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# Recommendations on best practice in the ethical governance of Sino-European biological and biomedical research collaborations

**BIONET EXPERT GROUP REPORT**

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SIXTH FRAMEWORK PROGRAMME

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# Foreword

## Professor Christoph Rehmann-Sutter
## Expert Group Co-Chair

Collaboration is the trick that makes great human achievements possible. Modern biomedical science in fields such as stem cell research, genetics, biobanking or pharmaceutical research, is no more just the solitary intellectual work of ingenious minds. Innovation happens largely within collaborations, big laboratory networks and international, interdisciplinary research consortia. And collaborative research takes place in the real world. Hence, the social reality of biomedical research inevitably contains politics, institutional power and inequalities regarding resources and power. In cultural and social processes not just scientific and humanitarian but also commercial interests materialize. It was no coincidence that the work of BIONET itself – which focussed on the ethics of European-Chinese research collaborations – was also such a collaborative undertaking. However, it was quintessentially a reflective sort of collaboration. This implied that it had to be mindful of its own implications and of the quality of cross-cultural interactions.

Here, BIONET's Expert Group presents its report containing an assessment of the most urgent ethical issues arising from Sino-European research collaboration in biomedical sciences and it concludes with 30 recommendations for improving ethical governance of such collaborations. Like all human work it is fallible and the recommendations will need to be reconsidered as circumstances change. But it is the best advice the Expert Group could find after three years of information gathering, mapping and deep, engaged discussions. It is directed to a multitude of actors and institutional bodies both in China and in Europe who together steer and shape research collaborations in real time.

The Expert Group is grateful to the BIONET project management, to all the partners in the BIONET consortium and to those innumerable people who have helped to realise the seven workshops and conferences (five of them in different cities in China) on a broad variety of challenging topics during the project's three year lifetime. We thank the Sixth Framework Programme of the European Union, the British Medical Research Council and the Wellcome Trust for financial support. A very helpful synergy emerged between BIONET and the work of UK Medical Research Council's 'China-UK Research Ethics (CURE)' Committee which presented the results of its work in conjunction with the BIONET Final Conference in September 2009 at the Wellcome Trust in London, where a draft of these recommendations were


**Biosafety at the Institute of Stem Cell Engineering, Changsha, Hunan**

discussed. I thank all contributors to this conference and the discussants in the audience, in particular Nick Bunnin, Hu Qingli, Detlef Niese, Peter Propping, Qi Guoming, Jochen Taupitz, Eero Vuorio and Zhu Wei, for ideas and constructive criticism, which has led to an improvement of many parts of this document.

In particular I thank the BIONET Research Fellow, Dr. Ayo Wahlberg, and the BIONET Coordinator, Professor Nikolas Rose for guiding a long and complicated institutional process with patience, reliable expertise, attention for details as well as for the big lines, for recognising all partners in their diversity and for their great friendship. Warmest thanks go to Professor Qiu Renzong who acted as Co-Chair of the Expert Group and whose vast knowledge, scholarly network and excellent bridge-building capacities between the far Eastern and the far Western parts of Eurasia have been of invaluable help. I thank all the members of the Expert Group very warmly for their engaged collaboration during all these years and for sharing their thoughts and expertise. Together we were able to reach a common language and understanding of moral issues, political-ethical topics, and committee work procedures. What has made the seemingly unattainable possible – to reach a joint and balanced assessment of bioethical issues of research between Chinese and European scholars from a variety of academic backgrounds, without imposing pre-set moral standards from one or the other side – has been the open mindedness of the members and their readiness to go beyond well-known intellectual routines, without giving up their ultimate concerns. For me, this has been a very rewarding personal experience.

**Christoph Rehmann-Sutter**
**Professor of Theory and Ethics in the Biosciences, University of Lübeck, Germany**

# Foreword

## Professor Qiu Renzong
## Expert Group Co-Chair

在Sixth Framework Programme of the European Union, the British Medical Research Council 以及 the Wellcome Trust 的支持下，BIONET经过三年的努力，终于在伦敦"善始善终"，落下了帷幕。以 Christoph Rehmann-Sutter 为主席的专家组，在三年之中聆听了来自不同领域的专家在四次研讨会和两次学术会议上对中欧生物医学和生物技术合作研究伦理管治的宝贵意见，拟订了"中欧生物医学合作研究伦理管治的最佳实践指南"（下面简称"指南"）。

这是所有专家组成员以及 BIONET 参与者三年辛勤劳动的结晶，但尤其要感谢作为专家组主席的 Christoph Rehmann-Sutter 教授的勤奋工作及其睿智的眼光，使得这份在中欧合作研究中具有里程碑意义"指南"得以高质量地完成。这份"指南"在规范今后中欧生物医学和生物技术合作研究，使之成为负责任研究中将起关键的作用，但我们也不低估贯彻落实"指南"中可能遇到的障碍和挑战。同时，中欧生物医学合作研究的丰富实践也将会进一步充实这份"指南"，使它与时俱进。回想这三年的历程，我们必须深切感谢 BIONET Research Fellow, Dr. Ayo Wahlberg和 BIONET Director, Professor Nikolas Rose 他们耐心的、艰苦组织协调工作，他们与专家组主席Christoph Rehmann-Sutter教授一起，在BIONET项目中是付出最多的，贡献最大的。作为我自己，我有幸与BIONET各位同事合作，尤其与 Christoph Rehmann-Sutter 教授在专家组内的合作，是一次难忘的经验，并希望今后与欧洲同行在生物医学研究及其临床应用的伦理管治方面能够有进一步有成效的、互惠的合作。

中国社会科学院哲学研究所/应用伦理研究中心教授 邱仁宗

With the support of the Sixth Framework Programme of the European Union, the UK Medical Research Council and the Wellcome Trust, the BIONET project held its concluding conference in London, where it was also kicked off three years ago. The project enjoyed a good start and finished with a good ending. Over the past three years, the BIONET Expert Group, chaired by Christoph Rehmann-Sutter, has listened to experts from different disciplines and has collected valuable suggestions over the four workshops and two conferences on European-Chinese biomedical and biotechnology research collaborations. As a result, the Expert Group has drawn up Recommendations on Best Practice for Ethical Governance of European-Chinese Biomedicine and Biotechnology Research Collaborations.

These Recommendations are the key results of three years of hard work done by all Expert Group members and BIONET participants. Special thanks is owed to the Chair of the Expert Group, as Professor Rehmann-Sutter's diligence and wisdom helped to achieve the delivery of these milestone

Recommendations on European-Chinese research collaborations. These Recommendations will play an important role in supervising future European-Chinese biomedical and biotechnical research collaborations. Yet we also cannot underestimate the possible obstacles and challenges the implementation of these Recommendations may face. Meanwhile it should be noted that further European-Chinese collaborative practices would enrich these Recommendations and provide valuable updates. Looking back at the past three years, we owe our most sincere gratitude to the persistence and hard organizational work done by BIONET Research Fellow, Dr. Ayo Wahlberg and BIONET Coordinator, Professor Nikolas Rose. They, together with Chair of Expert Group, have been most devoted to the BIONET project and contributed the most to its outcome. As for myself, I am honoured to have collaborated with all BIONET colleagues. It is especially a memorable experience to work with the Expert Group led by Christoph Rehmann-Sutter. I am looking forward to future collaborations with our European colleagues on the ethical governance of biomedical research and its clinical applications, with the prospect of producing fruitful and mutually beneficial results.

**Qiu Renzong**
**Applied Ethics Research Centre/ Institute of Philosophy Chinese Academy of Social Sciences**

# Executive summary

The BIONET Expert Group was composed of leading Chinese and European bioethics experts. Here the Group presents a **guide to best practice in ethical governance of European-Chinese biomedical research collaborations**. Governance, in this document, means steering of research on multiple levels, from inside and from outside. The 30 concrete recommendations are based on an open and mutually respectful and enriching process of substantial exchange of experience and expertise. They concern both regulatory and structural measures that should enable collaborative biomedical research between Chinese and European partners to be organized ethically. They should help to prevent the exploitation of unclear standards in transnational research collaborations and to protect those research participants and patients who become vulnerable in such settings.

## A. Basis and mandate

The BIONET Expert Group was co-chaired by a European and a Chinese scholar and composed of both Chinese and European experts. It worked on the basis of findings from six workshops and conferences (held in Beijing, Shanghai, Changsha, Xi'an, Shenzhen and London) between 2007 and 2009. They were organized within the framework of the EU-FP6 project BIONET, which was coordinated by the BIOS research centre at London School of Economics. Each of the focussed four-day workshops and conferences enabled intensive exchange between Chinese and European scientists, clinicians, lawyers, ethicists, regulators and social scientists about ethical and regulatory issues of collaborative research between Europe and China. They examined the forms of existing and raising European-Chinese collaborations in cutting-edge biomedical research fields such as reproductive and regenerative medicine, stem cell research, clinical trials of new drugs, biobanking and personal genomics.

The mandate was to elaborate recommendations for best practice in the ethical governance of European-Chinese biomedical research collaborations.

A preliminary version of the recommendations was presented and discussed at the BIONET final conference in London in September 2009 and the recommendations presented here have been revised in the light of those discussions.

## B. Problems identified

Issues in European-Chinese transnational research collaborations both in basic research and in the use of technology for research purposes can arise from social, cultural, moral, legal, political factors, and also from economical diversity among the persons, institutions and regions involved. This can lead to **unclear situations lacking regulatory coherence, multiple standards** and **gaps between governance**

**regimes**. New sources of conflicts of interests can emerge. There are also many **vulnerabilities** to be recognized among populations and groups who are potential participants in clinical trials, who may act as sample donors, or could be recipients of sub-standard therapies. In some countries or regions the systems of ethical and regulatory supervision are not yet fully developed. There is an unfulfilled and continuous need for capacity building on all levels in order to foster decision-making competence. And there are significant shortcomings in international governance and oversight. At present, there is no established international or inter-regional system of regulatory advice, ethical consultation and legal collaboration, which addresses unforeseen and emerging issues and could deal with unclear or suspicious cases, in order to protect those groups and individuals who may become vulnerable to powerful interests.

## C. Recommended regulatory measures

In many respects international standards already exist. But it is crucial for regulators to check whether the relevant international guidelines are adequately reflected in national legislations and to improve transparency and clarity regarding the applicable ethical review standards. There needs to be clarity for researchers about which rules apply for clinical trials and which for experimental therapy.

In order to address the possibility of cases of scientific misconduct, procedures should be in place that allow for suspension of a clinical trial.

For collaborations in the sector of biobanking it is important to make clear agreements about the kind of informed consent that donors will be required to give. The confidentiality of samples and related data must be protected, as must the privacy of the sample donors even where samples are shared across national borders. A controversial question in biobanks and genomics is whether, and how much, feedback about any personal clinically relevant information participants should be entitled to. We do not propose a single universal solution to this issue, but recommend that biobanks and genomics laboratories ensure that there are clear and transparent agreements on this question as part of the process of informed consent.

In stem cell research and reproductive medicine there are well-known and perhaps insurmountable regulatory discrepancies arising from the different interpretations of the moral status of the human embryo in different countries and regions. In all cases, however, it is crucial to clarify what procedures can be carried out on an embryo before implanting it in the uterus of a woman. The law must demand transparency regarding the conditions under which germ cells, embryos or embryonic tissue have been collected and must establish quality standards for 'clinical grade'

stem cells. In the translational context where research is applied to clinical practice, it is important that a thorough investigation of the safety and efficacy of experimental treatments is mandatory before offering them commercially to patients.

## D. Recommended structural measures

In all collaborative human subjects research projects it is vital that responsibilities and accountability are clearly assigned in advance. Transparency measures need to be taken to manage conflicts of interest. Capacity building measures on all professional levels involved in research are particularly important because they provide support and empowerment to decision-makers and to participants on all levels. They also help to avoid therapeutic misconception, coercion, undue inducement or influence. A key element in supervision of research is a system of independent and competent interdisciplinary ethics committees with supportive regulatory structures that encourages collaboration between different committees within countries and in-between countries. Adequate control and monitoring should be required in all participating countries where this does not already exist. To improve oversight, the effects of governance on the ground should be monitored using sensitive empirical research methods.

Especially for *clinical trials*, it is important that clinical trial results are publicly accessible regardless of the outcome of the trial and the location of the study site. Study designs should be made accessible through a clinical trial register.

For research in the fields of *genetics, genomics and for biobanking* it is crucial to separate different types of use of biobanks, in particular to make a clear distinction between medico-scientific biobanks and those used for forensic purposes. The purpose and use of the biobank should be explained to the donors and to the public. Biobanks need to establish guidelines for access to samples and data. Transnational biobanks should also develop an approach to benefit sharing that serves the public good. In cases of international fusion of biobanks, standards of fairness, accountability and transparency should be secured.

In *stem cell research, reproductive medicine* and *regenerative medicine*, each partner in an international collaboration should adhere to the laws of their own country. However, this does not necessarily mean that each project must be governed by the rules or the predominant moral views of the most restrictive partner country, as contractual arrangements can differ between partners in terms of the specific aspects of the research in which they will be involved.

We consider that one structural measure is particularly important: To establish a standing **Sino-European platform for research ethics**. This would be a sustainable framework for continuous improvement in research governance. It should be sensitive to

The recommendations set out a road map for developing ethical governance of research in international collaborations indicating the places where ethical issues can arise and sketching how to prevent them

unforeseen emerging issues in the progress of science, medicine and technologies and be a facilitator for continuous collaboration in bioethics between China and Europe.

## E. Aims and hopes

The Expert Group hopes that its recommendations for clarifying responsibility and supervision, improving transparency and building capacities on all levels will be attended to widely, and discussed both in Europe and in China. They are not written in stone but should be considered as key points for consideration, which need to be continually developed on the basis of new emerging insights and practices in biomedical research collaboration.

The recommendations are procedural in character, ie, they set out a **road map** for developing ethical governance of research in international collaborations, indicating the places where ethical issues can arise and sketching how to prevent them.

They refer to different layers of the networks of research governance, not only top-down regulation. Accordingly, they are **addressed to stakeholders** who participate on these different levels in steering international research, including national legislators, public oversight bodies and administrations, research funding agencies, research organizations, clinics, universities, individual scientists and private laboratories and also companies who are active in research.

**Beijing Genomics Institute**

# Chapter 1: Introduction

## 1. Aim

The aim of this report of the BIONET Expert Group is to provide a guide to best practice in ethical governance of European-Chinese collaboration in biomedical research.

