RESEARCH ETHICS COMMITTEES AND BIOMEDICAL RESEARCH IN FRANCE AND IN CHINA: COMPARING SYSTEMS AND REGULATION REGARDING INDEPENDENCE AND INFORMED CONSENT PRINCIPLES

LES COMITÉS D'ÉTHIQUE DE LA RECHERCHE ET LA RECHERCHE BIOMÉDICALE EN FRANCE ET EN CHINE : COMPARAISON DES SYSTÈMES ET DES RÈGLEMENTS CONCERNANT L'INDÉPENDANCE ET LES PRINCIPES DU CONSENTEMENT ÉCLAIRÉ

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ABSTRACT

International collaborations in biomedical research between eastern and western countries, such as China and France, require full consideration of ethical aspects and human rights for ensuring best practices, safety and dignity for the participants. Research Ethics Committees (RECs) reviewing biomedical research projects are central organs in the ethical governance of researches involving human beings internationally recognized as one of the guaranties for protecting human rights and wellbeing of the research participants. Countries like France and China engaged, at international level, to set up effective national ethical review systems.

This paper adopts a comparative law approach of the French and Chinese RECs' systems. It intends to provide, for each country, a description of the current RECs' organization and regulation in order to

Acknowledgements: This paper is a collaborative work performed in the PHC Xu Guangqi 2012 program, Project n° 27974QH, co-sponsored by the French and Chinese embassies and enabled through the cooperation between the Institute of Health and Medical Research (INSERM) Unit UMR1027, France, and the Law School of Shandong University, Shandong Province, Jinan, China. Particular acknowledgements to Meng Wen, Zihan Chen, Zheng Zhihang, Chen Xiuqin, PhD Students at Shandong University Law School, Jinan, China.

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give an overview of their shared characteristics and specificities. We address the general regulatory frameworks applying to French and Chinese RECs and we make a focus on two important topics for RECs' review namely the requirements for informed consent and the guarantees of independence. Ultimately, we provide an overview of the existing challenges to consider for improving research participants' protection in each country while allowing scientific activities to be responsibly carried out in the respect of cultural backgrounds.

KEYWORDS

Ethical review, Research ethics committees, Biomedical research, Clinical trial, China, France.

RÉSUMÉ

Les collaborations internationales dans la recherche biomédicale entre les pays de l'Est et de l'Ouest, tels que la Chine et la France, exigent un examen complet des aspects éthiques et des mesures liées au respect des droits de l'homme afin de garantir les meilleures pratiques, la sécurité et la dignité des participants. Les comités d'éthique de la recherche (CER) qui pratiquent l'examen des projets de recherche biomédicale sont des organes centraux de la gouvernance éthique des recherches impliquant l'être humain internationalement reconnus comme l'un des moyens de garantir la protection des droits de l'homme et le bien-être des participants à la recherche. De nombreux pays, comme la France et la Chine, se sont engagés, au niveau international, à mettre en place des systèmes nationaux efficaces d'examen éthique.

Cet article adopte une approche juridique comparative des systèmes français et chinois. Il donne, pour chaque pays, une description de l'organisation et de la réglementation actuelle des comités d'éthiques de la recherche et fournit un aperçu des caractéristiques communes et des spécificités de chaque système. Nous mettons ensuite l'accent sur deux sujets importants pour l'examen éthique des protocoles à savoir les exigences relatives au consentement éclairé et les garanties d'indépendance des comités. Enfin, nous identifions des défis à considérer pour améliorer la protection des participants dans chaque pays dans le respect des particularités culturelles.

MOTS-CLÉS

Comité d'éthique, recherche biomédicale, essais cliniques, Chine, France.

France and China are part of the top 10 international actors of Research and Development (R&D), including in health-related R&D. In 2011, France allocated 2.25% of its Gross Domestic Product (GDP) and is ranked 6th at international level while China allocated 1.84% of its GDP to scientific R&D and is ranked 2nd just after USA [1]. Part of these governmental investments is dedicated to health research projects, including international collaborative clinical trials. Today, two thirds of clinical drug trials relating to medicinal products available in Europe are conducted outside Europe, notably in China [2]. This internationalization of health research and collaborations between developed and developing countries calls for adequate protection of participants, oversight and regulation, notably through effective ethical review system.

Therefore, beside competent National Public Authorities (e.g. Ministries, Agencies) authorizing research activities, Research Ethics Committees (RECs) are essential governance organs in human health research fields for ensuring *a priori* responsible and quality research, particularly in biomedical research involving experiments on human beings(6) like drug trials or other interventions on human biological samples and the collection of personal data, including in multicentric or international researches.

