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The regulatory situation for clinical stem cell research in China

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Abstract

This chapter reviews the regulatory situation for clinical stem cell research in the People's Republic of China since the early 2000s. The paper is structured in four parts. Part I examines the regulatory conditions for the donation of human gametes and embryos and their use in basic and preclinical research. This involves an overview of China's regulatory rules for assisted reproductive technologies (ART) and its approach to the governance of human embryonic stem cell (hESC) research. Part II offers a summary of the regulatory and legal instruments that govern clinical trials and other forms of human subjects research in China. These instruments, most of which have been launched in the 1990s and early 2000s do not specifically address stem cell research, but they influence clinical stem cell research as horizontal regulatory rules. Part III focuses more specifically to the regulation of clinical stem cell research and applications, including the regulation of experimental (for-profit) interventions with stem cells that do not classify as clinical trials or systematic forms of clinical research. This Part documents the formation of a regulatory approach for clinical stem cell applications since the mid-2000s, which was still ongoing at the time of writing. The Conclusions discusses open questions and the repercussions of China's regulatory approach for stem cell research for domestic researchers, clinicians and corporations in China, as well as for international clinical and corporate collaborations.

Keywords: stem cell research, clinical translation, research regulation, life science governance, China.

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1 Introduction

This Chapter provides an overview of the regulatory landscape of clinical stem cell research in the People's Republic of China. It provides, first, an overview of the regulation for the donation of human gametes and embryos and for their use in basic and clinical research. The Chapter will then in Part II present an overview of all regulations and laws that were issued in China since the 1990s to govern human subjects research. While these regulations do not mention stem cell research as a distinct regulatory category, these rules affect clinical stem cell research horizontally. The final part of the Chapter introduces the stepwise formation of a regulatory approach especially for clinical stem cell applications. This process was initiated in the mid-2000s and is ongoing. The Chapter ends with a Conclusion that discusses open questions and the implications of China's current regulation of clinical stem cell research for both domestic researchers and international clinical collaborations.²

2 The regulation for the donation and use of human gametes and embryos

Two regulations have been issued in China to govern the donation of human gametes and embryos for research purposes. Both of these regulations focus exclusively on human embryonic stem cell research. The first concerns the sourcing of human embryos and oocytes in the context of IVF clinics. The second addresses the specific conditions under which human embryos can be produced and used research and clinical application. No regulation exists currently that addresses (a) somatic cell nuclear transfer techniques for research purposes (i.e. "therapeutic cloning"), (b) basic or preclinical research with iPS cells, and (c) research with human-animal hybrids.

2.1 The Ethics Guiding Principles for Assisted Reproductive Technology (Ministry of Health, 2001-2003)

² This Chapter is based on a working paper and two publications that the authors of this Chapter have published in 2013 and 2015:

1. Rosemann, A., Zhang, X., Sui, S., Su, Y., & Ely, A. (2013). Country report: Stem cell research in China. Working Paper, Centre for Bionetworking, University of Sussex. (This working paper forms the basis for Sections I – III of this Chapter).
2. Rosemann, A. (2013). Medical innovation and national experimental pluralism: Insights from clinical stem cell research and applications in China. *BioSocieties*, 8(1), 58-74. (This paper forms the basis for Sections 4 – 4.3 of this Chapter). (Palgrave MacMillan provides the right to the authors to use this information in this chapter).
3. Rosemann, A., & Sleeboom-Faulkner, M. (2015). New regulation for clinical stem cell research in China—expected impact and challenges for implementation. *Regenerative Medicine*, DOI 10.2217/rme.15.80. (This paper forms the basis for Sections 4.4 and 5 of this Chapter). (This article has been published under a Creative Commons CC-BY license, and we are allowed to use published this information in this chapter).