The recommendations presented in this report refer to different layers of the networks of research governance, not only top-down regulation. Correspondingly, they are addressed to stakeholders who participate on these different levels in steering international research, including national legislators, public oversight bodies and administrations, research funding agencies, research organizations, clinics, universities, individual scientists, private laboratories and also companies who are active in research.

## 2. Mandate

The European-Chinese Expert Group was constituted in April 2007 within BIONET, a Coordinated Action Project, funded by the European Union research framework program 6. BIONET is a 21-partner European-Chinese collaboration on ethical governance in the life sciences, coordinated by the London School of Economics and involving leading Chinese institutions such as the Beijing Genomics Institute (Beijing and Shenzhen), the Hunan Institute of Reproduction and Stem Cell Engineering (Changsha), Peking University Health Science Centre (Beijing), Peking Union Medical College (Beijing) and the Chinese Academy of Social Sciences (Beijing).

The mandate of the BIONET Expert Group has been to work towards standards and guidelines for best practice in the ethical governance of research in the life sciences and biomedicine, with a specific focus on Europe-China collaboration. It could also act as advisor to actual and potential research partnerships, help in the development and oversight of regulatory procedures and standards, and provide a resource for those wishing to regulate or evaluate research in the life sciences and biomedicine in collaborations between Europe and China.

Governance means steering of research on multiple levels, from inside and from outside. The 30 concrete recommendations in this report concern both regulatory and structural measures that should enable collaborative research to be organized ethically. They should help to prevent the exploitation of unclear standards in transnational research collaborations and to protect those research participants and patients who become vulnerable in such settings.

The BIONET Expert Group was composed of 10 experts from China and Europe. It worked on the basis of findings from 5 workshops and conferences all held in China (Beijing, Shanghai, Changsha, Xi'an and Shenzhen) between 2007 and 2009, organized within the framework of BIONET. Each of the focussed four-day workshops and conferences enabled intensive exchange between Chinese and

European scientists, clinicians, lawyers, ethicists, regulators and social scientists about ethical and regulatory issues of collaborative research between Europe and China. They examined the forms of existing and raising European-Chinese collaborations in cutting-edge biomedical research fields such as reproductive and regenerative medicine, stem cell research, clinical trials of new drugs, biobanking and personal genomics.

The Expert Group was aware of existing international ethical guidelines on human subjects research, such as the Declaration of Helsinki, the WHO/CIOMS guidelines and the ICH-GCP guidelines, as well as different national and international laws. The group does not attempt to replace or duplicate them but acknowledges that in the specific field of its work – collaborative research between Chinese and European partners – a need for improvement exists. The recommendations in this report are specifically aimed at Sino-European collaborations in biomedical research, though they may well be useful and relevant for cross-national research involving other countries.

The work of the Expert Group, which led to the recommendations in this document, has been guided by the vision of an open and mutually enriching, respectful process of exchange of experience and expertise between the European and Chinese BIONET partners.

A draft of the 30 recommendations was openly and critically discussed at the BIONET Final Conference held 1-4 September 2009 in London at the Wellcome Trust. On the basis of suggestions and criticisms the draft was substantially revised resulting in this final version.

## 3. Status of recommendations

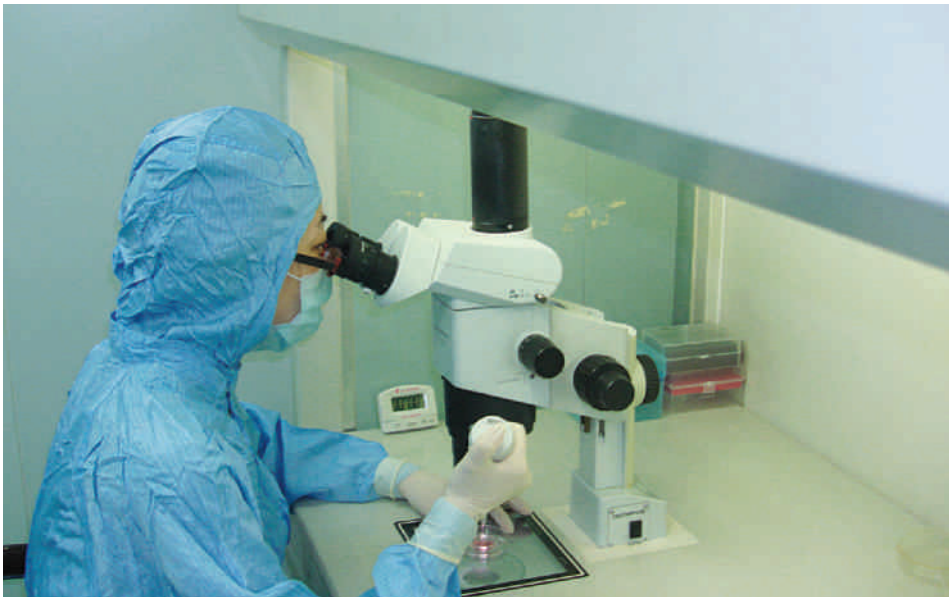
These recommendations have a purely advisory status. The Expert Group hopes that its recommendations contribute to:

- clarifying responsibility and supervision,
- improving transparency, and
- building capacities on all levels.

The ideas presented here should be widely heard and discussed. They are not carved in stone but should be seen as key points to consider. They need to be continually developed on the basis of emerging insights, new directions of research and changing conditions.

The recommendations are procedural in character. They set out a road map for developing a process of ethical governance of research in international collaborations, indicating the places where ethical issues can arise and sketching how to address them.

As a result, the recommendations do not have the character of guidelines. They positively refer to a series of existing international and national guidelines and laws on research ethics, such as those of the UNESCO, the Council of Europe,



**Stem cell scientist at work at the Institue of Stem Cell Engineering, Changsha, Hunan**

the Chinese Ministry of Health, the Chinese Ministry of Science and Technology and the World Medical Association's Declaration of Helsinki.

This report not only contains substantial recommendations but it also endorses a proposal for establishing a continuous and sustainable Sino-European Platform on Biomedical Research Ethics (SEPRE). Such a platform could enable continuous teamwork between European countries and China in matters of biomedical research ethics and it should be capable of reviewing the implementation of best practices in ethical governance of research collaborations in biomedicine and biotechnology as recommended by the BIONET Expert Group. It should provide continuous advice to research collaborations and to supervising and regulatory authorities in the future with regard to ethical implications of collaborative research between China and Europe. And it should conduct and stimulate open public discussions on the ethics of collaborative research between China, Europe and other countries.

## 4. Scope and limitations of the recommendations

In the tradition of good academic research, it is important for us to reflect on the process by which the Recommendations have been produced and the implications for their scope and limits. We believe that this will help readers to make a proper assessment of their value. Many of these difficulties are inherent to the Herculean task of creating consensus in bioethics recommendations for international collaborations in the field of the life sciences.

A. The recommendations are based on three years of discussion with bioethicists, social scientists and life scientists from China, and with participation from many, though not all European countries (13

Our aim is that our recommendations should function as advice to regulators on best practice rather than as a series of formal rules

countries in total). While we have had much engagement from the Chinese bioethics community, we would have liked to speak to more practicing researchers and clinicians, especially in the areas of human embryonic research and genetics, however it is always difficult to tempt practicing researchers away from their laboratories for discussions of this type. Inevitably, most of the participants at our events came from well-known laboratories, and were those who already had an interest in, and a commitment to, the bioethical and regulatory issues that were the topic of BIONET. Even though we had approximately 300 attendees at our various events, among who were a considerable number of clinicians and scientists, it was not easy to find those willing to discuss some of the most sensitive issues in their everyday practices. Similarly, while we did gain the attendance of many leading European biomedical researchers at our events, as is usual in Committees of this sort, the majority of those who were on our Steering Committee and Expert Group were bioethicists and social scientists.

B. The recommendations are based on discussion within the Expert Group, which met 13 times over the course of the three years, and for a total of 30 hours. Like any Group of this sort, we would have preferred more time for our deliberations. It should also be pointed out that while simultaneous translation was used for most of our discussions, the balance of contribution to the discussion came from European partners, although all partners had ample opportunity to comment in

**Epidemiology research in Dai Community, Yunnan Province**

writing on our successive drafts. There were undoubtedly problems of translation, and these were exacerbated by the fact that the language of debate among European bioethics does not always translate easily into Chinese. While the Group made great efforts to ensure that translation of meaning, and not simply of terms, was achieved, there were undoubtedly times when this hampered clear communication and clarification of some issues. These are the inevitable consequences of transnational discussions of this type, but they are nonetheless important to note.

C. The BIONET work plan set out the goal that the Expert Group would work to facilitate the establishment of standards and guidelines and to 'help in the development and oversight of regulatory procedures and standards'. While our recommendations tend towards the form of regulatory guidelines, our aim is that they should function as advice to regulators on best practice rather than as a series of formal rules. Further, our collaboration in some aspects of our work with the UK's Medical Research Council and its work on UK-China collaborations, and the lack of participation of similar bodies from other European countries, may mean that the regulatory and ethical regime of the UK weighed more heavily in our discussions than that from other European countries. It is also the case that many of the bioethics regulations being developed in China have also taken the UK regulatory frameworks as a model in some respects. Although BIONET aimed to facilitate scientific collaborations between the PRC and European researchers from different countries, it was challenging to try to embrace the many cultural, socio-political and regulatory differences among European countries, let alone the diversity within China. For this reason, we have included a recommendation for more qualitative, empirical research on these issues which would give more consideration to differences among European and Chinese approaches and their significance for the governance of EU-China collaborations.

D. Our recommendations focus on normative and regulatory issues, and they need to be supplemented with an understanding of the obstacles encountered in the relations between such a normative infrastructure and the actual problems encountered in the daily life of ethics boards, hospitals and clinics, laboratories, researchers, research subjects and patients. The limitations of our scope meant that we were not able to conduct detailed empirical research into the ways in which bioethics institutions work in interactions with science policy-making and the practical challenges of everyday life, either in China, or in European countries which differ in their own experience and practice in medical ethics. Further research is necessary to explore the actual functioning of bioethics institutions, the nature and availability of supervisory institutions,

problems of implementation and monitoring of regulations, and the daily practices under which patients, doctors and other medical professional meet. For this reason, while BIONET has made a valuable start, the work of researchers on the bioethical governance of biomedical research in China and in Europe, and in collaborations between these regions, is not yet completed.

## 5. Composition of the BIONET Expert Group

Doctor Ole **Döring**, German Institute of Global and Area Studies, Hamburg, Germany

Professor **Cong** Yali, Peking University Health Science Centre, Beijing, China

Professor Herbert **Gottweis**, Department of Political Science, University of Vienna, Austria

Professor Wolfgang **Hennig**, Institute of Genetics, University of Mainz, Germany & CAS-MPG Partner Institute for Computational Biology, Shanghai, China

Professor **Lu** Guangxiu, CITIC-Xiangya Reproductive and Genetic Hospital, Changsha, China

Professor Professor **Qiu** Renzong, Chinese Academy of Social Sciences, Beijing, China (**co-Chair**)

Professor Christoph **Rehmann-Sutter**, Institute for the History of Medicine and Science Studies, University of Lübeck, Germany (**Chair**)

Professor Genevra **Richardson**, School of Law, King's College, United Kingdom

Professor Margaret **Sleeboom-Faulkner**, Department of Anthropology, University of Sussex, United Kingdom

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# Chapter 2: Problems and Key Issues Identified

Many of the dilemmas faced by research ethics involve the difficult question of how to balance two very important interests, namely that of society – in the form of medical and scientific progress – and the interest of those who will put their health and life at risk in order to achieve such progress. While modern bioethics was born out of this very concern, the discourse and debates over the years have been shaped by time and context. Often the central dilemmas facing scientists, ethicists and policy-makers are similar regardless of where research takes place. Increasingly however, new scientific approaches and technologies, such as biobanking and stem cell research give rise to new moral and normative issues. Traditional biomedical research also poses new problems because research takes place in contexts increasingly dissimilar to those in which traditional research ethics was initially developed. To take an example, enrolment of subjects in multi-centre (which often means multinational) trials increased dramatically since the early 1980's[1]. And much of it is taking place in countries where the economic, social, political and cultural backgrounds are novel to those sponsoring or carrying out research. In fact, the number of developing country partners increased by 444 percent between 1992 and 1998[2]. To achieve a fine balance between normative universalism and operational context-sensitivity in this case requires dialogue between all partners involved.

The Sino-European forum BIONET has aimed at achieving just such a balance by conducting various workshops, conferences and other platforms for debate and discussion. As the BIONET participants have noted: 'Ethical governance (…) is not just about how guidelines and regulations are implemented and followed, rather it involves a complex system wherein research practice is guided by respect for the rule of law, transparency, scientific and ethical accountability, human rights and absence of corruption. It involves collaboration and coordination between not just individual scientists, but increasingly between an entire network of scientists (principal investigators, junior researchers and postgraduate students), university departments, commercial organisations, clinicians, patients, scientific journals, Ministry officials, local government departments and others'[3] The following provides an overview of the problems and key issues identified through this process.

## General Biomedical Research and Clinical Trials

### International Standards and context sensitivity

International research comes in various forms, sometimes involving multiple partners, sponsors, countries and trial sites. Given the particular focus of the Sino-European platform, the research in questions will involve Chinese partners and partners from at least one European country,

**1** For China, in 2007, an average relative annual growth rate of biopharmaceutical clinical trials of 47.0 % has been reported, which is the highest worldwide: Fabio A. Thiers, Anthony J. Sinskey and Ernst R. Berndt (2008), Trends in the globalization of clinical trials, Nature Reviews Drug Discovery 7: 13-14. Cf. Solomon R. Benatar (2007) New Perspectives on International Research Ethics, in Matti Häyry, Tuja Takala and Peter Herisosone-Kelly, Ethics in Biomedical Research: International Perspectives, Amsterdam and New York: Rodopi, p 10.

**2** Ibid.

**3** BIONET Final Report, www.bionet-china.org/pdfs/BIONET_Final_Report.pdf

and this at all levels: political, scientific and infrastructural. Such collaboration can easily give rise to differing and conflicting moral and legal issues. Often in multinational research, different rules may conflict and situations may lead to gaps in responsibility and accountability. Dealing with diverse types of governance can be tricky despite the existence of international guidelines and treaties. BIONET has recognized the issue of multinational governance as key to developing a smooth relationship between the partners involved[4]. Researchers and sponsors from Europe, for instance, may face unexpected cultural differences among their colleagues in the host population, and both partners may lack the experience or resources to tackle conflicting ethical and policy standards. For example, the accepted international standards for informed consent may contain requirements – such as signing individual consent forms – which cannot be practically implemented in certain remote areas and provinces, either due to illiteracy or established cultural practices of decision-making. Separating standards and procedures can be an important solution towards harmonizing requirements[5], in other words, while the requirement to obtain individual consent can be a universal standard, procedures of obtaining such consent (written form, audio-visual material, oral consent) can be elaborated according to need and context.

