and participate in the revision and formulation of biotechnology and bio-industry development laws, policies, projects and plans.
- To assume the management of biotechnology programs.
- To assume the management of bio-safety and bio-resource issues
- To involve in consultation on the policies and technologies related to bio-industry.
- To take responsibility the issues related to bio-association.
- To promote international exchanges on biotechnology.

### 2. Chinese Academy of Sciences (CAS)

The Chinese Academy of Sciences (CAS), founded in 1949 by the State Council, is a highly respected and powerful organisation within Chinese science. Election to membership is very prestigious and academicians are selected by nomination and ballot. The mission of CAS is to conduct research in basic and technological sciences (including the provision of scientific data and advice for governmental decision-making). Acting as a research agency, CAS runs over a hundred institutes. CAS and its institutes continue to receive the lion's share of government research funding.<sup>6</sup> One of the six divisions of CAS is life sciences and medicine. CAS funds 3 stem cell institutes: CURE delegates visited the Key Laboratory for Stem Cell Research at the IHS / SIBS in Shanghai.

<sup>4</sup> Du, Jiansheng et al (2004). «Stem cell mission to China, Singapore and South Korea» Report of a DTI Global Watch Mission, September 2004.

<sup>5</sup> <http://www.cncbd.org.cn/INTROE/INTRO/index1.html>

<sup>6</sup> Huang et al (2004), p.369.



CAS is also involved in training, running a university and a graduate school, as well as various information and publishing services.<sup>7</sup> Last but not least, CAS has a remit to promote high-technology enterprise.<sup>8</sup>

### 3. The National Natural Science Foundation of China (NSFC)

The National Natural Science Foundation of China (NSFC) directs, coordinates and funds basic research and applied basic research. It is also charged with identifying and fostering scientific talent and promotes science and technology.<sup>9</sup> The NSFC was set up in 1986, but only became fully independent from MOST in 2000. A few years later, in 2005, the NSFC adopted a new constitution, drawing on principles adopted by science foundations in developed countries. The new constitution includes a number of provisions designed to encourage good research practices and discourage corrupt or biased funding allocations. These include external peer review, transparency and a term limit of four years for members of the evaluation committee.<sup>10</sup> (The NSFC has posted an English translation of its constitution on its website.<sup>11</sup>) The NSFC has been held up as a model of good governance by a number of commentators.<sup>12</sup>

However, the amount of funds allocated by the NSFC remains relatively small, albeit rising even more rapidly than the general increase in government spending on R&D. In 2006, the NSFC budget was 3.4 billion yuan, which is only about 5% of annual government spending on science and technology.<sup>13</sup> Nature commented that the impact of the NSFC's constitution "depends on how well it can inspire other organizations... to take steps to improve the fair and effective deployment of their money".<sup>14</sup>

### 4. Ministry of Health (MOH) and MOH ethics committee

The mandate of the Ministry of Health (MOH), also sometimes translated as the Ministry for Public Health, is to promote health: as well as formulating and implementing policies to promote health development, the MOH's tasks include the supervision of medical institutions, medical education, the oversight of clinicians and other health professionals. Although the MOH's roles also include the development and organisation of medical science, technology and health research, this is not its primary focus. The MOH is also tasked to "guide the dissemination and application of medical achievements".<sup>15</sup>

The MOH also administers the State Administration of Traditional Chinese Medicine.<sup>16</sup> Other institutions affiliated to the MOH include CAMS, PUMC and China CDC (for further details on these bodies, please see below).

The MOH has had a central role in initiating bioethical regulation in China. The MOH receives advice from its own Ethics Committee. This Committee was originally formed to deal with issues arising from international collaborations but now deals with a broad range of bioethics issues. In addition to this national committee, the MOH also requires each of its research institutions to have its own ethics committee.

The commitment of the MOH to bioethical regulation appears to have been reinforced by the appointment of the new Minister of Health, Chen Zhu. The new Minister is an internationally recognised research scientist with overseas training and experience. His former positions include Director of the Chinese National Human Genome Centre and as a vice president of CAS.