The ‘Ethics Guiding Principles for Assisted Reproductive Technology’ have been issued by the Ministry of Health (MOH) between 2001 and 2003.³ These guidelines regulate the donation and transfer of human embryos and gametes for reproductive purposes and research. This document addresses stem cell research, by stipulating that all ART institutions must set up ethics committees, and that these committees must approve applications of human embryos to be donated for research (Hu, Min and Wei 2011; Cure 2009). The regulation affects the donation, circulation and use of human embryos, gametes and fetal tissue for research in four additional ways: (i) by stating that the buying and selling of human ova, sperm, embryos or fetal tissues is prohibited, (ii) by restricting the use of embryos for research to super-numerous embryos in the context of an IVF treatment, and by explicitly prohibiting the creation of IVF embryos for research only, (iii) by specifying that embryos and gametes must be voluntarily donated, on the basis of informed consent, and (iv) by forbidding hormonal super-stimulation, to harvest a larger number of oocytes. This regulation is backed up by punitive measures: IVF clinics or ART centers can lose their license if they violate these guidelines (Cure 2009).

2.1 The Ethics Guiding Principles for hESC research (Ministry of Health and Ministry of Science and Technology; 2003)

The derivation of human embryonic stem cells (hESC) and the use of these cells for research is regulated with the ‘Ethics Guiding Principles for hESC research’ (人胚胎干细胞研究伦理指导原则). Regulation occurs at a national level through ministerial guidelines, joint-issued in 2003 by the Ministry of Health (MOH) and the Ministry of Science and Technology (MOST). The core aspects of this regulation are that: (i) embryos are not allowed to be used for the derivation of hESC after 14 days post-conception, (ii) embryos used for research can not be implanted in human beings (prohibition of human reproductive cloning). The principles demand, furthermore, that institutions that are involved in hESC form an ethics committee that details regulatory rules and exact conditions under which research can be conducted. These principles have been criticized by members of the National Ethics Committee of the MOH in China because (a) they do not introduce a registration or licensing system of research institutes or clinics that conduct hESC research, (b) because they are not backed up by law, and (c) no clear control pathways for the principles are provided. Plans and efforts to revise this regulation, from the side of the MOH National Ethics Committee, are ongoing (Zhai 2007).

3 The regulation of human subjects research in China

Before introducing the regulations, laws and institutions that play a role in the governance of clinical stem cell research and applications in Section 4, we will first of

³ Please note, the Chinese Ministry of Health (MOH) was in 2012 renamed to the National Health and Family Planning Commission (NHFP). In this article we use both of these terms: For regulatory documents that were issued before 2012 we use the term Ministry of Health (MOH), and for regulatory documents that were issued after 2012 we use the term National Health and Family Planning Commission (NHFP).

all provide an outline of the regulations and laws that were issued since the 1990s to govern human subjects research in China. As will become clear in Section 4 of this Chapter, even though these regulations do not mention stem cell research, they play a role in the governance of clinical stem cell research and applications in China at a horizontal level.

3.1 The Foundation of a national-level ethics committee (MOH; 1998)

An important step for the governance of human subjects research in China was the foundation of the Ministry of Health's 'Ethics Committee on Biomedical research involving human subjects' in 1998. The Committee was renamed in 2000 as 'Medical Ethics Expert Committee'. Following a reform in 2007, the committee comprises 17 members from a multi-disciplinary background. These members have been instrumental in the formation of many of the regulatory documents discussed in this Chapter.

3.2 The Regulation on ethical review of biomedical research involving human subjects' (MOH; 2007)

The 'Regulation on ethical review of biomedical research involving human subjects' (涉及人的生物医学研究伦理审查办法 [试行]) addresses the formation of institutional review committees, and the procedures through which ethics review of human subjects research shall be conducted. A first document on the regulation of ethical review procedures was drafted in 1998. However, due to internal controversies the document was not endorsed (Hu, Min and Wei 2011). A revised version of the regulation was then issued by the MOH in 2007. According to this regulation – all – forms of research and experimental clinical interventions that involve human subjects require review by an ethics committee at the level of research institutes and hospitals. The regulation specifies information on the procedures and criteria for ethics committee review, the structure of the committees as well as details on informed consent procedures. This regulation has been of significance to clinical stem cell research and applications in China, because it requires mandatory EC approval at the level of medical institutions.