In such international collaborations a key issue at hand is the procedures by which standards are chosen and responsibilities are defined in order to achieve transparency. Another actor, the research ethics committee, can play an important role in ensuring harmonization between universal standards and appropriate local approaches. BIONET members particularly emphasized the role of review committees in ensuring that provisions are made for adherence to appropriate ethical procedures. It was recognized at various points during workshops and meetings that *awareness of the potential for conflict* was an important measure in preventing conflicts and working out adaptable solutions early on. Importantly, however, awareness can only be achieved through 'adequate and continuous training' of all actors involved[6], which may need to include extensive interdisciplinary and context-based knowledge.

**Participant recruitment**

In many research settings, be it in hospitals or remote areas, the main actor between the participant and the research team tends to be the participant's primary physician. Sometimes, the physician is herself or himself a member of the research team. This not only paves the way for a potential conflict of interest, but also requires a significant shift in the traditional doctor-patient relationship[7]. In the medical context, it is understood that the doctor or health care team will have the patients' best interest in mind. Once the physician puts on

**4** BIONET 3rd Workshop report, www.bionet-china.org/pdfs/BIONET_3rd_Workshop_Report.pdf

**5** Ruth Macklin (2008), Appropriate Ethical Standards, In: Ezekiel J. Emanuel, Christine Grady, Robert A. Crouch, Reidar K. Lie, David Wendler, The Oxford Textbook of Clinical Research Ethics, New York and Oxford: Oxford University Press p.714-5; Cong, Yali (2004), Doctor-Family-Patient Relationship: The Chinese Paradigm of Informed Consent, The Journal of Medicine and Philosophy 2004 29(2):149-178

**6** BIONET 3rd Workshop report, Report, www.bionet-china.org/pdfs/BIONET_3rd_Workshop_Report.pdf

**7** Franklin G. Miller (2009), Recruiting Research Participants, In: Ezekiel J. Emanuel, Christine Grady, Robert A. Crouch, Reidar K. Lie, David Wendler, The Oxford Textbook of Clinical Research Ethics, New York and Oxford: Oxford University Press p.397

the researcher's hat however, the line between therapy and research needs to be clearly defined. The physician may need to take extra steps in ensuring that the shift in the relationship has been explicitly made. Often, even in optimal situations, participants may feel undue pressure because the offer comes from a figure of authority whom 'patients are interested in pleasing or to whom they feel a debt of gratitude'[8]. It is not unlikely that in contexts where patients traditionally depend more heavily on the advice of their physician, or where the medical context requires physicians to be more paternalistic, the element of trust may play a much stronger role on the psyche of the participant. In fact, some data from China[9] suggests that many patients agree to enter research either with the hope of therapeutic benefit or to ensure a better relationship with their doctor.

In order to carry out the recruitment of participants without breaching ethical guidelines, physicians need to be aware of their conflicting roles. A participant at one of BIONET's workshops reported that in China, until very recently, it was common for physicians to take extra biological samples for research without obtaining informed consent from their patient-participant[10], a sign perhaps that the problematic nature of such actions are not always clear within the medical setting. Although the researcher-participant relationship is sometimes seen as similar to that of a contractual agreement, physicians fulfilling the dual role of physician-investigator, tend to enjoy a special position of trust arising from their position. The ethical problems arising from such interactions were explicitly and implicitly brought forward at various meetings, as was the concern that particular attention must be given to the protection of 'vulnerable' individuals and groups, ensuring that such participants are not systematically recruited due to their easy availability. At the same time, research must address the needs and priorities of the community or population in which it is carried out, without necessarily excluding 'vulnerable' subjects who may benefit – in the short-or longer term – from the fruits of research.[11]

Research ethics committees, can play an important role in ensuring harmonization between universal standards and appropriate local approaches

### Inducement and understanding

In order to fulfil the ethical requirements of participant recruitment, the procedure of informed consent must meet two important criteria: understanding and voluntariness. In other words, healthy volunteers and patients must first be enabled to understand that they are participating in research and not in a therapeutic intervention, and they must enter

**8** Ibid p.398

**9** Ibid

**10** BIONET 3rd Workshop report, Report, www.bionet-china.org/pdfs/BIONET_3rd_Workshop_Report.pdf

**11** Leslie A. Meltzer and James F. Childress (2008) 'What is Fair Participant Selection?', In: Ezekiel J. Emanuel, Christine Grady, Robert A. Crouch, Reidar K. Lie, David Wendler, The Oxford Textbook of Clinical Research Ethics, New York and Oxford: Oxford University Press p. 380

The distinction between therapy and research is central to informed consent... therapeutic misconception – the false belief of participants that they are consenting to a therapeutic procedure instead of an experimental one – is widespread in Chinese research contexts

research freely and voluntarily, that is without any form of coercion or undue inducement.

Although informed consent has been central to research ethics since its early days, disagreements persist regarding what participants need to understand, so that their consent can be said to be 'informed'.[12] In any case, the distinction between therapy and experiment (although not clear in some research circumstances) is central to this understanding. Participants must first and foremost understand that they are contributing to generalizeable knowledge, which may or may not lead to benefits for future patients, but will almost certainly be of no benefit to them. An important impediment to adequate informed consent is therapeutic misconception, the false expectation on the part of participants that they are in fact consenting to a therapeutic procedure instead of an experimental one.

Members of BIONET recognized that therapeutic misconception was widespread in Chinese research contexts, especially in socio-economically disadvantaged areas as it happens also in Europe under certain circumstances. A commentator at the 3rd BIONET workshop suggested that patients, physicians and administrators alike tended to regularly confuse medical care and research.[13] More dangerous still, another scholar suggested that researchers often exploit therapeutic misconception to 'lure' patients into participating in research.[14] This may turn out to be an important focus for future collaboration as it is a core requirement of research ethics that such misconception and perversion of consent procedures are eliminated.

This particular concern leads us to the second important facet of consent: voluntariness. Theorists continue to debate the appropriateness of various inducements for participation. While it is generally accepted that coercion (persuasion under force or threat) is definitely unacceptable, not everyone agrees on the distinctions between appropriate and undue form of influence and inducement.

This remains a central focus of much of this discourse, leading to concerns over what exactly might constitute exploitation of research participants. Various factors tipping the balance from adequate consent procedures to inappropriately obtained consent may include the educational and economic situation of participants, monetary, medical or other benefits offered and the relative position of power and trust enjoyed by those seeking consent and those giving it. It was suggested that individuals in China often enter research in order to get 'free health care'[15], a fact that remains an important concern in the establishment of any studies involving human participants.

### Conflict of interest

As suggested earlier, physician-investigators face a potential conflict of interest when recruiting their own patients or when acting from their

**12** David Wendler and Christine Grady (2008), What Should Research Participants Understand to Understand They are Participants in Research?, Bioethics Vol. 22 Issue 4, pp. 203-208, May 2008

**13** BIONET 3rd Workshop report, Report, www.bionet-china.org/pdfs/BIONET_3rd_Workshop_Report.pdf

**14** Ibid

**15** Ibid

position of authority and trust. As researchers, their goal cannot solely be the best interest and protection of participant, and the physician-investigator role can be a difficult balance to achieve. Regulatory bodies and research ethics committees have a particularly important role to play in the diffusion of this tension by ensuring that protective mechanisms are properly set up.

The problem is compounded by the fact that there is an increased financial interest in biomedical research, and in particular international biomedical research[16]. Commercial interest and profit may act not only as a supplementary incentive for local physician-investigators but may also pose a threat to their integrity, as well as to those of review committees and other administrative members if these also stand to profit from lucrative research. At the 3rd Workshop, a member of BIONET noted that the lure of financial profit were often a key cause behind exaggerated benefits being reported as well as downplaying possible adverse effects.[17] Deception regarding the true facts of research is of course impermissible, except perhaps for certain specific research studies (which have to go through extremely rigorous ethics review and that specifically require deception) and there needs to be clear demarcation regarding what constitutes adequate disclosure.

It is generally accepted that the independence and transparency of review committees is essential in ensuring that research is carried out with full integrity. The members of BIONET noted however, that there is a distinct lack of independence of ethical review committees as many are chaired by senior doctors of a hospital, and that external members often were not granted voting rights.[18] Regulations and oversight constitute another protection from the potentially exploitative nature of for-profit research. Members of BIONET noted, however, that China has no regulations covering the relationship between drug or equipment manufacturers and physicians-investigators or research ethics committee's members, and suggested that commercial interests may sometimes override participant protection.[19] The intricate and sometimes indirect influences on the independence and integrity of the main players may turn out to be one of the most difficult issues to solve, especially in the case of international research, where partners from two very different regions are used to working within very different social, political, administrative and legal contexts.

### Distribution of benefit

One of the central and often dividing concerns regarding international research – usually carried out by researchers from Western Europe or the US in developing countries or emerging economies – is the fear and reproach that in many cases researchers would conduct their studies and then leave without a second thought for the populations in which the studies or trials had been carried out. It is unclear

16 Trudo Lemmens (2008), Conflict of Interest in Medical Research, In: Ezekiel J. Emanuel, Christine Grady, Robert A. Crouch, Reidar K. Lie, David Wendler, The Oxford Textbook of Clinical Research Ethics, New York and Oxford: Oxford University Press p. 748

17 BIONET 3rd Workshop Report, Report, www.bionet-china.org/pdfs/BIONET_3rd_Workshop_Report.pdf

18 Ibid

19 Ibid

**'Hand-made cloning' at the Beijing Genomics Institute in Shenzhen**

whether such 'helicopter' or 'briefcase' research is frequent[20] but given the persistent 10/90 gap in the global research agenda (the sorry fact that 90 percent of the research resources go to diseases that affect only ten percent of the global population), it is likely that the real needs and priorities of local populations are often overlooked. Much has been said regarding what constitutes appropriate benefit to the communities participating in research, but a generalizeable benefit-sharing scheme still seems elusive.

Members of the BIONET, echoing thoughts from other bioethicists, have noted that capacity building through collaboration may in fact address some of the infrastructural and healthcare needs of participating populations. BIONET has suggested that such collaborative research should ideally contribute towards building and strengthening public health systems, clinics, universities and must include frameworks that facilitate data sharing between collaborating partners. Some BIONET members felt that attracting research and clinical trials to China may contribute towards improving scarce resources or towards supporting existing medical infrastructure[21] but this may require careful balancing of societal interest and the interest of research participants, so that the latter are not exploited in order to contribute to the former.

### Accountability and review capacity

Related to the issue of capacity building, many BIONET members have insisted on the need to train ethics committee members, especially under the emerging Chinese three-tier governance system, which would require knowledge of a multi-layered governance system. Members reported that while some institutions, in bigger cities such as Beijing and Shanghai have good

**20** Ezekiel J. Emanuel (2008) 'Benefits to Host Countries' In: Ezekiel J. Emanuel, Christine Grady, Robert A. Crouch, Reidar K. Lie, David Wendler, The Oxford Textbook of Clinical Research Ethics, New York and Oxford: Oxford University Press p.719

**21** BIONET 3rd Workshop Report, Report, www.bionet-china.org/pdfs/BIONET_3rd_Workshop_Report.pdf

experience in forming and running such committees, such expertise is not consistent across the country.[22]

Specific concerns identified on the BIONET platform include: differing capacity level, lack of independence, lack of resources to monitor research once approved, lack of information from researchers regarding the details of the study (risk-benefit analyses, informed consent and compensation), and lack of members with ethics qualification and lack of resources to train researchers in ethics. Finally it was noted that large gaps remain in the quality of informed consent procedures, such as explanation regarding randomization, placebos, other available treatments and risks.[23] The establishment of trained ethics committees and standardized review process was therefore identified as a key issue for BIONET recommendations.

Furthermore, BIONET members reiterated the need to establish monitoring and control systems. Such monitoring would include, for example in the case of clinical trials, the collection and reporting of safety, quality and efficacy data[24]. Members emphasized that the poor or fraudulent reporting of data were unethical practices and that the Chinese Ministry of Science and Technology has specifically addressed these concerns through the 2007 Regulation on Scientific Misconduct. Since, 70 cases of misconduct have been reported through a whistle-blower website.[25]

**Monitoring and Supervision**

Beyond the necessary steps for review and supervision outlined above, BIONET reached consensus on a significantly stringent supervision mechanism, involving the state and publishing procedures. Clinical trials need to be registered with authorities, which then should hold the right to suspend trials in cases of misconduct or severe adverse effects on participants. A current concern of review in many international studies is the lack of continuous monitoring of approved studies but the necessity of such monitoring is essential in the conduct of research. The importance of social and empirical research was recognized in evaluating regulatory frameworks that are put in place and the feasibility and efficacy of standards and procedures.

## Specific Ethical Issues Related to Biobanks

Biological samples (tissues, blood, urine etc.) have historically been collected and stored for various research purposes, but the advent of genetics and genomics, rapid and accurate DNA sequencing technologies has led to the emergence of a multitude of biobanks, which often include not only DNA or other biological samples, but also genealogical information, as well as health and lifestyle data. The establishment of biobanks however, also gives rise to ethical concerns regarding informed consent for future research or other uses, protection of privacy and confidentiality and the

**22** BIONET Final Report, www.bionet-china.org/pdfs/BIONET_Final_Report.pdf

**23** BIONET Final Report, www.bionet-china.org/pdfs/BIONET_Final_Report.pdf

**24** BIONET 3rd Workshop Report, Report, www.bionet-china.org/pdfs/BIONET_3rd_Workshop_Report.pdf

**25** BIONET 3rd Workshop Report

delicate nature of data arising from genetic research.

### Terminology and the nature of different biobanks

Because biological samples have been collected at different times, in different ways and for different purposes, the specimens themselves, their storage units and the system governing their access have been referred to by different terms[26]. Although one of the most common terms for such repository is 'biobank', members of BIONET noted that in certain circumstances, especially given potential language and cultural barriers, even a seemingly innocent term might be misinterpreted. Donors of biospecimens might give consent under the false impression that they are in fact depositing something on which they will get some kind of a return.[27] It was also noted that while this may seem a simple question of terminology, the exact raison d'être, purpose and roles of such biospecimen resources must be specified. This, as highlighted by the BIONET discussions, was essential in order for appropriate consent procedures. Clear fire walls may need to be established between medico-scientific biobanks, forensic biobanks, and therapeutic biobanks (for blood, tissue or organ donation). This does not only constitute a question of terminology but rather an important part of information and disclosure in consent procedures as well as transparency in governance.