### 5. Chinese Academy of Medical Sciences (CAMS) / Peking Union Medical College (PUMC)

The Chinese Academy of Medical Sciences (CAMS) is a large multidisciplinary institution for biomedical research.<sup>17</sup> The membership of CAMS consists of experts and professors with high levels of experience and academic expertise who have made outstanding contributions in the medical science field. (Membership of CAMS overlaps with CAS and the Chinese Academy of Engineering.) CAMS also works with "young outstanding experts with national or ministerial certification" and a small number of "Cheung Kong Scholars" who have returned from overseas. CAMS is directly funded by the State Council and funding has recently been increased.

Peking Union Medical College (PUMC) is one of the most prestigious medical schools in China. It was founded in 1906 with the joint support from the then-Chinese government and several British and American religious groups (thus the term 'Union'). In 1917, it was re-organized with the support of the Rockefeller Foundation. PUMC was described to us as having a similar model to Johns Hopkins Medical School. One hundred students per annum undertake an eight year

7 [http://english.cas.cn/eng2003/page/about\\_03.htm](http://english.cas.cn/eng2003/page/about_03.htm)

8 <http://english.cas.cn/eng2003/page/T46.asp> and <http://www.casholdings.com.cn/english/>

9 [http://nsfc.gov.cn/e\\_nsfc/2006/01au/01mr.htm](http://nsfc.gov.cn/e_nsfc/2006/01au/01mr.htm)

10 Heping, Jia (2005). "Chinese funding agency lays out its rules". Available from <http://www.scidev.net/news/index.cfm?fuseaction=printarticle&itemid=2027&language=1>

11 [http://www.nsfc.gov.cn/e\\_nsfc/2006/07con/index.htm](http://www.nsfc.gov.cn/e_nsfc/2006/07con/index.htm)

12 See, for example "New Accountability in China", Nature, 434, p.1053.

13 [http://www.nsfc.gov.cn/e\\_nsfc/desktop/dtxw.aspx@infoid=8859.htm](http://www.nsfc.gov.cn/e_nsfc/desktop/dtxw.aspx@infoid=8859.htm)

14 Nature editorial (2005). "New Accountability in China", Nature, 434, p.1053.

15 [http://english.gov.cn/2005-10/09/content\\_75326.htm](http://english.gov.cn/2005-10/09/content_75326.htm)

16 [http://english.gov.cn/2005-10/09/content\\_75326.htm](http://english.gov.cn/2005-10/09/content_75326.htm)

17 The CAMS / PUMC website (Chinese language only) may be found here: <http://www.cams.ac.cn/allnew/index.htm>

course with a medical PhD. The College recently began collaboration with Tsinghua University which is a large Beijing based university with a strong humanities and law base.

PUMC is affiliated with CAMS and both CAMS and PUMC function under the leadership of the MOH. A large group of institutions are funded by CAMS and jointly managed with PUMC. These include at least 18 research institutes, 5 academies, 6 or 7 clinical hospitals (including the PUMC hospital) and five specialist hospitals in areas including: Cardiovascular, Oncology, Haematology – each is the largest in China for its specialty.

CAMS also runs the Pathogen Biology Institute, a new national scientific research unit responsible for important national programs on pathogen biology. Its research priority is basic prevention and treatment technology for emerging epidemics and AIDS. It is engaged in consultation and academic exchanges on emerging infectious diseases with businesses and institutions both in China and abroad.

## 6. State Food and Drug Administration (SFDA)

We were informed that there are about 180 staff working at their headquarters in Beijing and over 40,000 staff working for the various provincial FDA offices. The SFDA licenses all new medicines including vaccines, biological products and devices. All such medicines and products developed in China have to undergo phase I, II and III testing under licence before approval for marketing.

The SFDA also requires every new drug introduced into China to be subject to further analysis in clinical trials, even if the drug already has FDA / MHRA approved. The rationale for this is that due to variation in metabolism there are potential differences in drug safety and efficacy in the Chinese population as compared with the previous trial population. The only exception to this is generic HIV treatments due to the 'Green Way' process. All other medicines and products have to be further tested by clinical trial before approval can be given. Generic drugs can proceed straight into phase II studies. Generic HIV treatments manufactured in China have to submit biosafety information but do not require further full clinical trial in China before being licensed for marketing.