3.3 Regulation on the Governance of Medical Institutions (State Council; 1994)

The 'Regulation on the governance of medical institutions' was issued by the State Council in 1994. It clarifies that informed consent is required for the conduct of surgical operations, special investigations, participation in clinical studies as well as experimental medical interventions. The regulation introduces performance rules for medical institutions such as registration procedures, required qualifications of medical staff and institutional safeguards that shall prevent the misuse of patients. An example is, a clause that specifies that that approval documents for treatments (that were provided by the Chinese health authority to a particular hospital) cannot be 'inherited', if the owner, or name of a hospital changes. This regulation is of relevancy for clinical SC research, in particular with regard to the governance of clinics that offer experimental for-profit interventions with stem cells. The Jilin Silicon Valley Hospital, for instance, was criticized by the media on the basis of this regulation. Reason: the hospital had changed its name and proprietor, but used the same approval license for its cellular treatments (issued by a local and a provincial

health bureau) in order to attract patients. The Chinese health authorities withdrew the license of the hospital shortly after this discovery.

3.4 The Drug Clinical Trial Regulations Law on Practicing Doctors (MOH; 1999)

This regulation protects patients by stating that doctors who violate a patient's privacy or who conduct experimental medical interventions without informed consent will be legally persecuted. Even though cases where this regulation has been applied in the context of stem cell-based forms of clinical intervention, this regulation offers a legal instrument could be applied to providers of experimental stem cell treatments, if these fail to sufficiently inform patients of medical risks or make exaggerated treatment claims (Cure 2009). In other words, based on this regulation, patients could sue doctors who offered experimental stem cell treatments based on fraudulent claims.

3.5 The Drug Administration Law (National People's Congress, 2001; amended in 2015)

The Drug Administration Law was issued by the National People's Congress and is implemented through the Chinese Ministry of Health (which since 2012 was renamed to the 'National Health and Family Planning Commission) and the Chinese State Food and Drug Administration (SFDA) (which since 2012 was renamed to the China Food and Drug Administration).⁴ The law has been amended in 2015 and covers the use of pharmaceutical products in research as well as routine clinical applications following market approval. It clarifies that GCP and GMP standards must be followed (Cure 2009). This regulation is of relevancy for the development of stem cell-based medicinal products once the Chinese regulators have issued a regulation for stem cell research that specifies the exact conditions for market approval under the authority of the China Food and Drug Administration.

3.6 The SFDA good clinical practice standards (SFDA; 1999-2003)

The State Food and Drug Administration (SFDA) good clinical practice standards (药物临床试验质量管理规范) were issued in a first version in 1999, and in a second more complete version in 2003. Both versions were drafted and issued by the SFDA. The SFDA GCP standards specify procedures for clinical trials in the context of market authorization pipeline and for the accreditation of medical institutions that take part in drug trials. The regulation requires that each hospital that conducts clinical trials acquire GCP certification (Cure 2009). An interesting feature is that GCP certification is based on examinations of high-level clinical staff (heads of department). They emphasize strict informed consent and review by ethics committees, and include provisions on how IRBs should be composed and be organized. The Chinese GCP standards draw actively on the ICH GCP standards. (Cure 2009). These SFDA GCP

⁴ Please note, the Chinese State Food and Drug Administration (SFDA) was in 2012 renamed to the China Food and Drug Administration (CFDA). In this article we use both of these terms: For regulatory documents that were issued before 2012 we use the term State Food and Drug Administration (SFDA), and for regulatory documents that were issued after 2012 we use the term China Food and Drug Administration (CFDA).

standards are of relevancy to hospitals that conduct clinical trials with SC in the context of an SFDA registered IND application.

3.7 The SFDA Guidance for human somatic cell therapy research and quality control of the products (SFDA 2003)

The Guidance for Human Somatic Cell Therapy Research and Quality Control of the Products (人体细胞治疗研究和制剂质量控制技术指导原则) forms an important precursory regulation for the clinical use of cells and stem cells. It was issued by the Chinese SFDA in 2003 and is still valid. The guidance addresses fundamental issues of therapy research with somatic cells. It focuses on aspects such as the collection, isolation and verification of somatic cells, the kind of (medical and personal) information that is required from cell donors, directives on the use and documentation of specific types of culture mediums, and a broad range of specifications on quality control. Quality control encompass measures for both pre-clinical research as well as production, culture and storage protocols of somatic cellular products in the context of clinical research. While this guidance is still valid at the time of writing, many of the biological characteristics and particularities of stem cell research are not – or only insufficiently – addressed in this document. This is one of the reasons why the Chinese SFDA and MOH in the late 2000s decided that a new and more comprehensive regulation for the regulation of clinical stem cell research is necessary.