### Confidentiality

Genetic data provide a particularly useful instrument for the purpose of identifying specific individuals, as proven by forensic DNA technology. However, the downside of this is that individuals and related groups can also be identified when they need not be. Genetically related medical and other information can be particularly sensitive and it is often desirable to keep the identity of donors and participants confidential. Biobanks therefore, especially those which hold personal medical, genealogical or other types of data alongside their sample, may have a particularly difficult task in keeping the identity of donors anonymous. The sensitivity of the information held by genetic data has given rise to much debate in bioethics regarding appropriate management of data and samples. BIONET recognized that appropriate measures must be taken to ensure the confidentiality of genetic data. However, bioethicists and policy-makers remain divided as to which mechanisms would ideally protect the identity of donors. Such mechanisms may include anonymization, reversibly or irreversibly linked, coding or encryption. It is understood that full anonymization is not possible because genetic and associated data can always be traced back to individuals but the BIONET process has led to the conclusion that the topic of anonymization must be addressed in such collaborative research.

**26** Bartha Maria Knoppers and Madeleine Saginur (2005), The Babel of genetic data terminology, Nat. Biotechnology 23:8, 925-7

**27** BIONET 4th Workshop Report, www.bionet-china.org/pdfs/BIONET_4th_Workshop_Report.pdf.

### Consent

Biobanking, of course, poses similar issues regarding informed consent as other biomedical research. However, it also poses additional problems: often it is impossible (and sometimes undesirable for scientific purposes) to specify in advance the exact use for the stored specimen. Basic research on certain specimens may open doors to new types of research, which can be crucial for medical progress, but which was not necessarily covered in the original consent. Again scholars remain divided on the appropriateness of various kinds of initial consent. While some propose broad or blanket consent, that might cover all types of biomedical research, or at least broad classes of research, others are strong proponents of specific consent, requiring re-consent for any new research. Questions have also been raised as to whether, broad or blanket consent, do at all meet the requirements of informed consent as we have traditionally known it.[28] The BIONET platform highlighted the importance of reaching an agreement over consent, especially in international collaboration.[29]

### Trust and community support

Establishing biobanks on a large scale within a population requires the support and trust of the participating community. BIONET recognized this as a particularly important factor in the success of such research endeavours. Members suggested various ways of reaching out and empowering the community, such as extensive and continued relationships and communication with the community participating, and an understanding of the kinds of participants and donors involved (eg, the difference between active participants and passive or indifferent participants).[30] The involvement and support of the participating community is key to the success of any research endeavour, especially when conducted in traditional, community-oriented settings, but they can be particularly crucial in the context of genetic research. Because genes are shared, and sometimes specific genetic markers are very closely shared in restricted, traditional settings, the participation of some of the members of a group results in the indirect participation of the entire group. As a result, the entire group may sometimes benefit or suffer from the implications of the study's findings. As pointed out at the BIONET fourth workshop, navigating the potential concerns arising from such research requires mutual understanding between researchers and participants, an extensive and long-term collaboration with the entire community and a good review of the aims of the research undertaken.[31]

### Risk and risk perception

The issue of (health or information related) risk in the context of biobanks is particularly interesting. In the case of clinical trials, the expected risk and discomfort are essentially related to the actual procedure or length or the trial. Simply transposing the

**28** Hofman, (2009), Broadening consent – and diluting ethics?, Journal of Medical Ethics; 35:125-129

**29** BIONET 4th Workshop Report, www.bionet-china.org/pdfs/BIONET_4th_Workshop_Report.pdf.

**30** BIONET 4th Workshop Report, www.bionet-china.org/pdfs/BIONET_4th_Workshop_Report.pdf.

**31** Ibid

The risks and benefits of biobanking are tied to the type of research that will be carried out with the biological sample, and not with the procedures of obtaining the sample in the first place. This needs to be made clear in the consent process

same attitude towards risk would be significantly ignoring the main ethical issues involved. In this case the risks, as with the benefits, are tied to the type of research that will be carried out with the biological sample, and not with the procedure of obtaining the sample in the first place. BIONET members recognized that simply stating in consent forms that the intervention involved an essentially pain-free procedure with little known risks would not necessarily count as good practice.[32] Rather, researchers and reviewers would need to concentrate on the fact that benefits and risks (including psychological, social and cultural risk) are essentially related to subsequent research with the sample and the findings thereof and significant efforts must be made to convey this fact to potential donors. This may require altering existing consent and related review procedures and significant attention from policy-makers in this field.

**Feedback**

There has been significant debate in bioethics regarding the possible disclosure of results from biobank research. While some commentators have suggested that a logical development of research should be that those who have participated are made aware of important findings, others have argued that the ethically correct stance to take is that only findings that are related to the illness or trait being studied should be communicated, and that only if this is statistically significant or if preventive or curative measures can be taken. Others point out that as important as the 'right to know' is the 'right not to know' one's genetic status[33]. In the case of biobanks, findings that apply to an entire group or community might make the problem of feedback and disclosure particularly delicate.

In an echo of the existing debate, the members of BIONET also debated the merits and risks of possible feedback. While some members suggested that clinically significant results should be shared, others questioned whether genetic research has reached a phase where such results could be called meaningful. Others felt that in order to reflect true benefit-sharing, all data and knowledge arising from research should be shared regularly.[34] The details of how feedback should take place, if at all, would need to be further addressed.

**Access and Data Sharing**

A final and important component in the governance of biobanks is the ethical standard regarding access to samples and data by other researchers. As with general biomedical research, international collaborations can be made more difficult due to conflicting national or regional laws and regulations regarding the movement and sharing of samples and associated data. Members and consultants at BIONET reiterated the importance of establishing standards for such international cooperation, which include scientific quality standards,

**32** Ibid

**33** Roberto Andorno (2004), The right not to know: an autonomy-based approach, Journal of Medical Ethics, 2004, vol. 30, n° 5, p. 435-440

**34** BIONET 4th Workshop Report, www.bionet-china.org/pdfs/BIONET_4th_Workshop_Report.pdf.

Peking University Third Hospital, Beijing

establishing standardized access procedures for researchers[35]. This may possibly present the most difficult task in the establishment of biobanks as they continue to emerge across the world, under very different legal backgrounds, some under public funding, others owned by private companies.[36]

## Specific Ethical Issues Related to Stem Cell Research

Stem cell research, still at a very early stage of its development, has been the target of much hope and criticism. While stem cells are seen as a possible cure for neurodegenerative disorders, nerve damage and many other illnesses, they are also the focus of much heated debate regarding their source and potentiality. China, alongside South Korea and Singapore, has emerged as a coveted location for stem-cell research, and has in turn generated its own debate regarding the procurement and use of stem cells for research and therapeutic purposes. Unlike many other governments (such as the US government until very recently), the Chinese government has recognized stem cell research as an important strategic topic and as such encourages stem cell research through funding.[37] Through its discussions, BIONET identified the following issues as particular concerns in Sino-European collaborative endeavours.

### Concerns regarding experimental therapy

Stem cell research is still in its early days and stem cell therapy still remains largely unproven. While all new treatments and interventions must go through an experimental phase, some fear that this stage has arrived a little too early in the case of stem cells. It was reported at the workshop that some clinics, for example in the Netherlands, have offered patients 'experimental' therapies for multiple sclerosis but such intervention remains controversial and unauthorized in most European countries.[38] However, there is growing concern regarding 'stem cell tourism'[39], which involves patients travelling to more permissive countries to undergo unproven regenerative medicine. Indeed BIONET members note in their final report that regulations notwithstanding, stem cell 'therapies' continue to be available to those patients willing to pay in both Europe and China.[40] As long as patients are willing to pay for unproven and unsafe treatment as their 'last resort' and as long as researchers and physicians agree to participate, knowing full well its dangers, stem-cell tourism might prove to be extremely difficult to regulate. While this problem will persist as long as regulations vary from country to country, collaborative partnerships may allow for certain harmonization and standardization, keeping the safety of patients as their primary concern and finding other ways to incentivize researchers.

**35** BIONET 4th Workshop Report, www.bionet-china.org/pdfs/BIONET_4th_Workshop_Report.pdf.

**36** Ibid

**37** BIONET 2nd Workshop Report, www.bionet-china.org/pdfs/BIONET_2nd_Workshop_Report.pdf.

**38** Ibid

**39** Peter Aldhouse (2008), 'New Task force to Tackle Stem-cell Tourism', New Scientist, 13 June 2008 www.newscientist.com/article/dn14137-new-task-force-to-tackle-stemcell-tourism.html

**40** BIONET Final Report, www.bionet-china.org/pdfs/BIONET_Final_Report.pdf.

Given the different attitudes towards stem cell research in European and Chinese cultures and politics, the development of overarching standards and harmonized regulations remains a key challenge in fruitful collaboration

**The diversity in regulation**

Once again, the regulatory sea proves to be difficult to navigate. In fact this diversity regarding the use of stem cells is quite prominent even within European countries.[41] It is therefore likely that international collaborations will face substantial worries in trying to adhere to regulatory standards. In stem cell research, as in other cases, BIONET tends to favour adherence to the laws of the countries involved, without necessarily downgrading regulation to the most restrictive partner country. In China, various soft laws exist regarding the use of embryonic stem cells, but concerns remain regarding enforcement and compliance, and the financial incentives leading researchers to take on unproven stem cell therapy. It was noted that the tendency from the Chinese government has often been to encourage scientific freedom and to minimize ethical and regulatory constraints[42]. Given also the different attitudes towards stem cell research in European and Chinese cultures and politics, the development of overarching standards and harmonized regulations remain a key challenge in fruitful collaboration.

**Source of stem cells**

One of the most divisive debates regarding the use of stem cells in research goes to their very source.[43] On the one hand are the philosophical debates regarding the potential of stem cells and the possible normative outcomes of this debate, and on the other hand are the concerns regarding the protection of those who will donate embryos for stem cell research. In Europe the laws and regulations differ significantly from country to country, with some country allowing the creation of embryos, even human-animal hybrids for the procurement of stem cells, while others severely restrict the creation of embryos or even the use of imported cell lines. While the debate in Europe has essentially revolved around the protection of the embryo, questions of dignity and respect for life giving rise to debates similar to those related to abortion, the reported general tendency in China still usually associates the beginning of ethically relevant life with birth[44]. This seemingly metaphysical and cultural distinction may in fact have given rise to very different attitudes towards stem cell research and use, as well as different policies and regulations.

BIONET members urged standards and frameworks to be developed regarding the manipulation of embryos both *in vitro* and *in utero*, as well as standards regarding quality and transparency.

Because the debate surrounding stem cells is fraught with very many philosophical, theological and cultural debates, participants at the 2nd Workshop concluded that each partner country must find 'the right mix of biology, metaphysics and culture

**41** BIONET 2nd Workshop Report, www.bionet-china.org/pdfs/BIONET_2nd_Workshop_Report.pdf.

**42** BIONET 2nd Workshop, www.bionet-china.org/pdfs/BIONET_2nd_Workshop_Report.pdf.

**43** C. Rehmann-Sutter, R. Porz, J. L. Scully (2009), Sourcing Human Embryonic Tissue: The Ethical Issues; (In: Ulrich Meyer et al., eds.: Fundamentals of Tissue Engineering and Regenerative Medicine. Berlin: Springer, pp. 37-46)

**44** Ibid

Each partner country must find 'the right mix of biology, metaphysics and culture to fit their country's narrative'

to fit their country's narrative'.[45] At the same time, some members also felt that such questions have to be addressed and the standards somewhat harmonized in order to avoid moral roadblocks and to actually make collaboration feasible.

The other related morally contentious issue remains the consent of those who donate embryos, where embryos are created for research purposes. Again the question of exploitation of those who are uneducated or might be induced or coerced into donate remains an issue. The donation of embryo is perhaps situated somewhere between clinical trials and tissue donation in the sense that it does not necessarily imply substantial physical risk or harm, but at the same time can present significant cultural and emotional concerns for donor parents, concerns utterly different to those related to tissue or blood donation for example. Such moral and emotional concerns can be particularly delicate for couples undergoing fertility treatment, who tend to be the usual donors 'spare' embryos for research purposes. Just as the moral status of embryos and the ensuing normative discussions are heavily dependent on cultural, traditional, historical practices as well as personal narratives, such considerations are crucial for the protection and respect of those donating embryos for research. Experts noted that including the experiences of donors within the ethical deliberations can be an important way of discovering important normative questions which may not seem intuitively obvious to researchers, ethicists or policy-makers.[46] The issue of embryo donation for research requires sensitivity on the part of researchers, support frameworks, the building of long-term relationships and trust between researchers and donors and open communication with participants and the public. Again, conflicting standards between Europe and China may come as obstacles in scientific partnership but recognizing the key concerns and moral issues are the first step towards harmonized ethical standards. Consensus between collaborating partners can prove to be as difficult to achieve in this field as with any other biomedical research but the process of ethical deliberation, it was noted, goes a long way towards establishing basic standards and agreements.

**45** Ibid
**46** Ibid

# Chapter 3: Terms and Definitions

The following definitions are proposed as explanations of key terms used in these recommendations and within the context of their intended field of operation:

1. Governance
2. Ethical Governance
3. Research Collaborations
4. Human subject research
5. Clinical trials
6. Biobanks
7. Participant
8. Anonymization
9. Personal Genomics
10. Stem Cell Research
11. Reproductive Medicine
12. Regenerative Medicine

**Governance:** Governance is an emerging technical term with a host of different definitions. Here, it is used to describe the processes of steering and regulation of social systems and institutions by a multitude of participants and at many different levels. In contrast to 'government', governance refers to an interaction between a diversity of steering authorities, integrating top-down regulation by the state and legitimate engagement of other players in society, including bottom-up dynamics. ('The concept of governance refers to the complex set of values, norms, processes and institutions by which society manages its development and resolves conflict, formally and informally. It involves the state, but also the civil society (economic and social actors, community-based institutions and unstructured groups, the media, etc) at the local, national, regional and global levels.'[47])

Research collaborations involve complex patterns of co-operation between people. They build at least short-term institutions that we call 'projects' or 'consortia'. Governance is a suitable term to refer to all processes that define which game will be played in the collaboration, and which rules need to be respected in playing this game. There is governance from inside the collaboration (by standard operation procedures, hierarchies, instructions by steering committees etc.) and governance from outside the collaboration (by law, government authorities, patient groups, citizen participation etc.).

