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Achim Rosemann

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Standardization as situation-specific achievement: regulatory diversity and the production of value in intercontinental collaborations in stem cell medicine

[1]Achim Rosemann

[1]Department of Anthropology, School of Global Studies, University of Sussex, Arts C 252, Brighton, BN1 9SJ, UK

Email: ar253@sussex.ac.uk, Tel: +447538329625

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Standardization as situation-specific achievement: regulatory diversity and the production of value in intercontinental collaborations in stem cell medicine

Abstract:

The article examines the role and challenges of scientific self-governance and standardization in inter-continental clinical research partnerships in stem cell medicine. The paper shows that – due to a high level of regulatory diversity – the enactment of internationally recognized standards in multi-country stem cell trials is a complex and highly situation-specific achievement. Standardization is imposed on a background of regulatory, institutional and epistemic-cultural heterogeneity, and implemented exclusively in the context of select clinical projects. Based on ethnographic data from the first trans-continental clinical trial infrastructure in stem cell medicine between China and the USA, the article demonstrates that locally evolved and international forms of experimental clinical research practices often co-exist in the same medical institutions. Researchers switch back and forth between these schemas, depending on the purposes of their research, the partners they work with, the geographic scale of research projects, and the contrasting demands for regulatory review, that result from these differences. Drawing on Birch's analysis of the role of standardization in international forms of capital production in the biosciences, the article argues that the integration of local knowledge institutions into the global bioeconomy does not necessarily result in the shutting down of localized forms of value production. In emerging fields of medical research, that are regulated in highly divergent ways across geographical regions, the coexistence of distinct modes of clinical translation allows also for the production of multiple forms of economic value, at varying spatial scales. This is especially so in countries with lenient regulations. As this paper shows, the long-standing absence of a regulatory framework for clinical stem cell applications in China, permits the situation-specific

adoption of internationally recognized standards in some contexts, while enabling the continuation of localized forms of value production in others.

Key-terms: China, regenerative stem cell medicine, clinical trials, situational standardization, scientific self-governance, research regulation, international collaborations

Introduction

In this article, I focus on processes of scientific self-governance and standardization in the context of intercontinental clinical research collaborations in the field of regenerative stem cell medicine. I will explore, furthermore, the implications of these processes on local clinical innovation practices, and the production of localized forms of economic value. The paper explores these issues by focusing on the formation of the China Spinal Cord Injury Network (China SCI Net), the first intercontinental clinical trials infrastructure in the stem cell field that has emerged between medical researchers in mainland China, Hong Kong, Taiwan and the USA.

The emergence of a global clinical trial landscape has been a key theme in the literature on industry-sponsored forms of clinical research on vaccines and drugs based on chemical compounds (Leach et al., 1999; Gikonyo, Bejon, Marsh, & Molyneux, 2008; Petryna 2009; Sariola, & Simpson, 2011). To date, however, no study has systematically focused on the formation of international clinical trials in the field of regenerative stem cell medicine. Existing academic work on the clinical translation of stem cell-based therapeutic approaches has focused either on processes of preclinical development (Cribb, et al., 2008; Martin, Brown and Kraft, 2008; Wainwright, et al., 2006), or on clinical research in the context of national jurisdictions, especially in the USA and in countries of the European Union (Wilson-Kovacs, Weber, & Hauskeller 2010; Webster, Haddad, & Waldby, 2011). A third body of work has been concerned with the provision of experimental for-profit interventions with stem cells, outside of the methodological format of the clinical trial. These studies have commented in particular on the situation in China (Song,

2011; Chen, & Gottweis, 2011; Rosemann, 2013a) and India (Bharadwaj, 2013; Sleeboom-Faulkner, & Patra 2011).

The development of regenerative stem cell medicine through internationally acknowledged multi-country clinical trial partnerships has remained unexplored so far. This is an important analytical shortcoming. A focus on the formation of international clinical trial infrastructures provides important opportunities to gain insights into the processes and challenges involved in the development, organization, and governance of large-scale, transcontinental clinical research collaborations in the field of regenerative stem cell medicine (as well as other emerging fields of medicine research). Of particular interest, in this respect, are processes of standardization, which in recent years have evolved as important concerns in the social study of medicine research (Timmermans, & Berg, 1997; Timmermans, & Epstein, 2010; Birch, 2012). The evolving field of clinical stem cell medicine forms an interesting case in this respect. In contrast to established forms of drug research, for clinical stem cell research there are as yet no internationally binding standards or harmonized global governance frameworks, and widely divergent regulatory conditions exist across (and within) countries. The governments of the USA, the European Union and some other countries have now developed legal arrangements for the licensing of stem cell-based medicinal products (Halme, & Kessler, 2006; Faulkner, 2012). In many other countries, however, including in population rich countries such as China and India – where unproven for-profit applications with stem cells constitute a huge market – the development of regulatory frameworks is evolving only gradually (Sleeboom-Faulkner, & Patra, 2011; Rosemann, 2013a). In China, the experimental clinical use of stem cells remained completely unregulated until January 2012, with the result that highly dissimilar types of clinical research and experimental for-profit

applications have surfaced since the early 2000s (Chen, 2009; Song, 2011; Rosemann, 2013a).