The core function of RECs is to assess, approve, reject or stop research protocols before and during their implementation. The role of RECs is internationally designed with regard to the protection of the bioethical principles, human rights, freedoms and wellbeing imposing the respect of human dignity, body integrity, self-determination and primacy of the human being in biomedical research. Worldwide, RECs are expected to act as guardians of the common good balancing the individual and the societal interest [3] with

(6) The WHO defines 'research involving human participants' as "any social science, biomedical, behavioural, or epidemiological activity that entails systematic collection or analysis of data with the intent to generate new knowledge; in which human beings (i) are exposed to manipulation, intervention, observation, or other interaction with investigators either directly or through alteration of their environment, or (ii) become individually identifiable through investigators' collection, preparation, or use of biological material or medical or other records". See the WHO ERC website, *Research policy, Developing proposals that meet ERC requirements*: http://www.who.int/rpc/research_ethics/guidelines/en/ (accessed on 25 November 2014).

the scientific interest of researches by performing a balance test between risks and benefits and promoting evidence-based medical progress. Their ultimate aim is to only approve sufficiently robust project in order to prevent the malpractices, the so-called "bad science" or "scientific misconducts", particularly where researches involve developing countries, where ethical review capacities are lacking, where ethical questions are specific [4-5] due to the diseases or traits involved in the research and/or specific cultural background, social inequalities etc. RECs approvals are also often decisive for research funders and scientific journals editors.

This international approach of ethical review derives from the common legacy of the Nuremberg Code [6], the World Medical Association (WMA) Declaration of Helsinki, 1964 [7], and of Tokyo [8], 1975, that outlined the criteria for formalizing the ethical review process and that explicitly mentioned the duty of the researcher to submit their research project to an independent Committee specifically designated for this purpose. The Belmont Report [9] redacted in the United States of America (USA) in 1979 as a reaction to ethical scandals(7) has also been an important step both for the establishment of RECs in this country and for the international community. The 2013 version of the WMA Declaration of Helsinki [10] highlights the central role of RECs and provides important details(8) about related procedures in Article 23. Other international texts establishing useful principles and good practices are also used by States and RECs, such as the Council for International Organizations of Medical Sciences (CIOMS) International Guidelines for Biomedical Research Involving Human Beings [11], the UNESCO Universal Declarations on bioethics, genomics, genetics and human rights [12,13,14] and were integrated through the French [15] and Chinese [16] Constitutions and regulations. In France, the positive impact of European law for structuring and standardizing practices, notably of the Council of Europe Oviedo Convention [17] and of the European Union (EU) regulations [18,19] must be acknowledged.

This article aims to analyze and compare the state-of-art of national capacities, in terms of RECs, of France and China. We will highlight common points of current ethical review systems, main differences and challenges that remain. For each country we briefly introduce historical elements about the emergence of RECs (Part 1), we analyze the structure and functioning of existing systems through the RECs composition, missions and related regulations (Part 2) in order to perform a specific comparison of the situation regarding informed consent and independence of RECs (Part 3).

I. A BRIEF HISTORY OF RECS IN FRANCE AND CHINA

A. In France: the process of setting up the "Comités de protection des personnes" (CPP) as French RECs

In France, the setting up of a RECs system has been long and troubled [20,21], as in other European countries such as Germany or the UK for example [22]. French RECs really began to exist in 1988 with the creation in French Law [23] of the Consultative Committees for the Protection of Persons involved in Biomedical Research – "Comités Consultatifs de Protection des Personnes se prêtant à des Recherches Biomédicales" (CCPPRB) that had a short lifespan before becoming the current Committees for the Protection of Persons – "Comités de Protection des Personnes" (CPP(9)). Before, the French Academy of Medicine – in 1977, and then the Physicians Order – "Ordre des Médecins" in 1979 followed by the French National Consultative Ethics Committee for life sciences and health (CCNE) Opinion n°2 of 1983 agreed on the necessity to institute independent ethics bodies that would protect persons in research activities and promoted their creation, notably to fulfill an important legal gap in this area. Indeed, before the Law of 1988, no legal text either protected research participants or imposed a system-

(7) E.g. Tuskegee Experiments, see Tuskegee University Bioethics Center, *About the USPHS Syphilis Study*. http://www.tuskegee.edu/about_us/centers_of_excellence/bioethics_center/about_the_usphs_syphilis_study.aspx (accessed on 22 July 2014).

(8) Article 23 states that "The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration." It continues stating that "The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions."