In this context, politics are understood as spanning over civil society, with its economy, social actors, community-based institutions, the media, scientific associations, the structures of the healthcare system, and other unstructured groups. This is both done formally by rules, regulations and laws, and also informally through the complex set of values and norms of the involved cultures and institutions.

**Ethical governance:** The concept of ethical governance arises from our understandings of the ways in which a governance system can be made both

**47** Thomas G Weiss 'Governance, Good Governance and Global Governance: Conceptual and Actual Challenges' (2000) 21 (5) Third World Quarterly 795-814.

practical and just, in diverse historical, cultural and normative contexts. The following aspects define ethical governance in particular:

- *Rule of law:* regulatory structures are in place, ethical institutions established, law is implemented, regulations and ethical guidelines secured;
- *Transparency* of scientific practice, medical applications, biomedical research and translation of research, of funding procedures;
- *Accountability:* clarity about who is responsible for what, under which conditions and with which consequences;
- *Respect for human rights* in biomedical research includes the protection of the rights of patients, and the legal and moral status of research subjects;
- *Participation* in decision-making;
- *Absence of corruption* in research and hospital settings, in the implementation of existing rules, and in obtaining science funding.[48]

In China, there is a frequently cited definition of good governance/ governing (*shanzhi*) as 'the best relations' between political state and civil society. Good governance is a state of rule in which public authority is shared among stake-holders to direct, control and regulate various social affairs, which will consequently result in 'a political process that is aimed at maximizing public welfare'.[49]

The term 'ethical governance' more specifically addresses the enhancement of justice and equity in promoting the welfare of the population and emphasises the importance of establishing an institution or a discipline that ensures ethical procedures. The objectives of ethical governance have intrinsic values. The core of ethical governance is to establish an ethical procedure rather than to pin down a substantive doctrine, to build the relevant capabilities and support adherence among key players. More specifically, ethical governance underpins a procedure where multi-stakeholder policy dialogues can be sustained.[50]

**Research collaborations:** These recommendations have a special focus on research collaborations that involve Chinese and European partners, participants or research sites. At the European side the involvement can either be on a national level or on the level of European Union research framework programmes. The collaborations can take a multitude of concrete forms and sizes. Collaborations among individual researchers, companies or institutions bring together, for instance, new or larger centres of excellence, or alternatively interdisciplinary research groups. Research collaborations can create particular links between science, medicine and technology or between university and industry. Not all involved partners may have the same understanding

**48** Herbert Gottweis, presentation at the BIONET Final Conference 1-4 Sept. 2009, London.

**49** Yu, K-P: Governance and Good Governance. Beijing: Social Science Academic Press 2000.

**50** Joy Zhang: 'Research report on governance'. BIONET Working Paper (2008).

'Ethical governance' addresses the enhancement of justice and equity in promoting the welfare of the population and emphasises the importance of establishing an institution or a discipline that ensures ethical procedures

of the concept of the 'research collaboration'. Collaborations can involve individuals, groups, institutions, sectors or nations. They can take place at different levels of collaboration, can incorporate different motives and different kinds of partners, organizing different collaborative activities, bringing different sorts of benefits and costs of collaborating and implications for research policy, reaching from one researcher going abroad and working in another laboratory to multinational clusters of university and industrial laboratories. They all share the need to adhere to ethical governance.

**Human subject research:** Human subject research includes experiments (also known as interventional studies) and observational studies. Human subjects are commonly participants in research on basic biology, clinical medicine, psychology, and all other social sciences. Research means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. The general term of human subject research includes different types of research such as clinical trials, research with donated tissues or cells and biobanks. In terms of ethical governance, human subjects should be respected as individuals within their social embeddedness.

**Clinical Trials:** A clinical trial (also clinical research) is a research study in human volunteers to address specific health questions. Carefully conducted clinical trials are the fastest and safest way to find treatments that work in people and ways to improve health. A clinical trial is a prospective biomedical research study of human subjects that is designed to answer specific questions about biomedical interventions. Interventions include but are not restricted to drugs, cells and other biological products, surgical procedures, radiologic procedures, devices, behavioural treatments, process-of-care changes, preventive care, etc. This definition includes Phase I to Phase IV trials. Clinical trials are used to determine whether new interventional measures are safe, efficacious, and effective.

A clinical trial can involve the participation of healthy volunteers in 'Phase I' studies, where a new compound is applied to humans for the first time, but in general, it is a patient-oriented research. Research conducted with human subjects (or on material of human origin such as tissues, specimens and cognitive phenomena) is that in which an investigator (or colleague) directly interacts with human subjects. Excluded from this definition are *in vitro* studies that utilize human tissues that cannot be linked to a living individual.

Although there are many definitions of clinical trials, they are generally considered to be biomedical or health-related research studies in human beings that follow a pre-defined protocol. Clinical trials include both interventional and observational types

of studies. Interventional studies are those in which the research subjects are assigned by the investigator to a treatment or other intervention, and their outcomes are measured. Observational studies are those in which individuals are observed and their outcomes are measured by the investigators.[51]

In both, human subjects research and clinical trial, the acceptability of recruitment of participants is a matter of legal, ethical and social definition. Eg, how to deal with minors, prisoners, death row inmates, and others who are not capable of full consent.

**Biobanks:** Biobanks are collections of human biological material that can be used for genetic analysis and for medical research purposes. Often they are combined with personal, medical, genealogical, environmental and lifestyle information about the individuals from whom the samples were collected. This information may be complemented by results of previous genetic analyses. Biobanks can have many different forms and size according to the type of samples that are stored and the medical-scientific domain, in which they are collected. Clinics, research projects and the judiciary field are typical sites for biobank collections. Some biobanks are organized in the shape of multi-use research infrastructures. The category 'biobank' encompasses pathology collections, repositories for specific diseases (eg, cancer registries), and population databases created to permit longitudinal studies of any disease or condition. The term 'genetic database' is sometimes used interchangeably.[52]

**Participant:** All clinical trials and biobanks have guidelines about who can participate. The factors that allow someone to participate in a clinical trial are called 'inclusion criteria' and those that disallow someone from participating are called 'exclusion criteria'. Using carefully defined inclusion and exclusion criteria is an important principle of medical research that helps to produce reliable results. These criteria are based on such factors as age, gender, the type and stage of a disease, previous treatment history, and other medical conditions. Before joining a clinical trial or biobank, a participant must qualify for the study. Some research studies seek participants with illnesses or conditions to be studied in the clinical trial, while others need healthy participants.

**Anonymization:** With regard to data or sample collections, the term 'anonymization' is used to describe technical or administrative measures, which aim at breaking or controlling the link between the collected data and/or material on the one hand and the participant from whom the samples and/or data were collected. These measures can have different forms and can be more or less sophisticated. A complete anonymization is ideally (though not always in the view of desired health information!) completely irreversible

**51** WHO: www.who.int/ictrp/en/; NIH Glossary of clinical research terms: www.clinicaltrials.gov/ (accessed 25 November 2009); Consortium of independent review boards: www.consortiumofirb.org/participant.htm; FDA: www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/default.htm

**52** Bernice Elger, Nikola Biller-Andorno, Alexandre Mauron and Alexander M.Capron (eds.): Ethical Issues in Governing Biobanks. Global Perspectives, Aldershot: Ashgate, 2008 p.1 Footnote 1. Herbert Gottweis and Alan Petersen (eds.): Biobanks. Governance in comparative perspective, London: Routledge, 2008 p. 5.

and entails the irreversible breaking of any possible links between data/sample and the participant, either from the side of the biobank or from the side of the participant or from the side of other parties who in the present or in the future might have an interest in re-identifying the samples or the data.

In principle, any sample of biomaterials containing the participant's DNA can be traced back to the participant by comparing DNA fingerprints. But if the group of participants is large or remains unknown, a retracing would be very complicated and cost-intensive. With regard to the degree of realization of the ideal, different technical terms and procedural definitions of 'anonymization' exist. If data is identifiable when it is collected then it will still be identifiable when it is retained in the research database, unless something specific is performed to anonymize it. Differing terms and norms about the measures of anonymization present serious barriers to an international framework.

**Personal Genomics:** Personal Genomics refers to an ensemble of technologies allowing the discovery of genetic information about a single given individual, which may also have implications for the related family. Knowledge extracted from previous biological studies on large cohorts is used to perform dedicated recommendations valid for this given individual.[53] The opposite to personal genomics is a strategy to identify general biological information from DNA samples that refer to groups of individuals. Personal genomics has applications such as the individual identifications of mutations or partial or full genotypes, risk factor identification (susceptibility, predispositions) or ancestry analysis. Personal genomics may eventually lead to personalized medicine, where patients can assess their individual genetic risks for diseases and take genotype specific drugs for prevention and/or medical treatments.

**Stem Cell Research:** Stem cells are distinguished from other cell types by two important characteristics. First, they are unspecialized cells capable of renewing themselves through cell division, sometimes after long periods of inactivity. Second, under certain physiologic or experimental conditions, they can be induced to become tissue- or organ-specific cells with special functions. In some organs, such as the gut and bone marrow, stem cells regularly divide to repair and replace worn out or damaged tissues. In other organs, however, such as the pancreas and the heart, stem cells only divide under special conditions.[54] Stem cells in the body after birth are called adult stem cells. Embryonic stem cells, typically taken from the inner cell mass of embryos at the blastocyst stage, are cells that can differentiate into all tissue- or organ-specific cells that make the body of the animal or human. For this ability they are called pluripotent.

**Reproductive medicine:** Reproductive medicine is a medical-

**53** Personal Genomics Blog: http://personomics.wordpress.com/personal-genomics/ (accessed 22 September 2009).

**54** National Institutes of Health (USA): http://stemcells.nih.gov/info/basics/basics1.asp (accessed 22 September 2009).

**Sequencing at the Beijing Genomics Institute**

surgical specialty, embedded in social, cultural and ethical considerations, concerned with the morphology, physiology, psychology, biochemistry, and pathology of reproduction, and on the biological and medical problems of fertility. It includes ovulation induction, diagnosis of infertility and recurrent pregnancy loss, and often assisted reproductive technologies such as egg and sperm donation, in vitro fertilization with embryo transfer, and intrafallopian transfer of zygotes.

**Regenerative medicine:**
Regenerative medicine is a broad definition for innovative medical therapies that aims at repairing, replacing, restoring and regenerating damaged or diseased cells, tissues and organs with the help of laboratory techniques. This broad field encompasses a variety of research areas including cell therapy, specially-grown tissues and cells (tissue engineering), biomaterials engineering, transplantation science, growth factors, laboratory-made compounds, and combinations of these approaches for the treatment of injuries and disease. Scientists worldwide are engaged in research activities that may enable repair of damaged heart muscle after a heart attack, replacement of skin for burn victims, restoration of movement after spinal cord injury and regeneration of pancreatic tissue to produce insulin for people with diabetes. Regenerative medicine promises to extend healthy life spans and improve the quality of life by supporting and activating the body's natural healing.

# Chapter 4: Towards a Joint Governance Agenda

As a result of its work between 2007 and 2009 the BIONET Expert Group has prepared a guide to best practice in ethical governance of biomedical research collaborations between Europe and China. The guide consists of a series of recommendations that concern both regulatory and structural measures. Taken together they should enable collaborative research to be organized ethically. They should help to prevent the exploitation of unclear standards in transnational research collaborations and to protect those research participants and patients who become vulnerable in such settings.

The recommendations are procedural in character. That is to say, they do not anticipate which specific solution should be found in each case. They rather set out a 'road map' for developing ethical governance of research in international collaborations, indicating the places where ethical issues can arise and sketching possible ways in which they may be prevented. Nevertheless they contribute to building an ethical framework for evaluating conduct and decision-making in collaborative research between EU and China. There is a set of ethical principles and core values underlying to this framework, which are shared by committed professionals and regulators who engage in collaborative research between EU and China.

The points that are recommended for consideration refer to different layers of the networks of research governance, not only to top-down regulation. Therefore, they are addressed to different kinds of stakeholders who participate on different levels in steering international research. **They include national legislators, public oversight bodies and administrations, research funding agencies, research organizations, clinics, universities, individual scientists and private laboratories and also companies who are active in research**. Under each recommendation point (below) some of the most obvious stakeholders are enumerated for whom the point is considered to be most relevant. These lists however are neither comprehensive nor exclusive.

In many ways, which we will point out with concrete examples, the expert group believes that ethical governance of international collaborative research between European and Chinese partners can best be realized **by clarifying responsibilities, by improving structures of fair supervision, by improving transparency and by building capacities**, which empowers those who participate in decisions on all levels, all the way down to research participants and patients. The Expert Group hopes that its recommendations will be widely attended to and discussed.

The recommendations are not written in stone but should be considered as indications of a direction of travel. Since research

Ethical governance of international research collaborations can best be realized by clarifying responsibilities, improving structures of fair supervision, improving transparency and building capacities which empower those who participate

is fluid and developing fast, the key points to consider need to be continually developed, on the basis of new emerging insights.

A first set of points concern all biomedical human subjects research fields in general. They are set out in the first part (A) below. Other points apply in particular to clinical trials (B), to biobanks and personal genomics (C), and to stem cell research, research in reproductive and regenerative medicine (D). These are the fields where the BIONET project has organized focused workshops and our points of concern, and our recommendations, arise from discussions in those workshops. In research ethics literature, many more issues are reflected upon than those selected here for the BIONET recommendations. The selection reflects the mapping of the field in the BIONET workshops and the particular relevance and concern in European-Chinese research collaborations.

## Shared underlying principles and values

1. The fundamental purpose of collaborative research in biological and biomedical fields between EU and China is to promote human health and the quality of life with safer, more effective, and more advanced biomedical science and technology which brings advantages to both sides of the collaboration. In reality however, scientific research is not always conducted to the highest standards. Further, as an essential economic productive force in contemporary societies, scientific research can also be misused.
2. Collaborative research between EU and China should maintain high standards of responsible research, ie, it should adhere to standards of research integrity and it should be committed to safeguarding and protecting the patients' and research subjects' rights and interests.
3. In cases of conflict, priority should be given to interests of patients/human subjects over scientific interests, social interests, and commercial interests in particular and conflicts of interest should be handled transparently by partners on both sides.
4. Mutual respect:

   • Mutual respect includes respect for the laws, regulations or guidelines of the other side. Collaborative agreements made with a foreign partner would be one-sided if they mentioned only the observance of the laws and regulations in the sponsoring country, not those in the host country. Mutual respect requires that each acknowledges the autonomy of the other side. The assumption is that issues such as regulatory gaps, or disagreements among scientists/bioethicists on one side need also to be resolved on this side. Interventions from

the other side may risk being counterproductive.