The argument in this paper is developed in two parts. First, I will show that the high level of regulatory diversity in the international landscape of clinical stem cell research, poses a significant challenge to the organization of cross-continental clinical trial collaborations. By focusing on the formation of the China Spinal Cord Injury Network (China SCI Net), the first trans-continental clinical trial infrastructure in stem cell medicine between China and the USA, the article will elucidate that the enactment of internationally recognized clinical research standards is a complex and highly situation-specific achievement. Standardization, as will be shown, relies on extensive forms of scientific self-governance, and requires far-reaching adjustments of local clinical research environments. Internationally approved methodological protocols are established against a background of regulatory, institutional and epistemic-cultural heterogeneity, and implemented in the situational context of the clinical trials organized by the China SCI Net. Exterior to the activities of the China SCI Net, we see that locally evolved and newly adopted (i.e. internationally accepted) forms of experimental clinical research practices exist side by side with each other, often in the same medical institutions. Researchers shift between these divergent schemas, depending on the purposes of their research, the partners they work with, the geographic scale of research projects, and the contrasting demands for regulatory review, that result from these differences. Second, based on these insights I will engage in a dialogue with a recent analysis of the role of standardization in the creation of value in the biosciences by sociologist Kean Birch (2012). I will argue that – in the regenerative medicine field – the integration of local knowledge institutions into the global bioeconomy does not necessarily result in the shutting down of

localized forms of value production. While the blocking of local forms of capital production in the biomedical sciences can be observed in particular in established fields of medical research, and in countries with stringent regulatory controls in place, in emerging fields of medicine research, a more diversified situation exists. In emerging socio-technical fields of medical research, such as regenerative stem cell medicine, which is regulated in highly divergent ways across (and often within) geographical regions, the close proximity between locally evolved and internationally recognized forms of clinical translation allows also for the production of multiple forms of economic and scientific value. Localized forms of value creation in medical institutions, that do not conform to the requirements of international scientific standard regimens, continue to exist – aside to participation in internationally approved, multi-country clinical research projects. Geographic location, and regulatory differences between these locations, is a key factor in explaining this situation. As this paper shows, the long-standing absence of a comprehensive regulatory framework for clinical stem cell applications in China permits the situation-specific adoption of internationally recognized standards in some contexts, while enabling the continuation of local forms of value production in others.

Empirical context and methodology

The empirical focal point of this article is an ethnographic study of the China Spinal Cord Injury Network (China SCI Net), an academic clinical trials infrastructure that involves more than twenty spinal cord injury (SCI) centers in mainland China, Hong Kong, and Taiwan. The Network is registered as a non-profit corporation in Hong

Kong, and was founded in 2005 by Professor Wise Young from Rutgers University in New Jersey, in close collaboration with leading researchers from Hong Kong and the Chinese mainland (Rosemann, 2013b). Since 2009, the China SCI Net has been paralleled by the Spinal Cord Injury Network USA (SCI Net USA), which comprises eight academic hospitals. The aim of this evolving transnational research economy is to develop and clinically assess stem cell-based combination therapies for spinal cord injury, and the licensing of successfully tested treatments in China, Hong Kong, Taiwan, the USA, and potentially other countries in the world. Until April 2014, the China SCI Net had conducted seven clinical studies. An initial noninterventional observational study was carried out between 2005 and 2008 in twenty-two hospitals to collect diagnostic and long-term follow-up data from up to 600 acute and chronic SCI patients. This study was followed by five phase I and II trials that have been conducted in chronic SCI patients, in two university hospitals in Hong Kong and one military hospital in China. Two of these studies tested the safety and efficacy of lithium in SCI patients, and three studies an experimental combination therapy of umbilical cord blood (UCB) mononuclear cells, lithium, and methylprednisolone. A Phase III trial incorporating more hospitals (including those in Taiwan) is being planned in 2014. The SCI Net USA has not yet conducted clinical trials, but Phase II and Phase III studies are in preparation. The UCB stem cells that are used in the trials of the Network are sponsored by the US-Taiwanese umbilical cord blood bank company Stemcyte. The organization of the trials itself is covered by financial resources raised within China and Hong Kong (Rosemann, 2013b).

The data presented in this article have been gathered during a period of ten months of ethnographic fieldwork in Hong Kong, Taiwan, and mainland China, between April 2010 and April 2011. The formation of the China SCI Net was

analyzed against the wider background of clinical stem cell research and applications in these regions, particularly in mainland China (Rosemann, 2011, 2013a). The data generated in Taiwan are not included in this article because the main activities of the Network during the fieldwork stage took place in Hong Kong and China.

Several methods of data collection were employed during the research process. Open-ended, in-depth interviews were conducted with twenty-eight people affiliated to the China SCI Net. These included senior executives, principal investigators, clinical researchers, and fundraisers, from ten participating hospitals and institutes. These interviews were either tape-recorded and transcribed verbatim, or recorded by hand during the interview process. All interviewees were explained the purposes of the research, and verbal consent to use interview data for academic publications was obtained. Documentary research was conducted using text sources provided by people from the Network and from the Internet. These documentary sources included scientific papers, opinion pieces, newspaper articles, blog contributions of researchers, as well as video-documentation of panel discussions and presentations during international symposia organized by the China SCI Net. The article draws, furthermore, on observations of scientific conferences, expert meetings, and visits to hospitals and research centers. The research that underlies this article has received ethical review and approval by the University of Sussex.

Data analysis was ongoing during fieldwork and in the months thereafter. Everyday work practices and organizational procedures were examined in relation to the institutional and regulatory orders, in whose context these activities took place (Smith 2005). By repeatedly reading and coding interview transcripts, field notes and relevant text sources I identified, in a first step, the different stages and procedures through which standardized research protocols were developed and implemented in

the context of the China SCI Net. Then, in a second step I explored the challenges to standardization, and the ways in which these difficulties were interpreted and tried to be solved. This second line of analysis was based on the constant comparative method (Boeije 2002) and triangulation of data from different sources. In a third step I examined the similarities and differences between locally evolved and internationally-recognized experimental clinical practices in hospitals that take part in international stem cell trials. In order to discern the specific forms of value creation that emerged from these distinct experimental practices, I relied on the investigation of interview data and the analysis of hospital websites, commonentary and opinion pieces, as well as advertising materials from the Internet.

Intercontinental stem cell trials and the role of scientific self-governance

> What we are trying to do is to bring the international standards of clinical trials to China. [W]hat we are doing is to bring in the concept of using all the modern standards on how to run a clinical [stem cell] trial, as it is recognized in the West, in the current time. All the conceptions of leading this network … evolve around that concept. […] First of all we had to promote the interest […] to bring in experts from around mainland China, Hong Kong, Taiwan […], to provide a platform. And the second level is, we would then bring in the knowledge as to how a clinical trial should be run, in an internationally recognized manner.
>
> (Prof Kwok-Fai So, Co-Director of China SCI Net) [i]

Multicountry clinical trial collaborations, such as the China SCI Net, represent the first projects in regenerative stem cell medicine where such processes of cross-border standardization can be observed.