Medicines are categorised into 4 groups:

- New drugs
- Generic drugs
- Changes of use
- Also changes of use

## 7. China Centre for Disease Control and Prevention (CDC)

The first Centre for Disease Control and Prevention was created in 1998 by the Shanghai government. This Shanghai Centre consolidated many institutions into a single new agency, modelled provided by the US Centers for Disease Control and Prevention (US CDC). It served as a model for the national level China Centre for Disease Control and Prevention (CDC), which was created in 2002 as "a policy response to the shifting of disease patterns, perception of disease, and governmental changes in China".<sup>18</sup>

China now has a system of regional and local CDC centres which conduct surveillance, collect health data and provide training and health care services. CDC has research centres and also collection / data collection outposts throughout regions. There are a total of approx 2,600 CDC surveillance centres throughout China. These have 40,000 computer terminals to collect the surveillance data, which is linked to hospitals. Central CDC has scientific / professional contact with these surveillance centres but they 'belong' to the local governments. Some of the surveillance data is available on MOH website, full data is internally accessed through the CDC website.

China CDC has a key role to play in coordinating and managing China's response to emerging infections.

- Organises and implements control and prevention plans for different kinds of diseases.
- Acts as national working group for diseases prevention, emergency relief, and construction of public health information systems.

In addition, China CDC conducts applied scientific research and aims to strengthen research on strategies and measures for disease control and prevention.<sup>19</sup> Medical research performed by China CDC can include involvement in clinical trials. CDC has 18 different sub centres for research with laboratories. Five of these research labs are for infectious disease. Others are for public health, hygiene etc. Those relating to infectious disease are:

- Institute for viral disease control and prevention
- National institute for parasitic disease
- National Centre for AIDS / STD control and prevention

<sup>18</sup> Jing Peng et al, 2003. "Public Health in China: The Shanghai CDC Perspective" American Journal of Public Health; 93(12): 1991–1993. <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1448136>

<sup>19</sup> <http://www.chinacdc.cn/n272562/n275958/index.html>

- National centre for tuberculosis control and prevention
- National centre for chronic and noncommunicable disease control

CDC has a strong interest in vaccine development and also infectious disease treatment eg antiviral treatments such as cytokines, interferons. Some clinical trials for related products are performed in CDC clinics. CDC does not design the trial protocols – these come from the research and development of the companies who have developed the product. These protocols are reviewed by SFDA and local ethics committees.

#### 8. National Institute for the Control of Pharmaceutical and Biological Products (NICPBP)

The National Institute for the Control of Pharmaceutical and Biological Products (NICPBP) is an agency of the SFDA. Their responsibilities include quality standards and technical services for drugs and biological products and medical equipment, including evaluating efficacy and safety for new drugs and biological products evaluation.<sup>20</sup> Within the NICPBP, the responsibilities of the “Biological Products Inspection Agency” include the inspection of imported biological products and national standards for biological products, material research, calibration, verification, and responsibility for the biological products standards material management.

## Appendix 3: UK legislation relating to stem cell research

### Human Fertilisation and Embryology Act 1990

This made creation, storage or use of embryos illegal unless authorised by a licence. It established the Human Fertilisation and Embryology Authority (HFEA). This HFEA was given the power to grant licences in relation to embryos. The Act set out the criteria under which such licences could be granted for the creation, storage or use of embryos for research purposes. The key points are outlined below.

- In order to grant a licence the HFEA was required to deem that the research was necessary or desirable for the purpose of:
  - a) Promoting advances in the treatment of infertility,
  - b) increasing knowledge about the causes of congenital disease,
  - c) increasing knowledge about the causes of miscarriages,
  - d) Developing more effective techniques of contraception, or
  - e) Developing methods for detecting the presence of gene or chromosome abnormalities in embryos before implantation.
- No embryo can be kept beyond the appearance of the primitive streak which is deemed to be no later than 14 days.
- No embryo can be placed in an animal.