4 The evolving regulatory approach for clinical stem cell research

In the subsequent paragraphs we provide a detailed overview of the evolving regulatory framework for clinical stem cell research and applications in China. At the moment of writing, the process of developing a regulatory framework that can be used for both clinical testing and market approval of stem cell treatments is still ongoing. Since 2009 a range of regulatory documents have been issued by the Chinese health authorities that have affected clinical research and experimental for-profit interventions in various ways. The most recent and far-going regulatory measure has been provided in 2015,

4.1 The Management Measures for the Clinical Use of Medical Technologies (MOH; 2009)

On May 1 2009 the MOH promulgated the “Management Measures for the Clinical Use of Medical Technologies” [医疗技术临床应用管理办法], a regulation that classified a range of new medical technologies and procedures into three categories. Stem cell transplant technology was grouped into category III, which included technologies considered as risky, ethically controversial and in need of clinical verification (Chen 2009). To implement the regulation the MOH assigned five institutions (ibid.: 271), among them the Chinese Medical Association, the Chinese Hospital Association and the Chinese Doctors Association. According to an associate of the MOH in Beijing, clinics that used SC transplantation technology were summoned to register at these institutions. These organizations in turn were assigned to grant licenses on the basis of newly formed assessment criteria and review and

inspection committees. In practice, this regulation has not yet been implemented for SC transplantation technologies. As stated by a senior SC scientist, who as a member of the Chinese Doctors Association was involved in the formulation of review criteria, there were widespread disagreements among experts of the assigned five institutions, over the precise characteristics of these criteria, over feasible implementation pathways, as well as the extent to which the situation should be controlled.

4.2 Notification on Self-Evaluation and Self-Correction Work regarding the Development of Clinical Stem Cell Clinical Research and Applications (NHFPC; 2012)

On January 6 2012, the National Health and Family Planning Commission NHFPC, the former MOH) issued a regulatory document called ‘Notification on Self-Evaluation and Self-Correction Work regarding the Development of Clinical Stem Cell Clinical Research and Applications’ [关于开展干细胞临床研究和应用自查自纠工作的通知].⁵ With this document the NHFPC initiated a one-year phase that was announced to be followed by a more comprehensive regulatory approach at a later point. In the January 2012 document, four subsequent stages of this forthcoming approach were announced: self-evaluation (*zicha*), self-correction (*ziji*), re-certification (*chongxin renzheng*), and standardized management (*guifan guanli*). The initial one-year phase that is set out in the 2012 document, however, addresses only the first two of these stages: self-evaluation and self-correction. Self-evaluation of the hospitals that carry out SC-based clinical research and applications shall occur in the following way. First, clinics are required to fill in the ‘Self-Evaluation Form for Inquiry into Conditions of Stem Cell Clinical Research and Applications’.⁶ In this form, clinics are asked to report truthfully on previously and currently developed kinds of clinical research and applications with stem cells. Information is requested on (1) types of cells and forms of cell-processing, (2) the disease types for which cells have been used, (3) forms of ethics and regulatory approval mechanisms, (4) informed consent procedures, (5) information on risks and experienced problems, (6) sources of funding and patient fees, (7) number of patients experimentally treated, and (8) publications or summarizing reports from clinical trials or other types of clinical studies. Second, this information is evaluated by province-level MOH workgroups, which are coordinated by the ‘Stem Cell Clinical Research and Application Standardization and Rectification Work and Leadership Group’, co-founded by the MOH and SFDA in Beijing (paragraph 2). The task of these province-level workgroups is to appraise the incoming data, to produce summarizing reports to Beijing (paragraph 4), and during later stages, to play an active role in the implementation and enforcement of the regulation (paragraph 2).

Self-correction means that all institutes that have not yet received approval, either by the MOH or the SFDA, must stop clinical stem cell research or application activities until approval has been obtained. Institutes that continue to carry out unauthorized clinical research or applications have been announced to be targeted as focal points for rectification (paragraph 2). On the other hand, clinical trials for stem

⁵ <http://www.moh.gov.cn/publicfiles/business/htmlfiles/mohkjjys/s3582/201201/53890.htm>

⁶ This document has been put on the MOH website.