Standards, as Brunsson and Jakobsson have pointed out, coordinate assemblages of things and people into new configurations, and in doing so transform existing practices, institutional arrangements, and related social orders (2000: 49). In the case of the China SCI Net this reconfiguration of things, practices, arrangements, and people is based on an interconnected sequence of organizational procedures, educational, and training activities, and the employment of a tailor-made monitoring and control system. In the absence of a harmonized global governance framework for clinical stem cell research, these efforts rest primarily on extensive forms of transnational scientific self-governance. Such project-internal forms of self-governance are strategic efforts to navigate through a diverse and internationally nonharmonized regulatory environment; the aim is to create compliance with the divergent requirements of drug regulatory authorities and related processes of peer review in multiple countries (*cf.* Wahlberg, et al., 2013). A focus on these processes of scientific self-governance, provides important insights into the ways in which scientists try to balance out regulatory disparities between regions and institutions, compensating for regulatory gaps, and creating congruence with the auditing demands of diverging regulatory and political systems (Sariola, & Simpson, 2011; Sleeboom-Faulkner, 2013).

Indeed, if data from clinical trials that are conducted in one country are to be used for investigational new drug applications in other countries (as in case of the China SCI Net, where data from Phase I/II trials conducted in Hong Kong and mainland China are to be used to obtain approval for Phase II and III trials in the USA, Taiwan, and Hong Kong), the basic regulatory requirements of these countries' drug regulatory authorities must be met. Clinical trials conducted by the Network in mainland China thus must be congruent with the methodological standards required

for the approval of later-stage (or parallel) trials, by the health authorities in Hong Kong, Taiwan, and the USA. I will now turn to the ways in which such transnational forms of scientific self-governance are enacted, and how standardization across involved institutions is achieved. Three central aspects shall be highlighted in this respect: selection, restructuring, and the forestalling of regulatory gaps.

Selection

Selection of the hospitals destined to take part in the Network's clinical trials is an ongoing process. This means that only some of the twenty-five hospitals that initially agreed to join the China SCI Net will ultimately participate in the organization's clinical trials. Selection depends, in essence, on the ability of affiliated centers to provide evidence that the standards and criteria required for participation in internationally recognized (multicenter) clinical trials can be met. A combination of external and internal assessment parameters is handled in this respect. External assessment parameters refer to outward qualification criteria of associated hospitals. These include the Chinese good clinical practice (GCP) certification (i.e., the recognition of hospitals as certified clinical trial units, following a qualification procedure under the National Health and Family Planning Commission [NHFPC; the former Ministry of Health]).[ii] They include, furthermore, the availability of good laboratory practice (GLP) accredited laboratory facilities.[iii] Internal assessment parameters refer to criteria that are imposed on affiliated hospitals by the Network itself. These internal qualification criteria can be divided into "performance-based" and "organizational" parameters. Organizational criteria cover aspects such as checks of hospital internal institutional review board (IRB) approval procedures, the

availability of the necessary technical instruments, adequate specialist staff, sufficient hospital beds, insurance protection for patients, and adherence to other technical and clinical conditions that are contractually defined between the China SCI Net's headquarter and affiliated hospitals. Performance-based assessment criteria have been exerted first in the context of the Network's observational clinical study that was conducted in twenty-two hospitals between 2005 and 2008, but have been applied in all further trials that the organization has conducted since then. Performance-based criteria focus, above all, on the compliance (of each participating hospital) to a clinical trial's protocol, which prescribes the exact clinical, methodological, technical, and organizational procedures of a study. The monitoring of protocol compliance involves the observation of the correct handling of inclusion and exclusion criteria, the conduct of physiological examinations and follow-up investigations, the accurate completion of data sheets, and informed consent procedures. These monitoring tasks are done from the Network's headquarters in Hong Kong, which is staffed by the organization's Vice-President Dr. Wendy Cheng, as well as a full-time GCP monitor, and a biostatistician. The headquarters operates under the supervision of the Network's board of directors. The Hong Kong office is the nerve center of the China SCI Net. All operations of the organization, as well as communication with affiliated hospitals, are coordinated from here. In addition to arranging the logistics of the Network's clinical trials, and the monitoring of the activities and performance of participating hospitals, the headquarters also plays a central role in the restructuring of institutional arrangements and practices in associated centers.

Restructuring

The formation of a standardized multi-enter clinical trial infrastructure that operates according to internationally recognized principles requires significant adjustments of local clinical research practices and conditions in Network-affiliated hospitals. These changes were achieved by an intensive training program and the implementation of performance-based assessment procedures, through which required institutional adjustments could be monitored, and —if necessary—corrected. Training for staff members of the relevant departments in the twenty-five associated research hospitals began in 2005, with three to four meetings per year until 2009. A first target was the standardization of neurological examination procedures to ensure valid and replicable assessment of the injury grade of spinal cord injury patients on the trial.

> When we first came here, the neurological assessment of spinal cord injury – almost everywhere – was completely haphazard. It ranged from, eh, you know … you take a pin, you put it here, you touch a patient, ask "Can you feel it?" There was no discipline … no common languages, no common neurological assessment of the patients."[iv]

Standardization of neurological assessment was the first in a long list of methodological, clinical, and organizational issues that were addressed. Training addressed aspects of clinical trial design, such as protocol development, quality assurance measures, the reliable use of outcome measures, long-term follow-up of patients, and the ethical and legal issues of clinical trials, as well as requirements by foreign drug regulatory authorities and international journals. In its training program, the China SCI Net did not work with an examination system. Instead, new contents and practices were transmitted through demonstrations and educational materials, and

compliance to newly introduced standards, protocols, and standardized procedures was then tested in practice.