(9) While CPP is an official acronym, "CPPs" is the unofficial acronym used here for designating several CPP.

atic ethical review of research protocols(10). With the Law of 1988, the basis for the first structure of RECs in France was established. After several years of practice, reflection [24,25] and improvements of the CCPPRB organization and mission, the French Law concerning the Public Health Policy of 2004 [26] created the CPP [27]. This law also aimed to implement the EU Directive 2001/20/EC, the "Clinical Trials Directive" [19] requiring systematic prior ethical assessments and public authorities' control of any clinical research project involving drug trials on human body. The Law concerning the Public Health Policy of 2004 has been notably implemented by the Decree n°2006-477 specifying applicable rules to CPPs and amending the French Code of Public Health [28]. The role of the CPP continues to evolve through the adoption of new Acts regulating biomedical research like the Bioethics Law of 2004 [29] requesting prior opinion of a CPP regarding the creation of human biological samples collections and the Bioethics Law of 2011 [30] modifying, among others, the criteria for authorizing research using human embryos or embryonic stem cells. Recently the new, yet unapplied, Law on research involving human beings [31] of 2012 tends to broaden their missions and create new modalities for ethical review applications [32].

B. In China: the process of setting up the Chinese Institutional Review Boards (IRBs) as Chinese RECs

In China, the term of "Ethics Committee" was first proposed in 1987 [33]. The further and more vivid awareness and discussions about such entity really began in 1988 as a result of the development of international exchanges performed with some domestic scholars that particularly visited the United States and Japan, such as Professor Li Benfu [34]. In July 1988, Zhang Kui, researcher in Peking Union Medical College, published papers called "The idea of the Hospital Ethics Committee and its establishment in China" [35] following the first Symposium about national ethics, legislation and sociality of euthanasia that contributed to develop the culture of Ethics Committees by explaining more their usefulness. Since then, the prelude of the practice of Ethics Committee has been opened. In 1991, an inter-hospital contract that is not a formal law, entitled the "Rules of Hospital Ethics Committee Organization" [36], was published by the Chinese Medical Association (CMA) at the Sixth National Medical Ethics Conference held in Chengdu. This document dealing with the setting up of Ethics Committees has then be taken into account and implemented in the process of developing Chinese RECs capacities [37]. The same year, according these rules, the Tianjin First Central Hospital, the Beijing Chaoyang Hospital, the Beijing Union Medical College Hospital and other hospitals were setting up Hospital Ethics Committee. Tasks of the Chinese Hospitals Ethics Committees varied and mainly focused on healthcare and medical practices rather than formal assessments of health researches. In 1998, the Ministry of Public Health worked out 'the approach of the ethical review involving human biomedical research' (trial implementation) that will be then further developed through regulation [38]. In 1999, the China Food and Drug Administration (CFDA) was established and on 1 September 1999 it adopted Good Clinical Practices (GCP, amended in June 2003) [39] whose Article 9 stated that "Ethics Committees shall be set up in the medical institutions participating in the clinical trials so as to guarantee the subjects' interests and to provide public assurance for that". Lastly the CFDA published in 2010 the Guidelines for Ethical Review Work of Drug Clinical Trials [40] intended to strengthen the Chinese capacities in terms of RECs by providing more guidance about the organization, responsibilities and ethical review procedure. Today the Hospital Ethics Committees are implementing prior review of research projects according to the above-cited guidelines and are considered as the Chinese RECs.

II. STRUCTURE AND FUNCTIONING OF RECS SYSTEMS IN FRANCE AND CHINA

A. In France: A territorial organization for interdisciplinary panels of health professionals, experts and citizens

Organization

France has currently 39 CPP established in delimited geographical areas, the inter-regions(11). Thus, the CPP have a territorial competence that leads the researchers to apply to the competent CPP in the area where the main investigator or the investigator

(10) Such an obligation for research promoters will be fixed for the first time at EU level in the context of research on medicines with the Clinical Trial Directive 2001/20/EC of 4 April 2001, see ref. 18.

(11) Ile-de-France Region (10 CPPs), North West (4 CPPs), West (6 CPPs), South West and Overseas collectivities (4 CPPs), South Mediterranean (5 CPPs), South Est (6 CPPs), East (4 CPPs).

coordinator is exercising its activities. Each inter-region has at least one CPP but some have several. This geographical coverage allows bettering the sharing of the workload, avoiding excessive costs induced by CPP that would not have sufficient activity, while allowing a reasonable delay for processing the dossiers and perform evaluation and discussions. The flexibility of the number of French CPP allows adapting to the necessities of French research activities by creating new CPP where it is relevant to do so. Each CPP needs to be certified (to obtain an "agrément" in French) in order to be legally recognized as a REC by the Ministry of Health. CPP certification is valid for 6 renewable years [41].