<http://61.49.18.65/publicfiles///business/cmsresources/mohkjjys/cmsrsdocument/doc13829.docx>
Translations of these two documents can be requested from the author of this article per email.

cell products that have obtained approval by the SFDA are expected to act in strict accordance with the requirements set out by the SFDA, and in compliance with the Chinese GCP standards (paragraph 2). The document has announced that no registration applications will be accepted by the MOH or the SFDA until July 1 2012 (paragraph 2). Information on how applications for registration will be handled, however, has not been provided in the text. Uncertainty also remains as to how non-compliance will be dealt with, and which role the MOH and its province-level workgroups will play in this. It is not clear, furthermore, whether military hospitals (that operate under the command of the Health Department of the Army General Logistics Department), will be subjected to the same review and approval procedures as state hospitals, or whether a different regulatory approach shall apply.

4.3 The March 2013 announcement of three inter-related draft regulations

On March 7 2013 the MOH published online three regulatory documents on clinical stem cell research for public feedback and commentary. These documents introduced the underlying rationale of the planned regulatory framework, an overview of its basic structure, central regulatory instruments and planned implementation structure. In contrast to initial media reports (Zornoza 2013) these documents did not yet constitute regulatory draft documents themselves, and they had no legal authority. This consultation formed the first publicly visible step toward regulatory intervention of clinical stem cell research and applications in China, since the above-mentioned January 6 2012 notification. It represents the first move toward realization of the third and the fourth of the four regulatory phases that the MOH announced in its 2012 notification (as introduced above): “Re-certification” [chongxin renzheng] and “Standardized Management” [guifan guanli], following from phases one and two: “self-evaluation” [zicha] and “self-correction” [ziji], which were initiated in the course of 2012.

The most important announcements in these documents were as follows. The approval of stem cell-based therapeutic applications must be based on phase I, II and III clinical trials. These trials must be approved by hospital-internal ethics committees and joint-expert committees of the NHFPC and CFDA. Clinical stem cell trials must follow from solid preclinical evidence that documents the safety and therapeutic potential of a candidate therapy in animal models. Clinical or corporate sponsors of these trials will not be allowed to charge patients for participation in these trials. The stem cell collection, purification, amplification, certification, packaging, storage and transport of the stem cells that shall be used for clinical trials, must occur in accordance with good laboratory practice (GLP) and good manufacturing practice (GMP) standards. Another announcement was that violation of these requirements would be subject to punishment procedures and legal persecution under the existing drug management law.

4.4 The Regulation for Clinical Stem Cell Research and the Stem Cell Preparations Quality Control and Pre-clinical Research Guidelines (NHFPC and CFDA; 2015)

Following the public consultation in 2013 another two years went by until a formal regulation for clinical stem cell research was published. On August 22, 2015 the

Chinese National Health and Family Planning Commission (NHFPC, the former Ministry of Health, MOH) and the China Food and Drug Administration (CFDA; the former SFDA) have issued two inter-related documents: (1) the Regulation for Clinical Stem Cell Research and (2) the Stem Cell Preparations Quality Control and Pre-clinical Research Guidelines. These documents form the long awaited follow up from the regulatory announcement that was issued in March 2013. The August 2015 ‘Regulation for clinical stem cell research’ presents itself as a ‘trial’ or ‘interim’ (试行) regulation. This is not unusual. In China, regulation usually starts out as a draft (草案) or trial regulation (试行). A ‘trial’ regulation should be regarded as valid as formal regulation, but it is flexible enough to leave space for change. The document announces the central elements of a regulatory foundation for the clinical translation of stem cell-based medicinal products and procedures. What does China’s future regulation for clinical stem cell trials look like? What challenges can be expected with regard to its implementation? And what impacts will the regulation have for domestic researchers, clinics and corporations in China and at an international level?