A crucial endeavor in this respect was the organization of the observational (i.e., non-interventional) trial CN100, a multicenter study that was conducted in twenty-two hospitals in mainland China, Hong Kong, and Taiwan. The purpose of this study was to collect long-term data from 600 chronic and acute spinal cord injury patients, in accordance with international recruitment and measurement protocols. In addition to the scientific value of this study—which was the first longitudinal observational study of chronic and acute spinal cord injury patients in China—it fulfilled a central function for the Network: to serve as a test trial of the ability of affiliated centers to recruit patients, to conduct standardized neurological assessments [based on the ASIA scheme, developed by the ISCS], to carry out long-term follow-ups, and to document data and data-collection procedures in the prescribed—standardized—fashion. This study helped in identifying various challenges:

> The first trial we held was an observational trial. To show that the hospitals can deliver the data … Now this study revealed a lot of problems I actually had heard about, but never really encountered, until to this point. The number one problem in China is really to get patients to come back [for follow-up investigations]. … But we [also] observed data that just could not have been. You know – patient data would be the same, over the whole year period. Suggesting that someone had examined the patients very carefully … It became very clear to us that we need to have very good controls of the protocol.[v]

Due to these problems, instead of the intended 600 patients only 386 patient profiles were completed in this first—entirely observational—study. These insights into local conditions and related challenges resulted in the wide-ranging restructuring of the control and monitoring structures through which the Network operated, such as the introduction of a supervisor–principal investigator double-signing system. With this system, each doctor or nurse involved in examination of patients has to "sign off" the data collection sheet with his or her supervisor and the principal investigator in the institute. Documentation protocols, moreover, were changed from paper to a computerized web-based system for data entry, in order to enhance data insertion and data analysis, and to permit continuous checks by the headquarters in Hong Kong. Identification of challenges in this observational study gave rise, too, to adjustments of training procedures, as well as the decision to work with a Contract Research Organization (CRO) during the forthcoming Phase III trial.[vi]

The forestalling of regulatory gaps

The selection of suitable hospitals, and adjustments of local clinical research practices and conditions, aim at the consistent implementation of fully standardized clinical research protocols. In contrast to multicenter clinical trials that are conducted in a single country, the project-internal forms of self-regulation, capacity building, and institutional restructuration that have been described constitute a long-term strategic endeavor to create congruence with the auditing demands of widely varying regulatory and legal systems. At the time of writing, the clinical trials of the Network had been approved exclusively by the regulatory authorities in Hong Kong and

mainland China, but the data from these trials will be used for investigational new drug applications (INDs) in the USA. This required an enduring anticipatory engagement with the review and approval criteria of the US Food and Drug Administration (FDA) with respect to the "acceptance of foreign clinical studies not conducted under an investigational new drug application (non-IND foreign clinical studies)" (Fink, 2008). This constant need for forms of "anticipatory audit" (Strathern, 2008: 308) requires the identification and forestalling of regulatory gaps between national jurisdictions from an early stage of the clinical translation process. A brief example will serve to illustrate this point. At the time of writing, the Health Department of the Army General Logistics Department in China (the regulatory agency that approved the China SCI Net's clinical studies in mainland China) did not mandatorily require that clinical studies should be conducted in compliance with ICH-GCP standards. Nor did it require the clinical trials to be conducted exclusively in hospitals certified by the Chinese MOH, as officially recognized clinical trial units. However, the US FDA's list of requirements for the acceptance of "non-IND foreign trials" (in the context of IND applications at the US FDA) states that "accordance with good clinical practice (GCP), including review and approval by an independent ethics committee (IEC)" is obligatory (Federal Register, 2008). In order to preempt any difficulty arising from these discrepancies, the China SCI Net tried to forestall regulatory gaps from the outset, and ensured their clinical trial protocols were fully GCP compliant and only MOH-certified hospitals were selected. Moreover, in addition to approval by the Army General Logistics Department in Beijing, ethics committee review was also sought by Western IRB, a for-profit IRB in the USA with close ties to the US FDA.

The emergence of new style of practice

In their analysis of the development of cancer clinical trials in the USA, Keating and Cambrosio described this process as the establishment of a "new style of biomedical practice" (2011: 3). This new style of practice encompassed the organization of clinical trials within a cooperative group system, and the development of most of the now commonly used methodological components of multicenter clinical trials. The work in cooperative groups evolved gradually since the mid-1950s, on the initiative of the U.S. National Cancer Institute (NCI). Specializing in specific forms of cancer, these groups involved hospitals, academic centers, and government departments, and constituted steady platforms for the design of new research and the conduct of clinical trials (ibid.: 86). These cooperative oncology groups soon expanded into national-level organizations with their own centralized institutions that were responsible for the coordination of all successive steps of the clinical translation process. In this system, decisions regarding the design of clinical trial protocols and the organization, execution, approval and statistical data analysis of clinical trials were no longer taken by individual investigators, but in a collectivist process by the cooperative's committees and its centralized administrational units (ibid.: 25–6).

In the China SCI Net we see processes of collectivization and standardization emerging that in several respects are similar to the cooperative clinical trial system described by Keating and Cambrosio. In the mid-2000s, at the time the China SCI Net was launched, the organization of an academia-based multicenter clinical trial infrastructure was still a radical novelty in the stem cell field in China. While standardized multicenter drug trials had been conducted in China by multinational pharmaceutical companies since the early 1990s (Cooper, 2006), clinical

experimentations with stem cells were for many years based largely on an "the-art-of-medicine" approach, in which tailor-made experimental treatments were designed for the idiosyncratic needs and disease conditions of individual patients (Rosemann, 2013a). Against this background, the formation of an internationally operating multicenter clinical trial infrastructure that would allow for the testing and marketization of stem cell-based medicinal products, not only in mainland China, but also in Hong Kong, Taiwan, and at a later point in the USA, was a radical and fundamentally new concept.