• Mutual respect is based on mutual understanding. In order to build the basis of such understanding, there is a need on each side to build cultural competence. Cultural competence is the ability to act in contexts of cultural differences. Two elements are central (1) An ability to communicate effectively with the other side and (2) a sufficient and robust understanding of the cultural beliefs and values of the other side, including sensitivity for variations within the culture.

5. The principle of reciprocity requires benefit sharing (including scientists/institutions, donors or vulnerable communities on both sides) concerning authorship, royalties, patents, access to data or/and samples, and profits.

6. Accountability and transparency mean that both sides in collaborative research between EU and China are accountable and responsible for their research team and all those involved in the research. Information on collaborative research between EU and China should be made transparent to other colleagues as well as to the lay public and taxpayers on both sides of the collaboration.

7. Public engagement measures are needed to facilitate public understanding of science and for public consultation and involvement.

8. Equal, equitable and just relationships prevent exploitation. Inadequate regulatory infrastructures and oversight processes without the necessary independence, as well as poverty, limited access to health-care

**Informed consent procedures, Reproductive and Genetic Hospital, Changsha**

services, illiteracy, and limited understanding of the nature of scientific research on the part of patients/subjects on either side may increase the possibility of exploitation. Therefore, capacity building both in science and ethics is imperative in collaborative research between EU and China.

9. Ethical governance is a value, defined by:

   • The rule of law: regulatory structures need to be in place; ethical institutions must be established; law must be implemented, regulations and ethical guidelines must be secured.

   • Transparency (of scientific practice, medical applications, biomedical research and translation of research into practice; of funding procedures): free and independent media are a key resource and an institutional prerequisite for transparency in this area.

   • Accountability that is clearly established and agreed: including such issues as who is responsible for what, under which condition, and with which consequences?

   • Respect for human rights in biomedical research, with regard to patients and research subjects.

   • Participation in processes of decision-making.

   • Absence of corruption (in research and hospital settings, in the implementation of existing rules and in obtaining science funding).

Processes matter. They have an ethical quality that matters. And it makes sense, to start small, in order to incite a larger movement.

A poetic image for this potential of cooperative governance is:

**抛砖引玉**
–Throw a brick to attract jade –

The brick that you throw will change its quality and you will be able to catch it again in a refined form. This is the underlying vision of these recommendations for ethical governance of Sino-European research collaborations.

# Chapter 5: BIONET Expert Group Recommendations

## A. Human subjects research and clinical trials in general.

With regard to all multinational research collaborations between China and countries of the EU, the BIONET Expert Group recommends the following points for consideration:

### 1. Regulatory coherence

**Integration of international ethical guidelines on research into national legislation, transparency and clarity regarding the applicable ethical review standards.**

*International ethical standards to protect human research subjects should be reflected in national regulation. The ethical review standards that must be adhered to in multinational projects need to be set out transparently and publicly.*

Many countries meet this requirement, but international research collaborations can include countries where standards remain legally unclear. In many respects international standards already exist. The relevant sources are the current Declaration of Helsinki, the current Guidelines of CIOMS/WHO, and the current ICH-Good Clinical Practice guidelines, for Europe the EU clinical research legislation and others. It is however important to note that international guidelines need national legal implementation to become legally binding. Further, in some areas of regulation different international guidelines may lack consistency with each other and decisions need to be made as to which regulations are to be followed. Therefore it is crucial for regulators to check whether the relevant international guidelines are adequately reflected in national legislation. Of course, the Expert Group does not have the authority to judge whether or not legislative measures need to be taken.

In multinational projects researchers should clarify in advance which ethical review standards will be adhered to: provided the international standards are respected, these might be the standards of the most rigorously regulated participants in the partnership, or the standards of the principal investigator, or the standards of those places where patients will be recruited. The applicable ethical standards need to be publicized and should be communicated to research participants when obtaining consent.

By 'national' we include here also regional (EU), and, if relevant, provincial regulation (in China). By 'regulation' we mean both formal law and authoritative guidelines.

Problems can arise with translation issues: It is not always straightforward to express the content of particular technical terms, standards and guidelines adequately in another language and within another cultural,

historical and social background.

*Directed to national and EU legislators and administrations.*

## 2. Gaps in regulations

### Clear assignment of accountability in the organization of international scientific studies

*(1) Clear responsibility and accountability within the organization of the project should be assigned to one person or one department in each participating country, who will oversee and have the power to manage research activities in that country.*

*(2) This assignment of responsibility should be made an obligatory requirement for conducting research/trials through national regulations.*

*(3) A clear assignment of responsibilities between collaborating partners in different countries should be a requirement.*

In multinational research collaborations, situations can arise in which the internal and external regulatory frameworks may differ between participating countries and groups involved. Accountabilities may be defined differently, producing a situation in which nobody assumes real responsibility. This may leave loopholes regarding responsibility and accountability. To prevent such loopholes, those responsible for the overall management of the study should assign in each country a person (or an institutional department) who is a national partner, who is accountable within the country, and assumes responsibility for the research activities in that country. In order to fulfil this role, this person/department needs adequate competencies, power, and resources. Responsibilities need to be clarified also amongst the international partners.

*Relevant to funding agencies, research organizations and companies (1); national administrations (2 and 3).*

## 3. Implementation of ethical standards on the ground

### Establishment and improvement of the structures necessary to implement ethical governance: research ethics committees and supporting regulatory structures.

*Countries should establish a system of independent research ethics committees with juridical, ethical, medico-scientific and local knowledge. Authorities should support their work so that it is of high quality, and ensure corresponding additional supporting and regulatory infrastructure for the realization and implementation of international and national ethical standards of research.*

*Additional infrastructure includes regulations and coordination*

BIONET workshop on reproductive technologies, April 2007, Beijing

*among administrative agencies. It may also include an authority that registers, licenses and oversees all human subject research. The research ethics committees should be accountable and have good working standards that include a maximum length of time for their reviews. They should also have the capacity to review informed consent documents before they are given to patients and can have a monitoring function.*

Ethical norms and standards must be understood, interpreted and realized within the circumstances of each country and its regions. The establishment of local or regional research ethics committees is a key requirement. Such committees should have the mandate to protect the health, wellbeing and rights of research participants. The research ethics committees should be independent institutionally from the research institution that applies for their opinion. They should be empowered to veto research applications, and to stop ongoing research, which is not compliant with applicable ethical norms or scientific standards. The committee should involve the necessary interdisciplinary expertise required for the proper execution of their work and responsibilities. Members should be trained, and their knowledge should be periodically updated. The commission should be provided with sufficient resources (finances, time, secretariat etc.) to fulfil its role.

Every research ethics committee should work according to transparent and publically available Standard Operating Procedures. To ensure efficiency and trust they should set a limit on the maximum time taken to reach a decision on each application. The regulatory framework should respect regional and cultural differences. The ethics committee should be able to

act on complaints from research participants, and to consider these in order to determine whether a project should be revised or discontinued.

Governance can also include federal approaches involving coordination between different parties with clearly defined roles and responsibilities. Indeed effective governance implies a coordination between different responsible authorities (like ministries of science and technology and ministries of health). All involved parties need adequate and continuous training in all relevant fields of expertise in order to be able to fulfil their functions to a high standard. This applies also to members of ethics committees.

Informed consent procedures involve written documents and descriptions of the procedure at the level of face-to-face communication. Research ethics committees should have the authority and capacity to revise them before they are used in the recruitment process.

*Relevant for legislators, regulators, funding agencies, hospitals, public research organizations.*

**4. Conflict of interests**

**Effective organizational measures to manage conflicts of interest.**

*Address problems generated by conflicts of interest.*

*(1) Those undertaking research collaborations must take appropriate precautions against potentially harmful conflicts of interest between the provision of health care, not-for-profit as well as for-profit research and economic interests at all levels.*

*(2) Names of members of supervising ethics committees should be made publicly available and any potential conflicts of interests should be disclosed.*

*(3) The interfaces between therapy and research need special attention in order to avoid undue inducement of patients to participate in research because of trust in, or dependence upon, their treating physicians, or recruitment of patients to research aggressive persuasion.*

*(4) Patients with life-threatening or untreatable diseases are vulnerable against offers of unproven and potentially unsafe treatments in research and commercial contexts. Here, a tight regulatory framework with an appropriate level of public or state supervision of the providers, together with proper counselling, is required to guarantee integrity and patient protection.*

(1) Conflicts of interest may exist everywhere and may be unavoidable. Under some circumstances they may be harmless. But research can bring significant financial or other

Conflicts of interest exist everywhere and may be unavoidable. They should always be made transparent and measures should be taken to avoid harmful effects. Patients should not be persuaded to agree to any research because they trust and/or are dependent upon their treating doctors of the clinic

benefits for researchers, their institutions or departments, clinics, and also for the supervising authorities. In this context, conflicts of interest can, at least in some cases, pose considerable risks for good research practice in case of research in humans for the research participants. Conflict of interest may arise in collaborations between Chinese and European researchers eg, if funding is coming from one country, and research takes place in the other country. It may also be the consequence of financial interests of a commercial sponsor or the prospect of personal benefits for the researchers. Conflicts of interest should always be made transparent, and measures should be taken to avoid and alleviate harmful effects. However there may be occasions where conflicts of interest can become problematic and where transparency alone may not be a sufficient counter-strategy.

(2) Names of members of ethics committees and their SOPs should be made public. Without appropriate precautions in place, international research collaborations can provide opportunities and also risks for undue selfish behaviour of individuals in key institutional or operative positions, which put at risk the safety, rights and well-being of research participants, negatively impact the quality of medical care, and compromise the integrity of research.

It is however not easily possible to define undue self-seeking behaviour in general, without reference to concrete situations and locations. And the question of who is to assume or be given the right to judge may also be problematic.

(3) Special attention should be paid to conflicts between the interests of patients for appropriate health care and the interests of researchers. Where therapeutic practice and research are mixed, as for instance in oncology or in clinics of reproductive medicine with in-house stem cell laboratories, an effective and visible separation of therapeutic and research practices should be maintained. As pointed out in the Declaration of Helsinki, patients should not be persuaded to agree to any research because they trust and/or are dependent upon their treating doctors or the clinic. There may be different methods to achieve this independence, for example by involving an independent person who has no personal interest in the research or therapy.

(4) Another constellation particularly prone to harmful conflicts of interest is the commercial offer of novel treatments. This is particularly the case in relation to the growth of international tourism for novel therapies, which are not available in one country but offered in another by private providers.

One significant area is the offer of novel, yet unsafe and clinically unproven stem cell therapies for otherwise incurable diseases, considered as "research" in a permissive country, to patients who might travel from other countries (eg, stem cell tourism). There is an obvious danger of exploitation of desperate patients' hopes and of their trust in the promises of cutting-edge research.

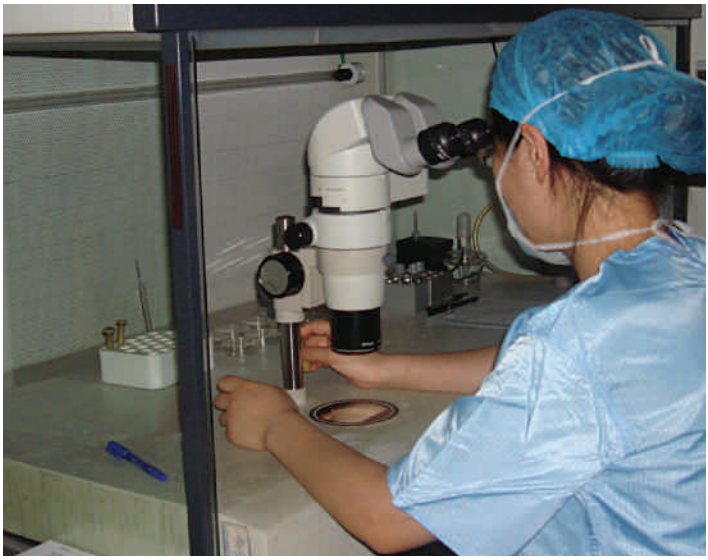
*Relevant for legislators and regulators, research institutions and ethics committees.*

**5. Building researchers' awareness of social and ethical implications of decisions**

**Support and empowerment of decision-makers and participants on all levels through adequate training.**

*(1) Decision-makers and participants on all levels need support and empowerment through adequate training. This training should be interdisciplinary and deep. It should raise awareness of all relevant implications of their decisions and practice. Training should include medico-scientific as well as socio-cultural, contextual knowledge, and communication skills such as training in how to adequately plan and perform informed consent procedures.*

*(2) Before any research collaborations are approved or begin, participating researchers must receive training on*



**Embryologist at work, CITIC-Xiangya Reproductive and Genetic Hospital, Changsha**

*how potential research participants are to be engaged with research, as well as on how informed consent is to be obtained, while focusing on the particularities of the kind of research at stake (eg, donation or participation in a trial) as well as the socio-economic and cultural context.*

The challenges for multinational governance of research include how to deal with the complexities of new research and also how to deal with the diversity of legal, moral and cultural traditions. Training can improve knowledge of one's own and others' socio-cultural contexts in depth, and therefore improve awareness of issues that might be raised by the practices in a study. Informed consent poses different challenges under different circumstances, including those situations where participants are not able to consent themselves – a situation which should be addressed in training.

An important issue is the education of the trainers and the financing of training schemes. The kind of training required also involves people with philosophical and social-science backgrounds, which can be an incentive to develop work in these fields.

Relevant to hospitals, universities, public health systems, sponsoring/ investigating companies, national administrations.