4.4.1 Overview of the ‘Trial’ (or ‘interim’) Regulation

The trial regulation applies to the clinical use of human autologous and allogeneic stem cells that are manipulated in vitro, with the exception of the routine transplantations of hematopoietic stem cells and of clinical trials that use stem cells that are affirmed as pharmaceutical products. Stem cell treatments have to pass through methodical clinical studies and follow from systematic preclinical evidence. These trials must comply with the Chinese ‘Quality Control Standards for Clinical Drug Trials’ (the Chinese good clinical practice [GCP] standards), which has guided the approval of new drugs by the China Food and Drug Administration (CFDA) since 2007. Furthermore, first-in-human clinical trials must be based on systematic evidence of preclinical research proving the therapeutic value and safety of a candidate treatment in appropriate animal models.

The standards and technical procedures for the collection, manufacturing and storage of stem cells for clinical use are laid down in the “Stem Cell Preparations Quality Control and Pre-clinical Research Guidelines”, a supplementary document published by the CFDA, which also specifies the required criteria for safety and efficacy assessment in the context of preclinical studies. Only level 3 hospitals – the highest ranked hospital category in China – are permitted to conduct stem cell clinical trials. To qualify, such hospitals must have established institutions for research, health care and teaching, and be in possession of the relevant professional qualifications. Hospitals must have ethics and academic committees capable of dealing adequately with adverse effects and preventing high-risk applications. Moreover, hospitals are required to establish stem cell preparation facilities that are compliant with international GMP standards.

Investigators applying for stem cell clinical trials must do so at provincial branches of the NHFPC and CFDA, and register the trials online at the Chinese Medicine Registry and Management System. The NHFPC and CFDA s will jointly review the projects at a provincial level with the help of specifically formed expert committees. These committees do not only review incoming applications but also will conduct on-site verification and evaluation of academic institutions, ethics committees and project management. If a clinical trial application is accepted, phase I of the trial can go ahead. Clinical trial progress reports must be submitted to the

authorities on a regular basis, and after each phase investigators need to report the research results to the provincial agencies. Based on these reports, decisions are made about progression to the next phase and ultimately about routine clinical application.

The regulation seeks to protect the interests of patients in the following ways. First of all, clinical investigators may not charge money for patients taking part in clinical studies, and hospitals are not allowed to advertise stem cell trials as treatments. Hospitals are required to fully inform patients of the potential risks of the research involved, and to arrange insurance coverage for human subjects for projects involving a high level of risk. In case of emergency, life-saving facilities need to be in place. Moreover, serious adverse events must be reported to the hospital ethics committee and the provincial health authorities, and will result in the immediate halt of the research project and withdrawal of approval for the application of the stem cell therapy concerned.

Stem cell clinical trials must be conducted in accordance with the '2007 Interim Regulation on the Review of Biomedical Research Involving Human Subjects' of the MOH (now NHFPC), and the 'Drug Administration Law', issued by the MOH in 2001 (and amended in 2015). Clinical trials using human embryonic stem cells must harvest and process the cells in line with the 'Guiding Principles for the Ethics for Human Embryonic Stem Cell Research', a joint-regulation issued in 2003 by the Ministry of Science and Technology and the MOH. With the new trial regulation stem cell-based treatments are no longer regulated as class III medical technology in accordance with the 2009 regulation for clinical stem cell applications [4], which indicates that the former regulation is no longer valid.

Medical institutions and staff who violate regulatory provisions are directly held responsible in accordance with specifically designed penal procedures. The provincial branches of the NHFPC and CFDA have the authority to suspend stem cell trials and to punish investigators and staff in line with appropriate laws and regulations.

4.4.2 Commentary

China has invested heavily into stem cell medicine in recent years. This has resulted in a growing body of publications and the development of new candidate therapies (Song 2011). Simultaneously, due to a permissive regulatory environment for clinical stem cell applications the country has witnessed the mushrooming of commercial stem cell clinics. Between 2002 and 2012, China became a global hub for the sale of unproven clinical for-profit interventions (Rosemann 2013). A first attempt to control this situation was undertaken in 2009 in the context of a new regulation for medical technologies (Sui and Sleeboom-Faulkner 2015). However, because of disagreements within the health authorities on feasible implementation pathways this regulation was never enforced for stem cell research and the number of unproven stem cell interventions was widely reported to grow (McMahon 2014; Sui and Sleeboom-Faulkner 2015). In 2012 the MOH undertook a renewed regulatory effort by introducing a notification, which stipulated that all medical institutions without prior approval from the MOH or the CFDA must stop clinical stem cell procedures. This notification had limited effect, mainly on state-supported scientific institutions. An article in *Nature* reported that three months after the ban, numerous clinics in China were continuing their services (Cyranoski 2012). Then, in March 2013, the NHFPC published three inter-related draft regulations for public comments. These documents announced stringent controls on experimental stem cell interventions and emphasized

clinical translation through systematic clinical trials overseen by the Chinese health authorities.