Similar to the cooperative oncology research groups described by Keating and Cambrosio, the China SCI Net established a centralized administrative structure, in which the monitoring of clinical and data collection procedures, statistical analysis, and decisions regarding protocol development and the selection of candidate therapies for future clinical trials were collectivized. These tasks were performed by specialist staff in Hong Kong, and by expert committees that comprised researchers from affiliated institutions and independent experts, from mainland China, Hong Kong and the USA. Together with the installing of a standardized research methodology that is suitable for the conduct of multicenter clinical trials, these changes have established a new style of clinical research practice in Network-affiliated hospitals that is based on extensive adjustments of local research procedures. As with the cooperative oncology groups in the USA, the China SCI Net functions as an "epistemic organization" in which clinical trials are not isolated events, but elements of an "integrated, open ended set of activities that stretch back and force in time" (Keating, & Cambrosio, 2011: 24). The design of new trials is built on previous trials, and the use of standardized methodological protocols allow for systematic comparison and meta-reviews of findings from multiple studies over time.

A fundamental difference with the cooperative group system described by Cambrosio and Keating is, however, that affiliated investigators of the China SCI Net are entirely free to conduct their own clinical studies, exterior to the organizational framework of the Network. A central reason for this is, of course, that the China SCI Net is an independent research groups that is neither a national-level organization nor structured around a government research institution (such as the NCI, which is at the center of the cooperative oncology group system in the USA). Thus, in contrast to the cooperative groups in the USA, where members are prevented from initiating investigator-initiated collaborations outside of the cooperative system, researchers from the China SCI Net can independently pursue their own projects. Membership is solely delimited to participation in the trials that the Network organizes. It does not impinge on, or restrict, any other activities that Network-affiliated investigators conduct in their own departments or institutions.

Indeed, as I will now show, exterior to the institutional framework of the China SCI Net a stream of highly divergent forms of clinical experimentation has been employed in recent years. In a hospital in North China, for example, a doctor had offered experimental for-profit therapies with olfactory ensheathing cells in hundreds of SCI patients. In other hospitals I visited, various non-controlled clinical pilot studies with stem cells were conducted, but none of these studies could be published in international journals because the methodology of these studies was described as insufficient (Young, 2008). In a clinic in South China, on the other hand, participation in rigorous RCTs (as part of the activities of the China SCI Net) coexisted with the conduct of less systematic clinical studies, in which experimental treatments with various cell types, and other experimental treatment approaches, were offered to patients, on a pay-to-participate schema. Apparently, these studies did not

entirely conform to international EBM clinical research standards. Attempts to publish results from these studies in internationally recognized academic journals repeatedly failed (*ibid*.).

However, in the context of my interviews with clinical researchers affiliated to the China SCI Net, it became clear, that a shift toward the employment of more systematic clinical studies was gradually taking shape in Network-affiliated hospitals. Most of the Principal Investigators with whom I spoke mentioned plans for trials with the use of control groups, and more rigidly handled inclusion criteria.[vii] One of the hospitals I visited was in the process of planning a larger Phase III trial and had set up a province-level multicenter clinical network to this end.[viii] These changes can, with high likelihood, be related to the extensive training and education program introduced by the China SCI Net.

Standardization as situation-specific achievement

Standards, as pointed out by sociologists Timmermans and Epstein, construct a state of stability and order across diversity and plural possibilities (2010: 71). As underlying scripts of rules, procedures and values, standards produce uniformities in behavioral practices, sociotechnical arrangements and knowledge (Timmermans, & Berg, 1997). For international scientific projects, standardization constitutes a crucial methodological requirement, because it enables systematized replication, assessment and validation of research findings across institutions, scientific communities and time. Barry (2006) has in this respect spoken of the creation of "technological zones," which he has defined as "space[s] within which differences between technical practices, procedures and forms have been reduced, or common standards have been

established" (ibid.: 239). While Barry recognizes that the establishment of such technological zones is contested and characterized by variation and changes over time, the concept implies that a shared standard has become the guiding norm, and is resulting in a reduction of differences between conflicting socio-technological practices.

In emerging technology fields, such as regenerative stem cell medicine, where state regulations are still evolving—and internationally harmonized regulatory frameworks are not yet in place, a more complex situation exists however. The case study of the China SCI Net indicates in this respect, that due to the high level of regulatory diversity in the stem cell field across (and also within) countries, the enactment of internationally recognized research standards in multi-country stem cell trials is a highly situation-specific achievement. Internationally approved clinical research protocols are established against a background of geographic, institutional, epistemic-cultural and regulatory heterogeneity, and implemented exclusively in the situational context of the clinical trials that the Network organizes. As shown in the previous section, outside of the activities of the China SCI Net, we see that locally evolved and newly adopted (i.e. internationally accepted) forms of experimental clinical research practices exist side by side with each other, often in the same medical institutions. If we conceive of the China SCI Net as the formation of a technological zone, in the sense Barry uses the term, it becomes clear that the existence of such zones can be highly temporary, and depends upon its activation in specific situational contexts. Standardized methodological norms and work arrangements across Network-affiliated hospitals are activated exclusively in the context of the Network's clinical trials; outside the context of these trials, heterogeneous clinical practices continue to exist.

This situation-specific character of transnational technological zones, in which established standards can lay dormant for a while, and switched on and off in relation to contextual demands, has not yet been systematically explored in the literature. The case study of the China SCI Net indicates in this respect, that in medical institutions that take part in such evolving transnational infrastructures, the adoption of homogenized clinical research standards may only be temporary and bound to participation in specific projects. Forms of clinical experimentation that have historically evolved in local institutions and more recently adopted (i.e. internationally recognized) clinical research practices, continue to exist side by side with each other. Researchers switch back and forth between these divergent schemas, depending on the purposes of their research, the partners they work with, the geographic scale of research projects, the targeted territorial scope of marketization, and the contrasting demands for regulatory review and approval that result from these differences. This situation differs fundamentally from the oncology research cooperatives described by Keating and Cambrosio (2011), where the adoption of a centrally defined set of research standards has become a permanent and obligatory requirement, and possibilities for clinical experimentation outside of the cooperative structure have become impossible.