Composition

Each CPP includes a total of 14 permanent members (two more than in the previous CCPPRB), with a possibility of having 14 additional non-permanent members [42]. The "medical and scientific panel", is composed of four persons competent in research (including two physicians), one biostatistician or epidemiologist, one general practitioner, one hospital pharmacist, and one nurse. The societal panel is composed of seven persons and includes one psychologist, one person qualified in ethics, two lawyers, two representatives of patients' associations, one social worker. A quorum of seven members is necessary to deal with a case and vote including, mandatorily, at least three people from each panel and a biostatistician or epidemiologist and a representative from patients' associations [43]. Additional experts can be invited according to the specificities of the cases under consideration.
The members are designated after a public call for application by the General Director of the competent Regional Health Agency (ARS) representing the State at regional level. Each member has a mandate of three years renewable, ending where the certification of the CPP ends [44]. In case of vacancy of a member, the same process applies for designating a substitute. French law forbids [45] to a member of a CPP to be also member of another CPP. Passed three unjustified absences the member is deemed as "dismissionary" and the General Director of the ARS processes to a replacement. Every member is obliged to confidentiality [46]. All the information about research projects, the organizers, stakeholders and participants in the research, the experimented products, objects or methods that have been debated into the sessions must be kept secret and not be disclosed to thirds [47]. Confidentiality duty aims to avoid unauthorized access to research documentation and other research data provided to the CPP by the applicant, including personal data [48], by appropriate measures. Any infringement to these duties is submitted to penal sanctions [49] under the French Penal Code. Each CPP has a board composed of an elected president(12), a vice-president, a treasurer and a secretary ensuring administrative tasks.

Networking

Each CPP is part of a National network that organizes exchanges and meetings between the members of the different CPPs. A National Conference of the CPPs, the "CNCP" [50], allows French RECs to share their knowledge and experiences. At international level, the CPP members can attend to networks initiatives such as the EURECNET, one that bring together national Research Ethics Committees (REC) associations, networks or comparable initiatives to the European level. EURONEC aims to interlink "European RECs with other bodies relevant in the field of research involving human participants like National Ethics Councils and the European Commission's ethical review system" [51].

B. In China: An institutional internal organization for an interdisciplinary panel of experts

Organization

Today in China, RECs are established in every big university, large hospitals and institutions performing research involving human beings. The exact number of Chinese IRBs is unknown but can be potentially high due to the number of health establishments concerned by health research and clinical trials. According to Professor Qingli Hu a statistical study performed in 2005 reported 335 RECs that have been registered with the CFDA [52]. An update of this mapping work would be useful. As a Chinese specificity the Ministry of Public Health established in 1998 a Medical Ethics Committee (MHMEC) that debate important bioethical issues and review certain research protocols presenting a National interest because of the characteristics of the study (international research cooperation). Thus the MHMEC must be considered as a REC, without any equivalent in France. The Provincial Ethics Committees, as well as the National MHMEC, are in charge of overseeing the IRBs activities.

(12) Elected according to the rules laid down in Article R. 1123-10 of the French Public Health Code.

Composition

Chinese IRBs, like French CPPs, are composed of an interdisciplinary group of a variable number of competent persons. This includes medical professionals, non-medical professionals (such as philosophers), legal experts, staff from other units, with a gender balance being maintained [53], this latter feature being not mandatory in France. Depending on the location and characteristics of the research, the IRB members can include representatives of ethnic minority groups in ethnic minority autonomous regions. As in France, it is regulated that the IRB members must have a balance between (bio)medical sciences and non-medical or social sciences [54]. According to the CFDA Guidelines, "the director (or an authorized person) will chair the ethical review meeting. An independent consultant may be invited to attend the meeting to provide advices when necessary; the principal investigator/promoter may participate in the meeting to present the protocol or explicate special issues. The secretary of the ethics committee should summarize the meeting's discussion and review decision to form the meeting records. The meeting records should have a procedure to get it approved" [55].

However, unlike the French law concerning CPPs, there is no mention of patients' representatives sitting on Chinese IRBs. In practice some Chinese IRBs normally includes community representatives. A recent study performed with 5 important Chinese IRBs has shown an existing lack of medical specialists and non-medical members among the investigated REC members [56]. There is no requirement for involving a methodologist. These lacks create issues about the societal representativeness of RECs and about the essential expertise needed to tackle complex or highly innovative research projects.

The nomination process of the members is obscure. The CFDA Guidelines of 2010 states that "[…] there should be documents in writing, which define an ethics committee's organizational structure, competent department, responsibilities, member qualification requirements, conditions and term for serving, work responsibilities of its office, establishment of procedures for selection and appointment of the member and office secretary and so on" [57].

The Guidelines continue stating that "a member of an ethics committee may be engaged, recommended persons, etc. The committee has a director and several deputy-directors who are elected by the committee members" [58].