The HFEA also has powers to inspect premises that are licensed and may revoke licences if it decides that the conditions under which they were given have been breached. The Act sets out criminal sanctions for performing research without the appropriate licence or breaching other prohibitions in the Act. The HFEA has a Code of Practice which included more detailed guidance for researchers on applying for licences and the expected standards and criteria for decision making.

The Act specifically prohibited replacing the nucleus of an embryo with that of another. Clearly, at the time the Act was drafted, embryo research was focused on developing techniques for artificial reproduction. In the decade following the Act research relating to embryo development, and in particular embryonic stem cell research progressed such that Parliament reviewed the relevant legislation and in 2001 passed two further pieces of legislation.

### 1. Human Fertilisation and Embryology (Research Purposes) Regulations 2001 (188)

These addressed the developing field of embryo and stem cell research and extended the possible research purposes to:

- a) increasing knowledge about the development of embryos;
- b) increasing knowledge about serious disease;
- c) enabling any such knowledge to be applied in developing treatments for serious disease.

### 2. Human Reproductive Cloning Act 2001

This created a criminal offence of placing in a woman any embryo created by any means other than fertilisation. It therefore outlawed use of SCNT to create an embryo for reproductive, as opposed to research purposes.

As there have been further changes in many fields relating to the 1990 Act a new Bill has been drafted to update this. At the time of writing this has completed its passage through the House of Lords and is awaiting debate in the House of Commons. In relation to research this Bill –

<sup>20</sup> <http://www.nicpbp.org.cn/cmsweb/> (in Chinese only)

## Human Fertilisation and Embryology Bill<sup>21</sup>

(completed passage through Parliament late 2008 after this report was completed by the CURE committee)

This contains several significant amendments. The most important is that it would allow the creation of 'human admixed embryos' – which contain both animal and human DNA with predominantly human DNA. This follows several years of consultation and debate about this possibility, including review by the Department of Health<sup>22</sup>, the HFEA, and the Academy of Medical Sciences (AMS). The Bill allows four categories of admixed embryos to be created:

1. 'Cytoplasmic hybrids': created by removing the nucleus from an animal cell and replacing it with the nucleus of a human cell. The only animal DNA left in the hybrid cell created will be the mitochondrial DNA. There has been considerable debate as to whether this mitochondrial DNA will persist or be replaced by human mitochondrial DNA.
2. 'True hybrids': created by combining an animal gamete with a human gamete.
3. 'Transgenic human embryo': created by introducing sequences of animal DNA into one or more cells of a human embryo.
4. 'Chimeric human embryos': altering a human embryo by adding animal cells to it.

The Bill will also make allowance for other categories of entities to be included as human admixed embryos should this be required in the future. It is worth noting that combinations of animal and human DNA have been created for many years at the 'animal end' of the spectrum to produce, for example, transgenic mice.

The Bill also allows for future Regulations to permit embryos to be replaced in women that been modified to prevent transmission of serious mitochondrial disease.

## Regulation of stem cell therapies in the UK

The statutes above relate to the use of embryos to derive stem cell lines. It is hoped that these lines may eventually be available for treatment purposes. For the lines to be used in this way in the UK there are several further regulatory processes that would have to be satisfied. These relate firstly to the human application of cell lines and secondly to use of cell lines as therapeutic products. These are regulated by two separate statutes and Regulatory authorities.

### 1. Human Tissue (Quality and Safety for Human Application) Regulations 2007

These are the transposition into UK law of the European Union Tissue and Cells Directive 2006. Under these Regulations the Human Tissue Authority (HTA) is given power to licence establishments to store, test, process or distribute cells for human application. This would include stem cell lines intended for human use. One requirement is that cells are derived and stored in a facility that meets set standards. These are met by using facilities that comply with Good Manufacturing Practice (GMP) standards.