The continuance of localized forms of value production

A key point is that the coexistence of distinct modes of clinical translation allows also for the production of multiple forms of economic value, at the level of local medical institutions. Localized forms of value creation, which would not be acceptable to drug regulatory agencies overseas, continue to exist – aside to participation in the

internationally approved, multi-country clinical research trials organized by the China SCI Net. As mentioned above, in a clinic in South China experimental treatments with various cell types were offered to patients in the context of clinical pilot studies, exterior to the hospital's involvement in the Network's stem cell trials. These experimental treatments have been offered to patients on a pay-to-participate schema. The intensive rehabilitation program that is now part of the China SCI Net's clinical trial protocols, was also developed in this hospital. While the efficacy of this experimental rehabilitation program shall be determined in the context of the network's clinical trials in the future, it is offered since 2012 in a private hospital in China on a for-profit basis, and advertised to domestic patients and to spinal cord injury patients from overseas. Another example that reflects the local forms of economic value production that have emerged in some of the institutions affiliated to the China SCI Net, are the experimental therapies of a clinical researcher from North China. This physician has offered experimental cell treatments to reportedly several thousands of patients, from more than eighty countries' during the last years (IANR 2010). This researcher did not, however, actively participate in the China SCI Net's clinical trials, but due to his long-standing experience he played an important advisory role in the selection and development of the surgical and cell transplantation procedures that were used in the Network's clinical trials.

The existence of such localized forms of value creation, that have emerged outside of the requirements of international standard regimens, aside to participation in internationally approved trials can also be observed in other international research projects in China. Let me illustrate this with the example of a collaboration between Neuralstem, a biotech company from the USA that develops stem cell-based therapies for neurodegenerative disorders, and a large military hospital in Beijing. Neuralstem

has received approval from the US FDA for Phase I and II stem cell trials for amyotrophic lateral sclerosis (ALS). These studies have been conducted in the USA since 2011. In December 2013 the company launched also a Phase I/II trial for the treatment of ischemic stroke in China. The trial is carried out in a well-known military hospital for brain disorders in Beijing. According to Richard Garr, the CEO of Neuralstem, the protocol of the China trial has been developed for use in the USA at a later point. It is performed in line with GCP standards, and based on the quality controls and protocols for expansion that are required by the US FDA (Ellis 2014). Of interest is that, aside to taking part in this high-profile international clinical research project, the hospital in Beijing has for many years offered experimental for-profit stem cell treatments, through its Stem Cell Therapy Centre. On its website the center advertises experimental treatments for a broad range of neurodegenerative disorders, that range from stroke, to cerebral palsy, to Parkinson's disease, Alzheimer's disease, spinal cord injury, and others.[ix] While reportedly 300 patients from various countries had been treated until 2011, in recent years the hospital seems to have focused in particular on the Chinese market for the treatment of cerebral palsy. These experimental for-profit stem cell treatments are widely advertized, both on the hospital's Chinese website, and on external Chinese language websites.[x]

These findings indicate, that the integration of local knowledge institutions into a global research economy does not unavoidably result in the shutting down of localized forms of value production, as recently argued by sociologist Kean Birch (2012). As Birch (2012) has pointed out, the incorporation of local institutions and locally derived inventions into a standardized global knowledge economy, is intrinsically accompanied by the closing of local market opportunities and knowledge exchanges. Localized forms of exchange and profit generation, which have emerged

in the original context of knowledge production, are terminated, through the mandatory use of international standards, unified research methodologies, and the application of legal instruments such as international intellectual property rights (IPR) and global trade rules (ibid.: 190). While Birch's argument may be valid in more established research fields in the biosciences where large-scale transnational corporations play a central role, and in countries in which comprehensive regulatory arrangements are in place, in emerging fields of medicine research, a more diversified situation exists.

The example of the China SCI Net has shown in this respect, that localized forms of value creation in medical institutions, that do not conform to the requirements of international scientific standard regimens, continue to exist – aside to participation in internationally approved, multi-country clinical research projects. But the coexistence of processes of clinical translation through the conduct of systematic forms of clinical trials, and the provision of experimental for-profit stem cell therapies, have also been documented in other medical institutions and companies in China (Chen, 2009; Song, 2011), as well as India (Sleeboom-Faulkner, & Patra 2011). As recently suggested by McMahon (2014), the provision of unproven stem cell intervention has itself developed into a global industry that is now provided to tens of thousands of patients and generate significant economic revenues.

Here, two issues deserve to be mentioned. The first is that participation of hospitals in international clinical research projects may increase the level of legitimacy for the provision of locally evolved experimental therapies. This, in turn, is likely to maximize local forms of value creation, also if these treatments have not been developed in accordance with internationally recognized clinical research standards. The second point is that the integration of hospitals into a multi-country

clinical trial infrastructure may foster the adoption of an evidence-based medicine (EBM) research culture – also in the context of local research projects. In the case of the China SCI Net, for example, several of the investigators with whom I spoke had started to conduct randomized controlled trials, including domestic multi-center studies, independently from the China SCI Net. These researchers reported that, in the field of spinal cord injury research, the shift toward more systematic clinical trials was driven in particular by discontent with the widespread availability of unproven for-profit stem cell therapies in China, and related concerns for patients.

Local value and the violation of property rights

A point that is thematically related to the argument of this article, albeit not central to it, is that possibilities for the continuation of localized forms of value creation are also linked to cross-national differences in the enforcement of intellectual property rights (IPR). In India, China and other rapidly developing countries the protection and enforcement of property rights is often problematic. In China and India, for example, a longstanding record of IPR infringements exists, including in the production of medicines (Brhlikova, et al., 2011; Mackay, & Liang, 2011). IPR infringements are also an issue in the field of regenerative stem cell medicine. For instance, the umbilical cord blood mononuclear cell / Lithium combination that is tested by the China SCI Net (and which has been patented by Stemcyte, the sponsor of the UCB cells) was experimentally applied by a clinical researcher in India even before the initial Phase I trial of the China SCI Net in Hong Kong had started, apparently without any legal consequences.[xi] Similar forms of IPR infringements were also expected in China, provided the tested treatment is proved to be safe and efficient.