According to the CFDA GCP of 2003, "[…] the decisions regarding review and approval of the protocol by the Ethics Committee shall be decided through discussion and voting. Ethics Committee members shall avoid participating in the clinical trial. Experts who are not members of the committee may be invited to attend the meeting when necessary, but may not vote. The Ethics Committee shall establish its working procedures[58]. Written records for all meetings and the resolutions adopted during meetings shall be kept for five years after the completion of a clinical trial" [59]. Members of Chinese IRBs have to respect confidentiality [60]. Also Chinese IRBs do not need to be mandatorily certified by the State in order to perform their work while this is a legal requirement for the French CPPs. The CFDA only has to be informed about the setting up of such RECs to register them [61]. However, they can win certification, notably at the International level, in order to be recognized as ensuring best practices in ethical reviews(13).

Networking

Lastly, there is no specific network of Chinese IRBs allowing the exchange of practices and reflections either at a Local or at the National level. However, as mentioned earlier, the expert committees at the National and Provincial levels do have the duty to supervise the IRBs, what can lead to a certain degree of standardization. Standardizations initiatives have been implemented like with the last CFDA Guidelines of 2010 (see particularly Annex 1 describing the "Main Content of Ethical review") but, to date, as in France, the standardization of practices remains a long running challenge.

C. In France: the fundamental role of the law for the CPPs' functioning rules

A legitimacy rooted by hard law

In France, the rules concerning the CPPs are codified in the Public Health Code [62], Articles L.1123 and articles R.1123-1 and following. Sanctions of misconduct or procedural infringements are regulated by administrative and penal law [63]. This legalistic approach aims to ensure legitimacy of CPPs and legal security thanks to a clear and strict framework. Indeed, the central role of CPPs deserved sufficient public authority oversight and harmonization of the research review system.

(13) E.g. The Ethics Committees of Nanfang Hospital in SMU (South Medical University) won several International organizations' certifications.

Missions of French CPPs (RECs)

The aims/tasks of the CPPs are fixed by the law. Their main activity is to provide an independent positive or negative opinion on protocols submitted to them of research involving human beings. The CPPs can approve, disapprove or ask for modifications of the protocol. They cannot terminate or suspend an already approved biomedical research. This is the competence of the National Agency of Health and Medical Products (ANSM). The CPPs are competent to know about any kind of research involving human beings, National or International. This explicitly includes research the collection or use of human biological samples for research purposes. Their approval of the research protocol is mandatory [64] but is not sufficient alone to allow the research to be performed [65]. The research promoter must also obtain necessary authorizations from competent authorities such as the French Ministry of Research and the Regional Health Agency, the National Agency for the Security of the Medicines and Health Products and/or the Biomedicine Agency for certain kinds of research involving human beings [66] with regard to the research characteristics, products and kind of samples to be used. Situations occurring during the research trigger application for a CPP opinion like where there is a substantial change [67] in the research or where there is a plan for collecting human biological samples [68]. In such identified cases, the CPP can ask for modifications of the research protocol. Each opinion from a CPP, whether it is positive or negative shall be motivated. In the case of negative side-effects that occurred during the research [69], the promoter must notify to the CPP. In any case, the CPP can ask the applicants to provide more documentation about the case at stake. The CPP enforces the laws and evaluates whether the scientific relevance of the protocol ensures the best protection of the persons, in the respect of their rights and ethical principles defined by the law. Quality criteria [70] of the research protocols are also fixed by law, notably through the French GCP [71] fixing requirements for the trial's planning, conduct, data management, the measures to protect participants' rights and for the responsibilities of the promoter and investigators.

Informed consent conditions and scope are particularly considered as well as privacy protection measures. However, until now, the CPP are not mandated to examine data protection issues. This specific task is currently undertaken by the French Data Protection Authority, the Commission Nationale Informatique et Libertés (CNIL). Regarding consent, the adequateness, exhaustiveness and understandability of the written information provided and the procedures envisaged to obtain the free informed consent from the participants are deeply considered. Where vulnerable persons (e.g. children [72], pregnant women [73] and persons deprived from freedom [74]) are involved, the promoter must also provide a solid justification, particularly when these persons are unable to give informed consent. The respect of other relevant participants' rights, such as for the right to withdraw from the research, as well as the related procedures ensuring their efficient exercise is scrutinized.

The CPP evaluates the necessity of providing the person with an additional period of reflection, the necessity to plan, in the protocol, for a ban on participating simultaneously in other researches or a period of exclusion from such participations [75], the adequacy and relevance of the research with regard to the risks and benefits balance, the adequacy between the research purposes and the means envisaged to reach these aims, the qualifications of the professionals involved, the modalities of recruitment in the research and the insurance provision for the participants [45]. The CPP also assesses the guarantees and measures intended to protect the persons regarding foreseeable risks involved, such as plans for quality control of the products or methodologies used and the related reactive measures.

Any research promoter must contract an insurance ensuring compensation of potential damages due to the research activity [76] and any participants must be affiliated to a social security regime.

Implications of the new EU Clinical Trial Regulation [20] on the French RECs system and legal framework will be minimal. Aside from new harmonized procedures, some procedural changes regarding the RECs' activities are planned(14).