### 2. Medicines for Human Use (Clinical trials) Regulations 2004

These are again a transposition of a 2001 European Directive relating to medicines for human use.<sup>23</sup> The Medicines and Healthcare Products Regulatory Agency (MHRA) is the UK regulator, licensing clinical trials and therapeutic use of medicinal products and devices.

Due to the differences across Europe in embryo research regulation these do not contain specific guidance for embryonic stem cells but such cells, if used in therapy are expected to fall under this Directive. MHRA, HTA, Gene Therapy Advisory Committee (GTAC) and HFEA are reviewing the regulatory pathway for potential embryonic stem cell derived therapies and a provisional route map is available on the web. [Ref: <http://www.dh.gov.uk/ab/GTAC/index.htm>]<sup>24</sup>

21 <http://www.publications.parliament.uk/pa/ld200708/ldbills/006/08006.i-iv.html>

22 [http://www.dh.gov.uk/en/Consultations/Responsestoconsultations/DH\\_4132358](http://www.dh.gov.uk/en/Consultations/Responsestoconsultations/DH_4132358)

23 Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use <http://europa.eu.int/eur-lex/lex/LexUriServ/LexUriServ.do?uri=CELEX:32001L0083:EN:HTML>

24 [http://www.hta.gov.uk/search.cfm?FaAreaI=CustomWidgets.content\\_view\\_1&cit\\_id=349&useCache=false](http://www.hta.gov.uk/search.cfm?FaAreaI=CustomWidgets.content_view_1&cit_id=349&useCache=false)

## Appendix 4: Stem cell science

In the early embryo the cells present have the ability to differentiate into any of the cell types which will eventually be present in the body (or other embryonic tissue, such as the placenta and membranes). These cells are described as totipotent. Once the embryo begins to develop (from about the 8 day stage) most cells will lose this totipotentiality and differentiate into specific cell types. Some cells, for example, those of the bone marrow, retain the ability to differentiate into several different cell types and are known as pluripotent cells. 'Stem cells' refers to those cells which retain the ability to differentiate into different cell types, rather than only being able to replicate into the same cell type again. Such cells could be derived from embryos, fetuses, umbilical blood or adult cells.

It is possible that stem cells could ultimately replace any damaged or degenerated tissue, for example, cardiac muscle after a heart attack, brain tissue in Parkinson's or Alzheimer's disease or pancreatic islet cells in type 1 diabetes. Stem cells given to the patient would differentiate into the tissue which requires replacement or repair. One difficulty with any transplantation procedure is that the human body can reject cells that do not exactly match those of the recipient. Using transplanted tissue originally from the recipient (autologous), would remove this problem and could also improve the availability of therapy. Thus the aim of therapeutic stem cell research is to create stem cells containing nuclear DNA from cells derived from the recipient which would not give rise to the risks of rejection. Such autologous transplantation has been widely available for years in the form of bone marrow harvesting and transplantation during chemotherapy for haematological malignancies.

Stem cells may also be used in vitro as models for cells and tissues with specific diseases enabling drug therapies to be tested or disease progression to be studied in detail.

### Sources of stem cells

There are three sources of stem cells.

#### 1. Embryonic

These are pluripotent cells (they can turn into any cell type). They could be used either:

- a) To create autologous matched cell lines using SCNT (stem cell nuclear transfer – see below). These can be created using cells from sufferers of a particular disease to provide models of disease and derive therapies. Eventually, these techniques might also be used to derive autologous embryonic stem cells from normal cells to provide cells or tissues to repair an individual's damaged organs or cells.
- b) To create cell lines that could be used by a large number of recipients. These lines can also be used to study the processes involved in cellular development and differentiation. Due to the lowered immunogenicity of embryonic cells it may be that a relatively small number of lines is required in order to provide matched tissue for a wide range of recipients.

#### 2. Fetal

Fetal cord blood contains adult type stem cells. Some organisations offer banking of this blood in the hope that in the future it may provide stem cells for the donor. At present the techniques do not exist to make this a reality. Fetal tissue has also been studied to provide multipotent cells to repair injured tissues such as neuronal cells in Parkinson's disease or spinal cord injury. After the embryonic stage most such fetal tissue will be, at most, multipotent, unless it can be modified to regain pluripotency.