Researchers of the China SCI Net stated, that legal prosecution of hospitals in China that would offer the combination of Lithium and UCB cells from somewhere other than Stemcyte is very unlikely. These researchers expected, that alternative UCB products would soon surface in the Chinese market (Rosemann, 2013b). For a theorization of processes of value creation in the global bioeconomy, the implicit acceptance of property right violations is important, because it refers to the profit potential of informal and illegal economic activities in the biotech sector. In this article, though, I have pointed to something else. I have shown that in emerging fields of medicine research, that are regulated in highly divergent ways across geographical regions, locally evolved clinical research and for-profit practices can continue to exist——parallel to the integration of local institutions into a standardized global research economy. In contrast to profits generated from IPR infringements, however, these localized forms of value creation usually do not take place outside of existing legal structures, and could not be prosecuted by international law.

Conclusions

This paper has illustrated that the heterogeneity of regulation, clinical research methodologies, and forms of commercialization that can be observed in the clinical stem cell field at a global level poses significant challenges to the organization of intercontinental clinical stem cell research projects. It has become clear, that the establishment of standardized clinical research practices across this level of diversity, is a highly situation-specific achievement. Internationally acceptable clinical research

practices exist alongside a broad range of locally evolved forms of clinical experimentation, often in the same medical institution. As I have shown, this coexistence of divergent socio-epistemic practices has enabled also the generation of multiple forms of economic value. I have suggested in this regard that – in contrast to a recent argument of Birch – the integration of local institutions into the global bioeconomy does not necessarily result in the shutting down of localized forms of value creation. The findings of this paper indicate, that the high level of generalization that underlies Birch's analysis of present-day processes of value creation in the global bioeconomy, leaves out some fundamental issues.

A first point is that in emerging fields of medicine research, such as stem cell research, the key actors are often not transnational corporations, as stated by Birch. In the field of regenerative stem cell medicine, large-scale pharmaceutical corporations have for many years been hesitant to invest. The main advances, and forms of profit making that have evolved in recent years, were made by small to mid-size biotech companies, usually in conjunction with academic institutions. In countries where clinical stem cell applications have been regulated at a low level, moreover, lucrative business opportunities have been exploited by private clinics, local investors, and even individual physicians (Rosemann 2013a; McMahon 2014). This suggests, that – in order to get a more nuanced picture of contemporary processes of value production in the biomedical sciences – it is necessary to depart from a more nuanced analysis of the different types of stakeholders that interact in the context of specific subfields of the biomedical sciences. The second point concerns the need to take into account variation in terms of geographic and regulatory location. In both, China and India state agencies have taken for many years now a very reluctant position in adopting stringent regulatory frameworks for clinical stem cell applications, and to harmonize

regulations with those issued in the USA and European Union. In my fieldwork in China in 2009 and 2010 various policy makers expressed fears that the adoption of procedures as handled by the US Food and Drug Administration, might suffocate local innovation and market opportunities in the stem cell field in China. Minimal regulatory intervention, from this perspective, may form a conscious political strategy to endorse localized forms of value creation, at least up to the point at which more profitable, exportable products have been developed (Sleeboom-Faulkner 2014). These geographically-based differences in policy positions, and their implications for processes of innovation and market exchange, must be clearly understood in a theory of value creation of the global bioeconomy. State agencies, as this example suggests, are not always complicit in adopting (or enforcing) internationally harmonized regulatory frameworks that prioritize global forms of exchange, above policy options that prioritize more localized forms of market activity. Third, geographic variation in the enforcement of international IPR agreements is another crucial factor that must be taken into account to fully comprehend the divergent ways in which economic value is created in the global biomedical economy. The implicit acceptance of property rights infringements in many countries refers also to the huge financial potential that the production of counterfeit medicines, and in the future probably soon - alternative stem cell products – generate.

References

Barry, A. (2006). Technological Zones. *European Journal of Social Theory*, 9(2), 239-253

Bharadwaj, A. (2013). Ethics of consensibility, subaltern ethicality: The clinical application of embryonic stem cells in India. *BioSocieties*, *8*(1), 25-40.

Birch, K. (2012). Knowledge, place, and power: geographies of value in the bioeconomy. *New Genetics and Society*, *31*(2), 183-201.

Boeije, H. (2002). A purposeful approach to the constant comparative method in the analysis of qualitative interviews. *Quality and quantity*, *36*(4), 391-409.

Brhlikova, P., Harper, I., Jeffery, R., Rawal, N., Subedi, M., & Santhosh, M. R. (2011). Trust and the regulation of pharmaceuticals: South Asia in a globalised world. *Global Health*, *7*(10).

Brunsson, N., & Jacobsson, B. (2000). *A World of Standards*. Oxford: Oxford Univ. Press.

Chen, H. (2009). Stem cell governance in China: from bench to bedside?. *New Genetics and Society*, *28*(3), 267–282.

Chen, H., & Gottweis, H. (2011). Stem cell treatments in china: Rethinking the

patient role in the global bio•economy. *Bioethics*.

Cooper, M. (2008). Experimental labour—offshoring clinical trials to China. *East Asian Science, Technology and Society*, *2*(1), 73-92.

Cribb, A., Wainwright, S., Williams, C., Farsides, B., & Michael, M. (2008). Towards the applied: the construction of ethical positions in stem cell translational research. *Medicine, Health Care and Philosophy*, *11*(3), 351-361.

Ellis, S. (2014) Neuralstem doses ischemic stroke patient with stem cells directly into the brain. Neuralstem Website, 5 February, 2014; URL: http://neuralstem.com/pharmaceuticals?id=206 (last accessed 10.9.2014).

Federal Register (2008). Human Subject Protection; Foreign Clinical Studies Not Conducted Under an Investigational New Drug Application, *Federal Register*, 73(82), pp. 22800-22816, URL: http://www.gpo.gov/fdsys/pkg/FR-2008-04-28/pdf/E8-9200.pdf (last accessed 20.4.2014).

Faulkner, A. (2012). Law's performativities: Shaping the emergence of regenerative medicine through European Union legislation. *Social studies of science*, *42*(5), 753-774.

Fink, D. W. (2009). FDA Regulation of Stem Cell–Based Products. *Science*, *324*(5935), 1662.

Gikonyo, C., Bejon, P., Marsh, V., & Molyneux, S. (2008). Taking social relationships seriously: lessons learned from the informed consent practices of a vaccine trial on the Kenyan Coast. Social Science & Medicine, 67, 708-720.