CPPs' sessions are not public [77] and the voted decisions and recommendations are not published but only communicated to the applicants and the authorities concerned. In case of negative opinion from a CPP, the research promoter cannot perform the research. Nevertheless the promoter can to apply to the Minister of Health for a second review of the same research protocol by another CPP to be designated by the Minister.

(14) E.g. For the timeline of research protocols' examination by CPPs fixed at 35 days in the French Public Health Code, Article R. 1123-24, because the Regulation fixes a deadline of 60 days for achieving the whole authorisation procedure of the trial, including the obtainment of authorisations from other authorities. The same deadline was in the previous EU Clinical Trial Directive. It is now strictly imposed by the Regulation.

D. In China: the major role of the National Administration's Guidelines

A soft law framework

In China, the law is not the main element used for regulation RECs activities. It is mainly Guidelines that are used to frame the Chinese IRBs composition, organization and ethical reviews activities. This creates legal uncertainty and is criticized by observers as not being sufficient to ensure efficient and impartial ethical review system. For example, it will be harder for participants to trial researchers on the sole basis of Administration Guidelines which are not legally binding, even if the Chinese Constitutional, Administrative or Tort laws provide protection of the main relevant legal principles for biomedical research like dignity and confidentiality. Relevant Chinese RECs regulations often refer to "internationally recognized principles" [78,79] but China would benefit from enacting specific laws.

Missions of Chinese RECs

The missions of Chinese IRBs are quite similar to the French CPP as they review research protocols concerning any biomedical research involving human beings, including those that involve the use of human biological samples or biotechnologies [80,81,82]. They can also provide recommendations on specific ethical issues occurring in the course of the research implementation [81]. According to the CFDA GCP of 2003 research promoters or the leader of the research program should submit their research protocol to the relevant, competent IRB, before starting their research activities. Indeed the CFDA GCP of 2003 states that "the protocol of the trial must be reviewed and approved by the Ethics Committee. When conducting a clinical trial, any amendment of the protocol may not be implemented without approval from the Ethics Committee. Any serious adverse events that occur during the trial shall be reported to the Ethics Committee in time" [83].
However, unlike in France, the Chinese regulations do not detail mandatory cases necessitating a new IRB approval.
Chinese IRBs are Hospital Ethics Committees, including in the context of university hospitals. Therefore they are competent where the promoter of the research pertains to this hospital or where patients from this hospital are involved. Assessments by IRBs, as in France, review ethical, legal and scientific aspects and guarantees of the research protocols. The CFDA Guidelines of 2010 plan situations where fast ethical reviews can be performed by one or two members of the IRB [84].
Review processes should be fixed by internal Standard Operational Procedures (SOPs). Whatever the kind of review process, Chinese IRBs particularly review aspects related to the protection and well-being of human participants, the protection of personal rights and interests. In this regard the CFDA GCP of 2003 states that "in a drug clinical trial, the human subject's rights and interests must be fully protected and the trial must also be ensured scientific and reliable. The human subject's rights and interests, safety and health must be higher than the consideration for science and social interests. Ethics Committee and informed consent form are important methods to protect the human subject" [85].
Among the elements that shall be checked according to the CFDA Guidelines of 2010 Annex 1, Chinese IRBs pay attention to the risks and benefits of the trials and their fair distribution among the targeted populations, the qualification of the research staffs involved, the methods used, the quality of the recruitment process the quality and authorizations of the site where the research will be performed, the standards for evaluating the efficiency of the trial and to monitor and report adverse events.
Protocols must plan the measures to protect privacy of participants and confidentiality of the data [86].
However there are no mandatory requirements regarding insurances protecting participants from the potential damages resulting from clinical trials(15) what is regrettable.

III. SPECIFIC COMPARISONS OF FRENCH AND CHINESE SYSTEMS REGARDING RECS INDEPENDENCE AND INFORMED CONSENT PROCESS

A. The challenges of independence

Independence of RECs is an essential requirement to ensure justice and impartiality in their decision-making process. As guardians against scientific misconducts, RECs must not be influenced by other factors than the ethical, legal and scientific robustness of the protocols. Their assessments must be exemplar, free from any economical or relational pressures

(15) Although the CFDA Guidelines of 2010, Annex 1, point 6.11, plan that this should part of the ethical review process, see ref. 41 (2010).

exercised by either internal or external actors. A lack of independence endangers the research participants as non objective decisions are and not only motivated by the sole balance between the protection of the persons and the scientific interest of the research. Several factors can affect the independence of RECs by creating risks of conflicts of interests, namely the legal lacks(16) and the organizational and funding system of the RECs.