#### 3. Adult

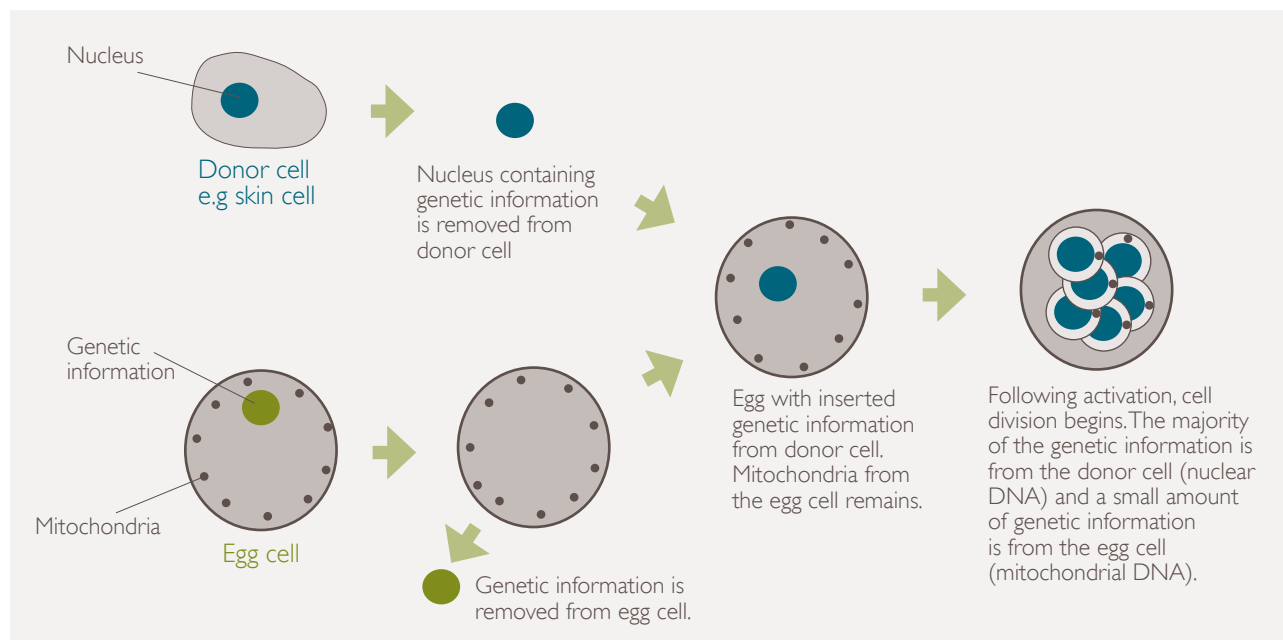
This is the most attractive route to remove many of the ethical arguments that arise over the use of gametes, embryos or fetuses.

Adult stem cells are already widely used in bone marrow transplantation where the multipotent bone marrow cells are reimplanted following chemotherapy to replace the bone marrow cells destroyed during therapy. Some success has been reported using similar cells to repair heart damage after infarction. There is however, dispute as to whether these cells actually differentiate into cardiac tissue or have other effects (for example, on the immune system) that improve outcomes in this situation.

Work has also focused on processes that could allow adult somatic (not gametes – eggs or spermatozoa) cells to be 'reprogrammed' to regain the properties of multipotency or, ideally, pluripotency. There have been some reports of success in this research but, as yet, none have been sufficient to be certain that this technique will be an effective source of stem cell lines.

### Somatic cell nuclear transfer (SCNT)

The nucleus from a normal (somatic) cell is removed and placed into an unfertilised egg. The cell then behaves as a fertilised egg and begins to develop as an embryo. Stem cells exactly matched to the donor of the nucleus can then be isolated from the embryo, be cultured, and encouraged to differentiate into specific cell types for study. The generation of embryos from which stem cells can be harvested using somatic cell nuclear transfer is extremely inefficient, with a success rate in animals currently less than 0.1%. Promising research in non-human primates has recently been reported, but the technique has not yet been achieved in humans. The egg used may either be human or animal. The latter creates an interspecies embryo of the type described in section 4A (5)b of the Bill. This is sometimes termed a 'cytoplasmic hybrid'.