Elements of the 2013 regulation have now been incorporated in the regulatory documents published in August 2015. The 2015 ‘trial’ regulation indicates an important step towards the improved governance and review of stem cell clinical research and applications in China. With the enforcement of systematic clinical studies required to comply with scientific principles, standardization, transparency and the improved protection of research subjects, the CFDA and NHFPC have established a framework intended to cater to the needs of researchers in China and internationally. The regulation rejects the use of unproven experimental for-profit interventions with stem cells (Song 2011), while introducing a clear strategy toward more responsible forms of clinical translation. The prohibition to advertise unproven stem cell treatment and charging patients for taking part in experimental studies alone could potentially result in the permanent halt of experimental for-profit interventions in a large number of hospitals that have profited from unclear regulations for years (McMahon 2014). Institutions that work under the publicized rules can be expected to raise methodological standards, improve the validity of research data, and subject patients to less risk.

However, the actual impact of the regulation depends on its enforcement and implementation. By sharing administrative duties for review and certification of clinical stem cell research and applications between provincial NHFPC and CFDA branches, and by training specialist staff and expert committees to operate at the provincial level, China’s health authorities create a regulatory infrastructure that promises to hit its target. The document’s grounding in the country’s ‘Drug Administration Law’ and the backing of its stipulations by punitive measures reinforces this impression. Implementation, nonetheless, can be expected to be a difficult and gradual process, with several challenges along the way. A first challenge will be to train sufficient numbers of staff, and to recruit well-qualified experts for independent review, so that incoming applications can be dealt with in a reliable and simultaneously efficient way. A further challenge concerns the geographical size of China, the country’s large number of medical institutions, and the lucrative business opportunities that have evolved in the stem cell field in recent years (McMahon and Thorsteinsdottir 2011). In the light of the well-established national and international networks of for-profit stem cell therapy providers in China (Sui and Sleeboom-Faulkner 2015), it will be difficult to control for-profit stem cell clinics. The problem of implementing the regulation to established institutions that seek to approve stem cell clinical trials is different from that of controlling stem cell clinics. While the new trial regulation delegitimizes unapproved for-profit stem cell interventions and provides a legal basis to close down such clinics, it does not provide concrete details on how the enforcement of such controls might occur. While the Chinese authorities in the last years have sporadically clamped down on for-profit stem cell clinics (Sui and Sleeboom-Faulkner 2015), it is unclear whether the resources, administrative infrastructure and the political will can be mobilised to counter these clinics on a large scale and on a nation-wide level. Enforcement of the regulation in the context of Level 3 hospitals, on the other hand, can be expected to be successful: China’s elite stem cell researchers have long-since demanded a kind of regulation that can legitimize their research and resulting clinical applications. It remains to be seen, however, how tightly oversight procedures for clinical stem cell applications will be organized, and whether the number of staff and available resources will be sufficient to assure dependable implementation.

Moreover, variation can be expected in the interpretation of regulation and policies among the provinces. Will these divergent interpretations thwart homogenous implementation? Despite possible variation across provinces, it is clear in the trial regulation that all research and commercial activities fall under the responsibility of the main units of the NHFPC and the CFDA in Beijing, which prohibit unauthorized for-profit interventions at the national level. Exemptions from the national standard at the provincial level (which has proven a hindrance for the effective regulation of autologous stem cell treatments in the USA (Knoepler 2014)) are not possible.

It is also not clear to what extent the regulation affect practices in army and police hospitals, which have their own regulatory bodies and where much of the commercial stem cell activities have been located in recent years (Yuan et al 2012). Much will depend on the political prioritization of tackling all experimental stem cell therapy providers, ranging from small for-profit providers to powerful military organizations.