Management of conflict of interests

In France, the law explicitly imposes that the CPPs work totally independently stating that "cannot validly participate to deliberation persons that are not independent from the promoter or the investigator of the evaluated research" [87]. This principle has been particularly reinforced from 2011, as a part of the global reinforcement of sanitary security measures [88].

Since the Law concerning Public Health Policy of 2004 [89], each CPP member is obliged to declare that he is not independent or in a situation creating an incompatible conflict of interests with the full and fair exercise of his mission [90]. This mandatory prior declaration applies before becoming a member of a CPP, or an invited external advisor, and whenever necessary before ethical reviews, on a case-by-case basis. Conflict of interests aims any direct or indirect links with research sponsors/promoters or investigators, with a particular focus on commercial actors. Each CPP must adopt its internal regulation according to an official standard fixed by an Ordinance from the French Ministry of Health [91] which reminds this obligation and specify the nature of the link to declare that can be professional, familial, personal, economic, punctual or not, past (for 5 years [92]) or present relationships that could impact the decision-making. Furthermore, any member must confirm within this declaration that he knows his obligation to declare such links wherever it is necessary to ensure a fair accomplishment of their missions. In case of declared conflict of interests the member will not participate to the review of the protocol. An opinion delivered with an undeclared conflict of interests may be invalidated by an Administrative Court. A copy of each declaration is addressed to the CPP President, recorded and inserted in the annual report of activity [93] transferred to the regional State representative, "le Préfet de Région". Then, the competent Regional Direction of Social and Sanitary Affairs (DRASS), placed under the authority of the "Préfet de Région", publishes these declarations for transparency purposes.

We can notice that there is no mention of links with participants but only with promoter or investigators. Whereas this can be explained through the necessary involvement of patients' organization representatives in the CPPs it could also be discussed as a weakness.

The law states that if CPPs make a decisional mistake causing damages, the State responsibility is engaged [94] for potential compensation. Therefore the State regulates a lot their functioning notably to ensure impartiality.

In China, observers noted cases where the IRBs members were sometimes influenced in their ethical review [95]. While the general anticorruption law reinforced in 2011 [96] apply to RECs, clearer rules regarding specifically the independence of RECs progressively emerged. Indeed, CFDA GCP of 1999 fixed the principle of independent, fair and transparent assessment in Article 4. However, the Article 9 weakened this principle by stating that "the constitution and work of the committee are relatively independent, free of any participants' influence". This relativity was difficult to understand and could not be considered as guaranteeing independent practices. Today IRBs should clearly work independently as the CFDA GCP of 2003 [97] and the CFDA Guidelines of 2010 [98] recommend. This shall also include solicited external advisors. According to the latter it is the responsibility of the REC to ensure that the independence safeguards are in place and effective [99]. If these advances must be acknowledged, other organizational problems should be considered regarding the safeguard of independence. One of them could relate to the US IRB historical model used in China to develop RECs system. Indeed, this IRB model is criticized in France because it is seen as only performing minimal ethical reviews of research protocols undertaken by internal teams, thus creating risks for independent reviews or risk of an "ethical placebo" [100] system. Indeed, Chinese IRBs mainly deal with projects promoted by internal physicians and members of the Chinese IRBs are often also employed by the host establishment of the REC. This can attempt to their independence and orient their decision towards systematic approvals in order to avoid being blamed or badly considered by important professionals involved in the hospital's research activities. In China, members of the IRB do not have mandatory obligation to formally declare conflicts of interests, unlike in France where such a procedure is a legal constraint systematically

(16) E.g. about the REC members' status or about the role and responsibilities of research actors, from the promoter to the participants.

requested through a written declaration. However, since 2010, the CFDA Guidelines(17) intends to change the situation by advising the recording of a signed declaration of conflict of interest for each IRB member [101]. Furthermore, REC members agree to make public their name, what would facilitate controls and would allow a sort of societal vigilance from the public and participants.

Remuneration of the REC members

The members of the CPP are not remunerated for doing their work that is done for the public interest. This symbolic position would allow that the CPPs members be not only motivated by monetary concerns(18). While the reporter of the decisions and recommendations can be paid, others can only receive compensation of fees or, as for liberal practitioners, compensation in case of loss of wages.
In China, IRBs' members are often hospital employees. The Chinese relevant regulation does not provide details about the remuneration of IRBs members for their work within the Committee. Each institution can decide about this question individually what can lead to abuses or inequalities.