Halme, D. G., & Kessler, D. A. (2006). FDA regulation of stem-cell–based therapies. *New England Journal of Medicine, 355*(16), 1730-1735.

Keating, P., & Cambrosio, A. (2011). *Cancer on trial: oncology as a new style of practice*. University of Chicago Press.

Leach, M., Hilton, S., Greenwood, B. M., Manneh, E., Dibba, B., Wilkins, A., et al. (1999). An evaluation of the informed consent procedure used during a trial Haemophilus Influenzae type B conjugate vaccine undertaken in The Gambia, West Africa. *Social Science & Medicine*, *148*(2), 139-148.

Mackey, T. K., & Liang, B. A. (2011). The global counterfeit drug trade: patient safety and public health risks. *Journal of pharmaceutical sciences*, *100*(11), 4571-4579.

Martin, P., Brown, N., & Kraft, A. (2008). From bedside to bench? Communities of promise, translational research and the making of blood stem cells. *Science as Culture*, *17*(1), 29-41.

McMahon, D. S. (2014). The global industry for unproven stem cell interventions and stem cell tourism. *Tissue Engineering and Regenerative Medicine, 11*(1), 1-9.

Petryna, A. (2009). *When experiments travel: clinical trials and the global search for human subjects*. Princeton University Press.

Rosemann, A. (2011). Modalities of value, exchange, solidarity: the social life of stem cells in China. *New Genetics and Society*, *30*(2), 181-192.

Rosemann, A. (2013a) Medical Innovation and National Experimental Pluralism: Insights from Clinical Stem Cell Research and Applications in China. *Biosocieties*, *8*(1): 58-74.

Rosemann, A. (2013b). Scientific Multipolarisation: Its Impact on International Clinical Research Collaborations and Theoretical Implications. *Science Technology & Society*, *18*(3), 339-359.

Sariola, S., and B. Simpson (2011). Theorising the 'human subject'in biomedical research: International clinical trials and bioethics discourses in contemporary Sri Lanka. *Social Science & Medicine*, *73*(4): 515-521.

Sleeboom-Faulkner, M. and P.K. Patra (2011). Experimental stem cell therapy: Biohierarchies and bionetworking in Japan and India, *Social Studies of Science*, 41(5), 645-666.

Sleeboom-Faulkner, M. (2014) Regulation of Cell Research and Therapy International Standardisation and National Home-Keeping, Presentation, China Cell

Therapy Conference, June 20, 2014, Shanghai.

Smith, D. E. (2005). *Institutional ethnography: A sociology for people*. Rowman Altamira.

Song, P. (2010). Biotech pilgrims and the transnational quest for stem cell cures. *Medical Anthropology*, *29*(4), 384-402.

Song, P. (2011). The proliferation of stem cell therapies in post-Mao China: problematizing ethical regulation. *New Genetics and Society*, *30*(2), 141–153.

Strathern, M. (2000). *Audit cultures: Anthropological studies in accountability, ethics and the academy*. Routledge.

Timmermans, S., and Berg, M. (1997). Standardization in Action: Achieving Local Universality through Medical Protocols. *Social Studies of Science*, 27: 273-305.

Timmermans, S., and Epstein, S. (2010). A world of standards but not a standard world: toward a sociology of standards and standardization. *Annual Review of Sociology*, 36, 69-89.

Wahlberg, A., Rehmann-Sutter, C., Sleeboom-Faulkner, M., Lu, G., Döring, O., Cong, Y., ... & Rose, N. (2013). From global bioethics to ethical governance of biomedical research collaborations. *Social Science & Medicine*, *98*, 293-300.

Wainwright, S. P., Williams, C., Michael, M., Farsides, B., & Cribb, A. (2006). From bench to bedside? Biomedical scientists' expectations of stem cell science as a future therapy for diabetes. *Social Science & Medicine*, *63*(8), 2052-2064.

Webster, A., Haddad, C., & Waldby, C. (2011). Experimental heterogeneity and standardisation: stem cell products and the clinical trial process. *BioSocieties*, *6*(4), 401-419.

Wilson • Kovacs, D. M., Weber, S., & Hauskeller, C. (2010). Stem cells clinical trials for cardiac repair: regulation as practical accomplishment. *Sociology of Health & Illness*, *32*(1), 89-105.

Young, W. (2008). SCI: Is the cure in China?. Video of conference presentation, *Spinal Cord Injury – what are the barriers to cure?, Workshop,* Bedford Massachusetts, March 29, 2008, URL: http://www.spinalcordworkshop.org/portfolio-type/wise-young-md-phd-spinal-cord-injury-is-the-cure-in-china/ (last accessed April 27, 2014)

[i] Interview Kwok-Fai So, Hong Kong, January 7, 2011.

[ii] Interview Wise Young, Hong Kong, June 24, 2010.

[iii] Interview Kent Tsang, Hong Kong, January 7, 2011.

[iv] Interview Wise Young, Hong Kong, June 24, 2010.

[v] Same source as in note iv.

[vi] Same source as in note iv.

[vii] Only some of these trials were with cells or stem cells. Others were surgical trials, comparing different techniques and operation times.

[viii] Interview Nr. 20, senior researcher, South East China, September 7, 2010.

[ix] Website of Stem Cell Therapy Centre, Bayi Hospital; URL: http://www.81scc.com/en/zxjs.asp

[x] The Chinese language website of the Bayi Hospital on wich these experimental stem cell treatments are advertised can be found here: URL: http://www.zznews.cn/yst/jdft/920140708281730.html
This and other websites on which these therapies are advertised, have an interactive live-chat-function, that allows interested patients to get information on the treatment from hospital staff.

[xi] This was reported by the researcher who conducted these experiments, at a conference in Taiwan in April 2010.

Highlights

- The paper explores standardization and self-governance in global stem cell trials
- Standardization in stem cell trials is a highly situation-specific achievement
- Locally evolved and international research standards coexist in the same hospitals
- This coexistence of diverging standards enables multiple forms of profit production
- The adoption of international standards does not stop local forms of value creation