The promise of greater dependability of approval procedures for the clinical development of stem cell treatments and greater compatibility with international procedures should be a relief to many stem cell scientists in China. The absence of a functioning regulatory framework for clinical stem cell research for many years has deprived researchers and R&D companies of the possibility to apply for the official registration of newly developed candidate treatments (Rosemann 2013). It has also limited the opportunity for building international clinical research collaborations (Zhang 2012). By introducing systematic approval procedures for stem cell clinical trials the forthcoming regulation will strengthen domestic innovation trajectories, facilitate collaborations with foreign researchers, and also allow for joint-applications for the approval of candidate therapies at drug regulatory authorities in China and in other countries.

The trial regulation's commitment to systematic preclinical studies, clinical trials, reliable quality controls, the Chinese GCP standards, GMP and external review by independent expert committees promises to create congruence with both, the benchmarks set out in the 'Guidelines for the Clinical Translation of Stem Cells' of the International Society for Stem Cell Research (ISSCR 2008), and the standards for clinical stem cell research handled by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA).

5 Conclusion and Final Questions

The new trial regulation provides a basis to define experimental for profit interventions with stem cells in China as illegal and to investigate and punish stem cell clinics that operate outside the supervision of the NHFPC and the CFDA. The focus of this new regulation, however, is exclusively on the governance of clinical research. It does not stipulate any details on how the transition from clinical trials to routine clinical use and market approval shall be handled. This leaves many questions to be answered that will be crucial for corporations and international collaborations that strive for the joint-application of stem cell treatments at drug regulatory authorities in China and other countries. Because information on marketing conditions is absent in the publicized regulation, it is extremely difficult to discuss its implications for international collaborations. A possible explanation to the lack of information on market approval in the current regulation is that no agreement on this point has been reached yet between involved stakeholders.

Unclear is also what procedures will be handled for the clinical use of stem cells that are affirmed as pharmaceutical products, and also what criteria the NHFCP and the CFDA handle in order to define pharmaceutical stem cell products. Clearly designated subcategories of different types of stem cell interventions have not yet been published. However, such definitions will be of crucial importance to determine the relevant regulatory authority (the NHFCP or the CFDA, or different subunits). The fact that the CFDA is closely involved in the drafting and implementation of this regulation suggests that at least some stem cell based applications will be classified as medicinal products. No matter how, the fact that this important point remains undefined suggests that harmonization with regulatory agencies in the USA, Europe and other highly developed countries is still a long way off. These uncertainties might cause confusion for biotech companies, especially those that produce stem cells as quantifiable batch products from a single cell line, as for instance Geron has done with its human embryonic stem cell product (Knoepfler 2013). Another question is what type of clinical studies the NHFCP and CFDA require to allow the go-ahead from clinic to the market and routine use. While in a former, now invalid draft of the new regulation that was issued for public consultation in 2013 it was stated that systematic controlled phase I-III trials would be required (Xinhua 2013), the current regulation only speaks of clinical trials that shall be conducted according to scientific principles. Do China's health regulators leave this question deliberately open, so as to have the flexibility to follow the current Japanese model rather than the USA or EU model, which allows for conditional and time-limited market approval after successful clinical studies with relatively small number of patients (Azuma 2015)? Another issue that remains unclear is whether the new regulation in China leaves space for the conduct of experimental clinical interventions with stem cells outside of the format of the clinical trial (for instance as a 'last resort' treatment in individual patients after all existing interventions have failed) and how these forms of clinical experimentation will be reviewed and approved. A further question is how the regulation will impact the affordability of stem cell trials. The requirement of systematic preclinical research, the availability of GMP laboratories, and clinical translation through systematic clinical trials will significantly increase the costs of clinical translation. Accordingly, the introduction of the new regulations may have drawbacks for less well-endowed research institutes (Sui and Sleeboom-Faulkner 2015). With increased costs and a system that allows clinical studies solely in qualified tier three hospitals, only a limited number of investigators and research institutions will be enabled to conduct clinical stem cell trials. The resulting unequal access to financial resources may redefine opportunities to clinical innovations in the stem cell field. It remains to be seen whether this new situation will reignite a new brain drain to the private sector or abroad.

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