### 6. Protection of research subjects from therapeutic misconception and undue inducement

**Empowerment and effective information of potential research participants to avoid therapeutic misconception, coercion, undue inducement or influence.**

*(1) The empowerment of potential research participants protects against therapeutic misconception in research – the condition where participants believe that the primary purpose of a clinical trial or other research study is therapeutic. Empowerment means education of all those who are involved in recruitment decisions, including the participants. Undue inducements to participate in a research study are not acceptable.*

*(2) Study participants should be selected from groups who are sufficiently educated to understand what it means to voluntarily participate in the study, and are situated in a social and economic situation that allows free decisions. Exceptions from this rule should be carefully described and justified.*

*(3) Before any research collaborations are approved or begin, a detailed analysis of factors that can lead to coercion, undue inducement or undue influence of potential research participants must be prepared together with strategies to offset or counteract these.*

(1) Whenever only participation in a clinical trial provides access

Truly voluntary participation in a research study requires a full understanding of the implications of such participation. If important medical knowledge cannot be gained through research with competent volunteers, the inclusion of participants with restricted or absent competence can be legitimate provided such research serves to benefit that particular population or group

to specific therapies or healthcare in general, special care should be taken to minimize the risk of therapeutic misconception – the condition where participants believe that the primary purpose of a clinical trial or other research study is therapeutic. False expectations, false hopes, poor education of potential research participants or unfavourable economic conditions should not be exploited to persuade patients to participate in a clinical trial.

(2) Truly voluntary participation in a research study requires a full understanding of the implications of such participation. If potential participants are selected from groups with a sufficient educational, economic and social status it is more likely that decisions to participate in a research project are truly free without misconceptions and inducement. However there are exceptions that must be described with care. If important medical knowledge cannot be gained through research with competent volunteers the inclusion of participants with restricted or absent competence can be legitimate, even necessary (and consistent with international ethical guidelines), provided such research serves to benefit that particular population or group (group-specific benefit). This includes clinical research in children, mentally disabled or in patients with dementia. Patients with acute but transient inability to consent (eg, coma) represent a specific subgroup.

(3) Research applicants should present a plan how to train researchers who will be involved in the informed consent process. Before the project is accepted, researchers should have conducted a detailed analysis of which factors could lead to undue inducement. These may include the socio-economic status of potential participants, potential therapeutic misconceptions, the physical setting of interactions between researchers and potential research participants (as well as those persons present), and the relationship between the person explaining the research and the potential research participants. This analysis should be part of the documentation provided for ethical review.

*Relevant to hospitals, universities, public health systems, sponsoring/ investigating companies, national administrations.*

### 7. Ongoing control and monitoring

**Establishment of adequate control and monitoring structures in all participating countries.**

*(1) Adequate control and monitoring systems in all participating countries should be established, and continually adapted to the current state and*

*diversity of research practices.*

*(2) Research institutions who want to participate in multinational projects need to fulfil certain minimal requirements. This concerns institutional capabilities and individual professional qualifications.*

*(3) The disclosure and publication of ethical governance procedures should be a condition of peer reviewed publication of research findings in scientific journals.*

Good governance implies transparency and trust. Both can be improved and sustainably guaranteed through control and monitoring systems. Measures of control should be adapted, and be appropriate to these objectives.

One approach to ensure that capacity building is not only regarded as a desirable additional option, but a core aspect of the research design, is to set certain minimum professional standards as a requirement for participating in international research. This would act as a strong incentive to those planning research, and at the same time ensure the capabilities of those actively responsible for research.

Transparency regarding the review processes, regulatory situation and the supervision procedures can be a key element for improving ethical governance of research. A mechanism for the implementation of this transparency can be provided by peer-reviewed journals if they make this transparency a requirement for publications.

*Relevant to national authorities and administrations, journal editors.*

### 8. Cooperation between the research ethics committees, and fairness in multinational projects

**Collaboration between research ethics committees within the countries and beyond, with special attention to the fairness of selection of patient groups.**

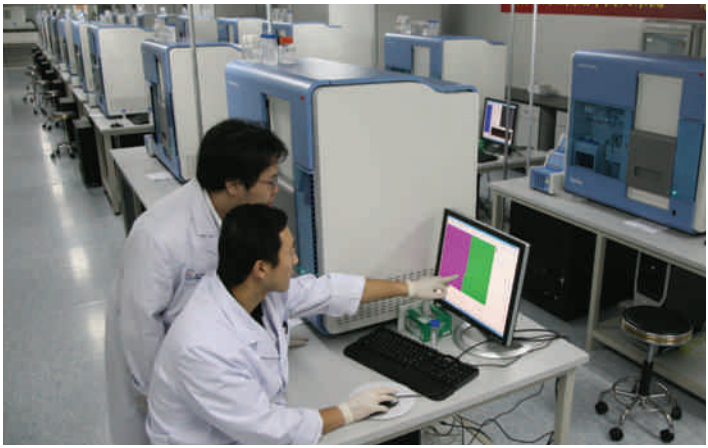
*(1) Cooperation between research ethics committees should be ensured by establishing platforms for mutual exchange of experiences and insight (including across national borders), and by clarifying the responsibilities for reviewing multicenter studies in a mutually agreeable way.*

*(2) In such reviews special attention should be paid to the fairness of selection of patients.*

*(3) Research collaborations in certain cases must be reviewed by ethics committees in both China and Europe, then in a successful application the European and the Chinese ethics committees can reach a joint decision.*

(1) Many studies involve more than one research site and are subject to review by multiple research ethics committees. There is no single universally applicable way

Genomic analysis at Beijing Genomics Institute



of sharing responsibilities among these committees. However, it should be clearly defined how they cooperate, and the processes should be mutually acceptable. Research ethics committees can improve their work by sharing experiences from case studies, and by discussing common issues together. Cooperation should transcend national borders. Cooperation and exchange visits among members of ethical review committees in different countries should be encouraged in order to promote harmonization (not unification) of definitions, rules and basic procedures, such as filing systems registry etc.

(2) The geographic and socio-cultural inclusion criteria of participants into studies should relate to the intended use and benefit of the product.

(3) If research collaborations involving Chinese and European partners must be reviewed by ethics committees on both sides, the committees should work towards a joint opinion, whenever feasible.

*Relevant for ethics committees, national authorities and administrations, sponsors of trials.*

### 9. Education and Training

**Capacity building on all professional levels involved in research.**

*Education and Training must be a central requirement.*

*(1) Learning opportunities arising from each international collaborative research project should be explored.*

*(2) This should be done by systematically including platforms where experiences emerging in the collaborative work and participants' views can be exchanged and reflective learning can take place.*

Education and Training are key components of multinational governance of research.

Not all aspects of a certain study can be fully anticipated because each study will be unique in some ways. Therefore, projects should be

planned and conducted as learning platforms. Each international collaborative research project offers unique opportunities for participants and representatives in all roles and functions for mutual learning. Important aspects and challenges of the research process should be systematically recorded and studied, possibly in cooperation with an international body such as the WHO. If this incurs costs, these need to be built into the research funding, If the financial contributions are unequal between the partners, it is important that the most dependent party is enabled to contribute to this process.

A multinational research project is a short term institution that distributes power, roles and practices. It may encompass large differences in socio-cultural understanding of relevant issues such as informed consent, the role of medicine, fair decision-making procedures etc. Such a distribution of power, roles and practices can be assessed from different points of view. One point of view is effectiveness: it can be functional or dysfunctional in reaching the study goals. Another point of view is respect: it can be just, sensible or alienated, or even exploitative of certain participant groups. A third point of view is cross-cultural understanding: it can develop key practices like informed consent contextually; in some cases conflicting understandings and incongruent expectations can emerge.

*Relevant for hospitals, researchers, universities, public health systems, sponsoring/ researching companies, national administrations.*

### 10. Understanding of effects of governance

**Empirical research into the reality of ethical governance of biological and biomedical research.**

*Empirical research into the realities of ethical governance of research should be encouraged. In the definition of research and funding programmes, social sciences and ethics should be included upstream.*

In order to monitor the quality and the effects of regulations and oversight procedures but also for defining research and funding programmes, reliable empirical evidence from social sciences research is necessary. For instance it is important to undertake in depth studies of informed consent procedures in different parts of the countries involved, to examine how it is seen from different perspectives, and in particular from the participants' perspectives. It is also important to study the work and the topics of ethics review committees, the kind of issues they face. In addition, social studies of clinical trials and biological laboratory research can provide crucial evidence for improving the regulation and

oversight procedures.

*Relevant to research funding agencies, universities.*

**11. Data sharing**

**Establishment of frameworks that encourage sharing of data among partners while maintaining privacy of research participants and confidentiality of sensitive personal data.**

*Frameworks should be created that allow the sharing of data among the partners while ensuring privacy of research participants and confidentiality of their personal data.*

In order to enhance the mutual benefit of transnational research, the results should be shared among partners. There can be standardized collaboration agreements and agreements about the publications coming from joint research projects. However, even if not legally required, all necessary precautions must be in place to protect the privacy of research participants and the confidentiality of their personal data. This relates in particular to health information, which is always considered sensitive. Any restrictions regarding the use of data, which were set by the research participant during the informed consent process or at any other process, should be strictly observed.

*Relevant for research institutions and companies.*

## B. Additional points concerning clinical trials.

For clinical trials the following points are of particular importance:

**12. Overlap of innovative therapy and research**

**Clarification of distinction of clinical trials from experimental therapy.**

*Non-ambiguous and clear definitions should be provided to differentiate experimental therapeutic interventions and clinical research. An independent body should be identified which will make the final ruling regarding unclear cases.*

The defining criteria of what should be treated under the rules of 'research' (clinical trials) and what should be treated as innovative or experimental therapy should be set out clearly in order to clarify what falls under the different regimes. A public body independent of the researcher or research institution should be defined who provides final ruling for all ambiguous cases.

*Relevant for medical professionals, regulators.*

**13. Register**

**Regulatory oversight, public disclosure of study designs and results through a clinical trial register and certification system for research ethics committees.**

On-site sampling for biobank research, Yunnan province

*State oversight should include (1) a study register for clinical trials and (2) a certification system for research ethics committees in the countries involved.*

One concrete measure that improves transparency in research is the requirement that all ongoing clinical trials register in a publicly accessible WHO certified study register. Whenever possible, existing registries should be preferred over the creation of new ones.

Furthermore, good standards of work and trust should be guaranteed through the operations of independent research ethics committees. Their members should make their judgments independently from their institution and should be independent on the sponsor of the trial. The committee should work under a certification framework and standard operation procedures that clarify composition, responsibilities, professional standards and education of its members. Supervision and certification of research ethics commission can also be done by medical academies or other capable bodies and is not necessarily everywhere a task of the state.

*Relevant for national authorities, research ethics committees, scientific and medical academics.*

**14. Scientific misconduct**

**Procedures for a suspension of a trial in cases of scientific misconduct.**

*The responsible authority, and the criteria to be used, for the suspension of a trial in cases of fraudulent conduct should be clarified. Those who report misconduct should be protected.*

Scientific misconduct or fraud in research should not be tolerated. If researchers violate rules of trust or scientific/professional standards, it should be possible to suspend a study, if this is necessary to protect research participants or if the objectives of a study can no longer be achieved.

The rules, the authority and responsibilities for handling such a process should be established and be transparent for all parties. Those who report misconduct need adequate protection.

*Relevant to state authorities, university administrations.*

**15. Availability of results**

**Publication of all clinical trial data regardless of the outcome or the location of study site.**

*Publication of the results of all clinical trials regardless of the outcome or the location of the research is indispensable, and should be made a requirement.*

All clinical trials should lead to published results, regardless of where they are conducted, and independent of whether the results are in the sponsor's or researchers interest.

This requirement can be realized in different ways. Whenever possible results of clinical trials should be published in a peer reviewed journal. If a research report will not be publishable in a peer reviewed journal, results can still be made put in the public domain through a publicly accessible result register. In such circumstances it should be ensured that the published information is reliable, objective and fact based.

*Relevant for researchers, commercial and public sponsors, research institutions.*

## C. Additional points concerning biobanking and personal genomics.

For research in the fields of genetics, genomics and biobanking the following points are of particular importance:

**16. Accountability and appropriate governance**

**Accountability and appropriate governance structures of biobanks.**

*Clarify governance structure of biobanks.*

*(1) Acknowledge differences in institutional form and purpose of biobanks.*

*(2) Transparency regarding who is accountable for what should be a requirement.*

*(3) Keep research and biobanking functions separate and transparent.*

*(4) Require auditing, monitoring and public reporting also about financial issues.*

A biobank requires appropriate and clear external and internal processes and regulations, which should be laid down in a charter and standard operating procedures.

Without demanding a particular corporate identity, or independence in the legal sense, such regulations should always clarify roles and accountabilities. They should be transparent for collaborators and participants as well as for external persons who may interact with the biobank in some way.

A biobank may have a research purpose on its own. In such circumstances, the collection of samples and information has no other aim than to support this particular research. However, many biobanks aim to establish a research infrastructure, which can be used for multiple purposes. In addition, biobanks established for a specific purpose may change their function at a later stage, and a collection of biomaterials with connected personal information may be used for research purposes other than the original one. Therefore, biobanks should be regularly audited, monitored and should publish reports about their activities regularly. Reports should also clarify the financial stakes involved. Ultimately, biobanks should be fully accountable to the public.

*Relevant for biobanks, national regulators, research ethics commissions, researchers.*

## 17. Informed consent and ethical value

### Agreement about the kind of donors' informed consent that will be asked for.

*International collaborations in biobanking and personal genomics studies should be based on an agreement about the kind of donors' consent that will be asked for.*

The process for obtaining informed consent from potential sample donors should be agreed upon when initiating the biobank process and should be clear and transparent to all participants in the project. This relates in particular to the specificity of the consent: Is it a specific consent valid only for one research purpose or is it a broad consent allowing other future research use? As a precondition for successful international collaborations, an agreement on the informed consent process is necessary.

Research ethics committees may be used as proxies for donors consent if it is the case that informed consent for a change of purpose cannot be obtained because the donor has died, is not identifiable, or otherwise obtaining consent is technically not feasible.

When deciding about the breadth and detail of informed consent in collaborative research, donors' rights and other ethical


**Sino-Danish Research Collaborations with the BGI in Shenzhen**

principles should be considered as well, such as public good, or distributive justice. However, the respect of free self-determination of donors is primary and no definition of public good can justify coercion on potential donors to agree, or to circumvent their free decision-making. In any case, the process needs to be clear and transparent to donors before they participate.

There is a link between consent and access policies: The acceptability of broad consent is dependent in part on the donor's trust in the access policies adopted by the biobank to secure and control access to personal data.

*Relevant for national regulators, research ethics commissions, biobanks, researchers.*

### 18. Confidentiality

**Confidentiality of samples and related data and protection of privacy of sample donors.**

*Confidentiality of the genetic data and other health information of an individual should be ensured. This requires appropriate measures for the anonymization of the samples and data if this is possible. Donors should always be informed about the level and mode of anonymization.*

The required process for the level and mode of anonymization of samples and data should be clarified for different types of genetic/genomic or health research. It is important to note that genetic information can also be generated indirectly, for instance through patterns of gene expression. And it is also important to note that fully irreversibly anonymization is not possible in genetic research, because samples can, in principle, be traced back by genetic fingerprinting. Therefore, trust in the biobank essentially depends on the trustworthiness of processes and policies which protect confidentiality, privacy, and are used for anonymization of samples and data.