## Appendix 5: Site visits

### Meetings April 2007

#### CURE visit to China

#### 1 April – 5 April: Bionet workshop

Informed consent in reproductive genetics and stem cell technology and the role of Ethical Review Boards

Separate Bionet report available.

[http://www.bionet-china.org/pdfs/BIONET\\_Ist\\_Workshop\\_Report.pdf](http://www.bionet-china.org/pdfs/BIONET_Ist_Workshop_Report.pdf)

As part of the Bionet workshop, CURE delegates visited the following institutions:

- Beijing Genomics Institute
- 3rd Hospital Beijing; ART clinic of the hospital

#### 6 April

*China National Centre for Biotechnology Development (CNCBD)*

Dr Qinghua Zhao

Director, Division International Cooperation

Yutao Hua

Medical Biotech Division

Hongbo Fu (Susie)

Assistant Researcher, Division Int Cooperation

Stem cell researchers

Prof Xuetao Pei (Tony)

Director, Beijing Institute Transfusion Medicine  
Chief Scientist, 'Stem cell and tissue engineering' programme in 863 (High tech) programme

Prof Alex Zhang

Director Cell therapy Centre, Beijing Institute Genomics

Prof Hongkui Deng

Cell Biology and Genetics, Peking University

National Policy Committee of ISSCR



Prof Qi Zhou	Stem cell and Regenerative Medicine Centre Institute of Zoology, CAS
<i>Sinovac</i>	
Mr Weidong Yin	CEO
Mr Zhang Jiansan	Deputy General Manager
Ms Nan Wang	Vice President for R+D
Mr Su Lin	Director for vaccine production Head of Influenza research
Ms Guang (Helen) Yang	International Business Manager
<i>Tsinghua University</i>	
Professor Rao Zihe	President, Nankai University (member of CAS)
<b>7 April</b>	
Professor Renzong Qiu	Chinese Academy of Social sciences Ministry of Health Ethics Committee
Dr Brendon Smith	Head LSE China
<b>8 April</b>	
<i>Chinese Academy of Sciences (CAS)</i>	
Professor Chen Zhu	Vice-president
Professor George Fu Gau	Director-General Institute of Microbiology
Mrs Chen Sai-Juan	Haematologist
Xu Ang	Bureau of International Cooperation
<b>9 April</b>	
<i>Chinese Academy of Medical Sciences (CAMS) / Peking Union Medical College (PUMC)</i>	
Prof Zhan Qimin	Vice-president CAMS and Director State Key Laboratory of Molecular Oncology
Dr Wei Qiang	Virus research, Inst of laboratory animal science
*Dr Ye Tiehu	Director Clinical Trial Centre, Chair ethics committee, PUMC
Dr Li Taisheng	Infectious Disease Specialist, PUMC
*Dr Tian Guoqing	Vice Director Department TCM
Dr Wang Jianwei	Director ID laboratory, Institute of Pathogen Biology (infectious diseases)
Wang Anyou	Master for Management of Health Service
Yuhong Jiang	Programme Officer
<i>Ministry of Health (MoH)</i>	
Ge Lijun	Director, Division of European, American and Oceanian Affairs, Department of International Cooperation
Qi Guoming,	Director of Chinese Medical Ethics Expert Committee of MoH
Prof Renzong Qiu	Deputy Director
Li Shunwei	Professor of Neuropsychiatry
Wang Jinqian	Dept Med Sci Tech & Education, MOH Division of Technology Appraisal and Promotion
<i>Chinese Centre for Disease Control and Prevention (CDC)</i>	
Professor Wang Yu	Director CDC
Professor Dong Xiaoping	Director Division S+T, CDC
Professor Yong-Zhen Zhang	Chief, Department RABIES of Haemorrhagic Fever
Xu Yuelong	Deputy Director CDC
Ms Zheng Liping	Program Officer
<b>10 April</b>	
<i>You An Hospital / Capital University of Medical Sciences</i>	
Professor Ning Li*	President You An Hospital (transplant surgeon)
Professor Che	V-President and Chair ethics committee
Professor Jin Ronghua	Chief Physician
Professor Wa	Foreign Affairs
Professor Jao	Director clinical trial centre
Assoc Prof Huang Chun	Vice-President of You-An Hospital
Dao Rina	Attorney-at-law, Genesis Law Firm, member ethics committee You An Hospital
Professor Duan Zhong-ping	Vice-President You-An Hospital, Director artificial liver treatment & training centre
Professor Hao Wu	Director Dept Infect Diseases