If anonymization is not possible for legal reasons eg, in certain studies related to drug

development, it is important to inform possible donors about this fact beforehand.

*Relevant for national regulators, research ethics committees, researchers, biobank institutions.*

### 19. Purpose and use of biobanks

**Transparency and clarity to donors and the public regarding the purpose and use of a biobank. A change of the purpose (eg, forensic use of a research biobank) requires consent by the donors.**

*The purpose and objective of biobanks should be clearly defined and transparent to research participants. Changes to the purpose of the biobank, for instance from basic research to therapeutic applications, or to forensic use may require new informed consent, if there are possible implications for the donors. Any legal requirements, which impact on the donor's consent or the purpose of the biobank should be disclosed.*

A confusion of roles or purposes of biospecimen resources is problematic where donors have consented to a research purpose but not to forensic use. If a research biobank is opened for forensic purposes, other considerations would be important for those donating than those considerations that actually have been considered by potential donors. Significant differences also exist between biobanks for basic research and biobanks for therapeutic applications (such as umbilical cord blood). If the purpose of the biobank changes in a significant way, and significant new implications need to be considered for donors, a new informed consent should be required. Any legal requirements which could enforce the use of biobank samples for other purposes than those defined in the informed consent process eg, forensic use, disclosure to insurers or any use by governmental institutions (eg, health statistics) should be disclosed to participants.

*Relevant for researchers, biobank institutions.*

### 20. International collaboration between biobanks

**International collaboration or integration of biobanks consistent with rules of fairness, accountability and transparency.**

*An international collaboration or integration of biobanks should be consistent with rules of fairness and transparency. Clear accountability and responsibility structures are key.*

International scientific collaborations may include the integration of smaller biospecimen resources within larger biobanks across national borders. In such situations issues may arise that are

Biobank operators should consider when starting the project how the potential benefits generated with samples and data in the biobank may be shared with contributors of materials

similar to those well known in multinational clinical trials and other international research collaborations. Collaboration should be consistent with the recommendations concerning international studies (see above). The ethical values of fairness, accountability and transparency need to be interpreted regarding the particular circumstances of the consortium and respected.

*Relevant for regulators, biobank institutions.*

**21. Access to samples and data**

**Guidelines for access to samples and clinical data.**

*Biobanks should establish guidelines and policies for sample distribution and clinical data sharing. Access to biobanks should be based on scientific not political or financial considerations. The conditions of access should be transparent for donors. Legal restrictions should be disclosed.*

Access to biospecimens and data for research is crucial for biological and medical research, for example for genome wide association studies, proteomics or metabolomics. In order to best serve the needs of the research community while protecting the rights and well being of research participants, biospecimen resources should prepare clear and practical access policies. Such policies should protect confidentiality of sensitive personal information of the donor such as health information. Fairness, scientific merit and the objective of the biobank should be the guiding values for granting access, but public compliance with public requirements is also a key value. This aim can be supported by including representation of donors in access committees.

*Relevant for biobank institutions.*

**22. Distributive justice of profit**

**Fair benefit sharing.**

*Benefit sharing schemes for biospecimens cannot include intellectual property rights to donors of biospecimens but should aim to contribute to the public good.*

Inventions and data arising from research using biospecimens may have commercial value. It is not possible to grant intellectual property rights to donors of samples and information, because they contributed material requirements without participation in the invention itself, and this is the subject of intellectual property rights. However the benefit of research goes beyond financial benefit, to include general benefits to the health of the patient population, the general population, or to the progress of medical knowledge.

Biobank operators should consider when starting the project how the potential benefits generated with the samples and data in the biobank may be shared with contributors of materials.

*Relevant for biobank institutions.*

### 23. Feedback of medically relevant genetic information to donors

**Clear and transparent rules regarding the feedback of individual information to donors as part of the informed consent.**

*Clear agreement about the possible feedback of individual information between donors and biobank should be included in the informed consent process. Personal genetic information should in general not be communicated to participants; it should be disclosed only in exceptional cases, never without scientific validation of results, never without the patient's explicit wish, and never without adequate clinical genetic counselling.*

Participants of a biobank should be informed about important research results generated with the samples kept by the biobanks. Information should be factual and based on aggregated data.

Personal health information generated from the sample(s) donated to the biobank including genetic information should only be provided to the sample donor, on the basis of validated evidence following free and informed consent prior to disclosure and in the context of genetic counselling where appropriate. These requirements are more easily fulfilled in clinical contexts than in research contexts. Therefore, expectations that cannot be met responsibly should not be raised. The right to be informed about preventable medical risks can also be met with general news announcements, annual reports or website announcements, perhaps accompanied by procedures to make individualized tests available on request. Sample donors should be informed during the informed consent process regarding the information they can expect from the biobank and how individual data will be handled.

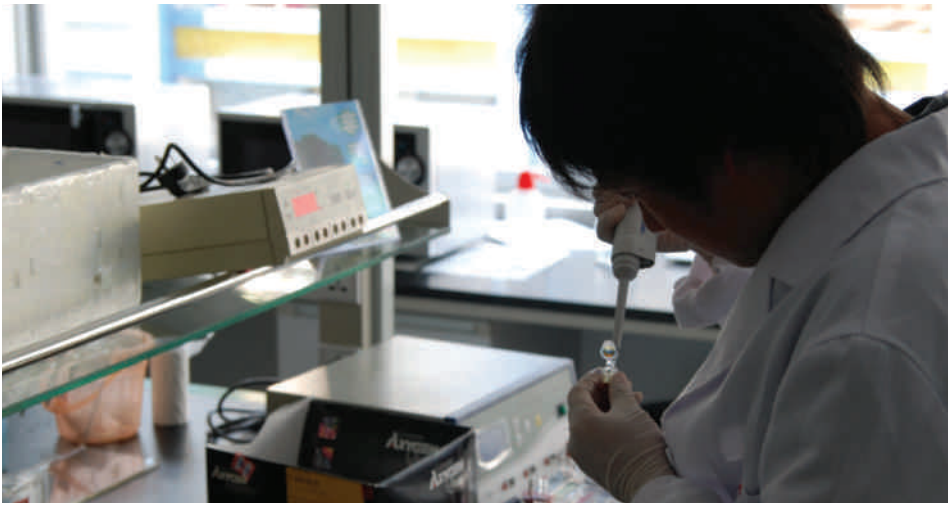
*Relevant for national regulators, biobank institutions, research ethics committees.*

### 24. Availability of pharmacogenomic information

**Pharmacogenomic information considered in drug development and dosage.**

*Pharmacogenomic information related to medicinal products should be made available in order to support and limit confidence in the generalizability of results of drug trials.*

The efficacy and safety of pharmaceuticals often varies



Scientist at work, Beijing Genomics Institute, Shenzhen

between different population groups. This has relevance where clinical trials are conducted on one population group, but the drug is to be made available to a different population group. Pharmacogenomic information related to a medicinal product may thus be important in order to understand how far the results of a drug trial can be generalized to other populations, and to protect the safety of patients. Therefore, pharmacogenomic information should be made adequately available in agreement with relevant regulatory authorities.

*Relevant to sponsors.*

## D. Additional points concerning stem cell research, reproductive and regenerative medicine.

For research in these areas the following points are of particular importance:

**25. Safety for patients**

**Investigation of the safety and efficacy of treatment with stem cells in state-of-art trials before offering them to patients.**

*Treatment with stem cells should first be classified as novel therapy. While some uses have been clinically evaluated and are successfully used, many proposed applications have not been subject to rigorous clinical trials to demonstrate efficacy and safety. Any uses of stem cell therapies that have not been so evaluated should be planned as controlled clinical trials, and only undertaken on the basis of pre-clinical study before they are offered to patients. Rigorous scientific and ethical review should always be required prior to any such use. Partner countries should establish an enforceable safety regime.*

Novel treatments with stem cells that still lack substantial proof of safety and efficacy should be planned in the form of clinical trials

and reviewed both scientifically and ethically, according to the relevant international guidelines of Good Clinical Practice, such as Declaration of Helsinki, CIOMS/ WHO Guidelines and national laws or regulations. Like drugs, stem cells products should be of appropriate therapeutic quality and fulfil the internationally accepted safety standards set by the profession. Partner countries need an enforceable safety regime because there may be pressures or incentives to bypass the rules.

In some cases clinicians may wish to provide innovative therapy or experimental treatment without clinical trials in order to meet the clinical needs of a patient with intractable disease. Innovative therapy does not qualify as a clinical trial or a research study, because it aims at improving the individual patient's condition, not at producing generalizable knowledge, as a clinical trial or research does.

Under the following conditions the use of stem cell products as innovative therapy or experimental treatment may be justified:

- Where the medical personnel and the institute conducting this therapy are appropriately qualified;
- If innovative therapy is used only on a case-by-case basis for patients who suffer serious or intractable disease where there is no existing effective therapy;
- Where the innovative therapy is subject to scientific and ethical review;
- Where there is valid informed consent from the patient, who agrees voluntarily to receive this treatment knowing this is an unproven and experimental therapy and that there is no clear understanding of its risks/ benefits ratio;
- Where medical care is provided in the case of complications or/and adverse events;
- Where negative outcomes and adverse events are truthfully reported;
- Where, on the basis of experiences of individual patients with positive outcomes, clinicians intend to move to clinical trials.

Applicable regulatory and scientific guidelines for development of such products should be followed if and where they exist. If such guidelines exist in one legislation but are absent in another researchers are encouraged to take notice of existing guidelines even though they are not legally binding for the country where the investigation takes place.

*Relevant to research ethics committees, regulators, scientists and physicians.*

Regulations should guarantee that the health, wellbeing, rights and psychosocial integrity of the child and woman have absolute priority and will not be diminished by other interests. Every woman has the right to a free and informed consent or dissent

**26. Public compliance, discrepancies in the legal status of embryos between different legal systems**

**Adherence to the laws of the countries involved, without necessarily generalizing regulation of the most restrictive partner country.**

*Researchers should be asked to declare whether parts of the research cannot be undertaken in their respective countries due to legal limitations.*

Any research, specifically research involving embryonic cells, should respect the laws of the countries involved. Research ethics commissions should request a legal compliance statement before approving the project. The duties, rights and legal situation of the involved researchers as well as of the research subjects should be clarified.

This does not necessarily mean that all actions (such as the creation of embryos for research purposes, therapeutic cloning, the use of certain categories of 'spare' embryos from IVF, the use of artificially grown eggs and sperm, human-animal chimera) must be legal in all countries involved in a project. Harmonization does not always mean homogeneity and equal standards. Working contracts between partners from different countries do not necessarily imply that the rules or predominant moral views of the most restrictive partner country should be applied to the whole research partnerships. Some countries will, for instance, not apply their laws to the activities of researchers if they work in another country where this activity is legal while others will. Case-by-case solutions can be considered. But an assessment of consistency with national regulations (public compliance) with regard to all countries involved, according to the nature of their involvement, should precede the beginning of research activities in an international partnership.

*Relevant for research ethics committees, researchers.*

**27. Implantation of embryos**

**Clarification of what is allowed to be done to an embryo in vitro and clarification of what is allowed to be done to an embryo before implanting it in the uterus of a woman.**

*What can be done to an embryo in the laboratory and which kinds of embryos can be implanted into a woman's uterus should be clarified.*

In research, no manipulation of the embryo before or after the beginning of its development, such as pharmacological or genetic interventions or nuclear transfer, should be conducted except where it is clearly permitted

by the appropriate regulations. Regulations should guarantee that the health, wellbeing, rights and psychosocial integrity of the child and the woman have absolute priority and will not be diminished by other interests. Every woman has the right to a free and informed consent or dissent.

This is particularly relevant for European-Chinese research collaborations, in order to avoid situations where a lack of clarity enables researchers to undertake research in another region that they would not be permitted to do in their own countries.

*Relevant to legislators.*

### 28. Banking and international exchange of cells and tissue

**Transparency regarding under which conditions germ cells, embryos or embryonic tissue has been collected.**

*Stem cell and tissue banks should be required to declare under which conditions the materials have been collected.*

Storing, banking and international exchange of embryos, eggs, sperm, cells and tissue originating from the human body need clear regulation. Such bio-banks, and all academic or commercial providers should be required to declare, transparently, under which conditions the materials they offer have been collected. Materials should only be imported and used for research if they have been collected under conditions which are either similar or equivalent to those valid in the receiving country, or explicitly acceptable according to national regulation. Nobody should be coerced by unfavourable circumstances or by relations of dependency to donate cells, tissues, eggs, sperm, embryos or other materials for research, banking or treatment purposes.

*Relevant for legislators, hospitals, researchers.*

### 29. Quality of transplanted cells or tissues

**Quality standards for 'clinical grade' stem cells.**

*Strict quality standards determining which kinds of human tissue can be transplanted into a human subject should be specified and adhered to.*

A key issue of safety is the quality standards including bacterial and viral contamination applied during production of cells, which are foreseen for human use. This includes genetic manipulation and cell culture conditions (eg, use of animal feeder cells, virus vectors etc). The principles of Good Manufacturing Practice should be applied as much as possible.

*Relevant to regulators, researchers.*

# A Sino-European platform for biomedical research ethics should be established

## E. Sustainability of cooperation in ethical governance

One recommendation has been found to be of particular significance for guaranteeing continuity of the process of collaboration and teamwork between Europe and China in ethical governance of research. This recommendation is the logical implication of recommendations 1 to 29.

**30. Continuous bioethics collaboration**

**A Sino-European platform for research ethics.**

*A Sino-European platform for biomedical research ethics should be established.*

A standing platform can enable sustainable teamwork and provide continuous advice to research collaborations between European and Chinese partners in human subjects research.

The platform should have an advisory role. It should meet regularly, observe the collaborative human subjects research practice from an ethical perspective and make recommendations to all parties involved. Recommendations should be explained and discussed publicly. The platform could consist of two Chairpersons, one from China, the other from Europe, a set of experts from participating countries, representatives of main fields of human subjects research and a secretariat.

The budget needs to be large enough to conduct regular meetings, to invite experts from outside and to publish the recommendations in Chinese and English.

*Relevant to funding agencies, research institutions, state authorities.*

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