Li Yiting	Director of Office Capital University of Medical Sciences
Huiping Yan	Vice Director and Secretary of the Beijing Medical Ethics Association
Xinyue Chen	emerging ID
Mrs Lu	ID Interpreter

Academic Bioethicists  
Professor Li Benfu  
Professor Yali Cong

## October 2007 – CURE visit to China

Programme

### 9 - 11 October

Bionet workshop, Shanghai

Ethical governance of reproductive and stem cell research and stem cell banks

Separate Bionet report available.

[http://www.bionet-china.org/pdfs/BIONET\\_2nd\\_Workshop\\_Report.pdf](http://www.bionet-china.org/pdfs/BIONET_2nd_Workshop_Report.pdf)

### 12 October

Sinovac / CDC clinic trial base

Clinical site staff

Review of vaccine trial – phase II trial of Panflu (H5N1 vaccine)

### 13 October

Professor Huizhen Sheng

### 15 October

Chinese Academy of Medical Sciences / Ministry of Health

Professors Qiu Renzong

Professor Xiaomai Zhai

State Food and Drug Administration (SFDA)

Chen Xingyu

Director, Division of Cooperation

Weng Xinyu

Department of Drug Safety and Inspection

Zhang Yanli

Department of Drug Registration

Li Jinju

Department of Drug Safety and Inspection

### 16 October

Institute of Health Sciences, Shanghai

Discussion with researchers and tour of facility

Shanghai Institute of Medical Genetics

### 17 October

Huashan Hospital / Fudan University

## November 2007 – CNCBD delegation to UK

### Delegates

Ms Cao Cai,

Deputy director

Certification Committee for Drugs, SFDA

Prof Zhou Qi

State Key Lab of Reproductive Biology

Institute of Zoology

CAS

Prof Zhang Yu

Cell Therapy Center, Xuan Wu Hospital

Mr Shi Dongsheng

Director of Administration Office

China National Center for Biotechnology Development

Mr Zheng Yuguo

Director Medicine Biotechnology Division

China National Center for Biotechnology Development

Mr Hua Yutao

Project Manager, Bio-business Division

China National Center for Biotechnology Development

## Programme

26 November

Dr Janet Wisely	National Research Ethics Service
Dr Mark Bale	Deputy Director of Scientific Development and Bioethics, Department of Health (England)
Dr Stephen Minger	Stem cell researcher King's College London, Human Tissue Authority
Professor Brian Salter	Global Biopolitics Research Group, Human Tissue Authority

## 27 November

*Medicines and Healthcare Devices Regulatory Authority (MHRA)*

Dr Chris O'Toole	Head of Research, Human Fertilisation and Embryology Authority
Dr Marc Taylor	Deputy Director, Research Standards and Governance, Department of Health (England)

MRC senior staff

Diana Dunstan	Director of Research Management Group
Jane Lee	Director of Corporate Affairs Group
Tony Peatfield	Head of Corporate Policy
Catherine Elliott	Clinical Research Ethics and Liaison

CURE members

## 28 November

Oxford University / MRC facilities  
MRC Human Immunology Unit  
Oxford Centre for Diabetes and Endocrinology and Metabolism  
Ludwig Institute for Cancer research



Medical Research Council  
20 Park Crescent  
London  
W1B 1AL

Tel 020 7636 5422  
[www.mrc.ac.uk](http://www.mrc.ac.uk)

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