Funding system of the RECs

In France, concerning the funding of CPPs, each year, members of the CPP deliberate on the provisional budget necessary for their activity and transmit their deliberation to the Regional Health Agency. From 2013, the CPPs' budget is submitted to the laws applying to public budgetary accountability [102]. Thus legal statute of CPPs tends to turn on the independent administrative authority model. The national budget for CPPs is a Ministerial endowment ("dotation ministérielle" in French) planned within the organic Financial Law adopted each year. The amount of budget dedicated to the CPPs is spread by public authorities to all the CPPs, according to their legitimate needs. The constitution of this national endowment is ensured thanks to taxes paid by the pharmaceutical industries, in a participatory system that prevent direct attempt to influence from private sector. In 2012, the total budget for French CPPs was 3.5 Million Euros and expenses tend to increase each year (e.g. 3.35 Millions for 2011) [103]. Another interesting element related to the independence assurance of CPPs relates to the accreditation system ("agrément" in French) requiring that each CPP be officially recognized by the French Ministry of Health before starting their activities. This process allows controlling, among others, the respect of conflict of interests' rules. Indeed, the French Ministry of Health receive the annual reports previously provided by the CPPs to the competent "Préfet de Région" and will use them for deciding about the renewal of the accreditation for 6 years, to refuse the renewal or to withdraw it.
The Chinese IRBs are funded by their host establishment and not by a Ministerial budget shared among the RECs. This can have important impact due to the economical differences existing between rich hospitals (city hospitals) and poorer one (country hospitals).

Perspectives

With a prospective view, the new Law on research involving human being of 2012 (unapplied yet) will officially create a new National Commission on Research Involving Human Beings [104] whose the main mission is to manage French CPPs activities and to randomly designate the competent CPP for processing an ethical review application. This measure intends to reinforce the independence in ethical reviews, avoid favoritism between applicants and CPPs and will thus end with the previous (but still current) geographical organization of CPPs competency. This National Commission still not exists.
While the last CFDA Guidelines of 2010 insists on the need of independence of RECs members, corruption still remain a reality in the absence of real public authorities' control(19) of RECs composition, qualifications and potential conflict of interest.

B. The challenges of altruist participation to the research

The rationale of the prohibition of direct financial gains

Various countries express different views on this issue. For the majority (e.g. European countries), presenting research project as an activity providing pecuniary

(17) Before the CFDA Guidelines of 2010 Chinese IRB members should refrain from participating in session where they were in relations which could affect their opinion. Such an individual abstention system based on individual's responsibility and integrity was a specificity of the Chinese REC system.

(18) This also causes certain difficulties to find people due to the huge workload of the CPPs.

(19) CFDA, Guidelines, see ref. 41, Article 4 opens the possibility of control on the RECs activities by the Chinese CFDA but the practice of such a control will need to be followed and transparently reported.

advantages is unethical and must be forbidden. Such a practice is creating incentive that can outweigh the main goal of scientific health research that is to participate to the common good, to a better global knowledge of diseases, as a humanitarian and altruist act. Such a financial motivation seems to contradict the spirit of research participation and could particularly have a negative impact on certain social categories that will be tempted, whatever the consequences, to participate to profitable researches. This could lead to endanger both the participant's health and in some cases impact the scientific value of the research. For others, the assumed minority, it is part of the benefit sharing approach to gratify participants with money, as a sort of return on personal investment.

While this latter position is ethically doubtful due to existing alternatives the WMA Declaration of Helsinki of 2013 remains silent and only states in Article 15 that "appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured" [105]. At European level the Council of Europe Additional Protocol to the Oviedo Convention on Biomedical research states in Article 12 the necessity to ensure absence of undue influence, 'including that of a financial nature' [106], on the participant.

The situation in France and China

In France research participants do not earn remuneration for their participation. French law fixes a principle of compensation for suffered constraints according to the research risks, excepted for most of vulnerable persons. Such restrictions aims to protect vulnerable persons whose participation and decision-making involve thirds which could be driven by financial interests and tempted to bias the final choice. However, pregnant women are eligible to this compensation [107]. The maximum amount of perceived annual compensations is limited to 4500 Euros by Ordinance [108] and selected participants for compensation are inscribed in a registry [109] managed by public authorities. The responsibility of the promoter is engaged for any undue payments of the participants.

In China, participants can be paid for their involvement in the research. This practice is arising important ethical issues, notably where some people with economic difficulties, like students, can be enrolled in several biomedical researches jeopardizing both their health and the quality of research results, notably by cheating at the recruitment tests [110]. Participants are not protected about parallel participations in several studies and do not have specific insurance that would cover potential damages, unlike in France. Thus, none legal provision is protecting against the professionalization of research participants that can earn more participating in research projects than if they would have a 'normal job'. As China is more and more attractive in for performing scientific research, the IRBs missions regarding ethical review process of international researches involving Chinese participants should be strengthened in order to avoid unethical researches from foreign researchers (E.g. the recent 'Golden Rice case' concerning an unlawful and unethical health research involving children and genetically modified food that was carried out in the Hunan province by an American university) [111].

C. The challenges of informed consent

The practice of informed consent to biomedical research implements the fundamental principle of autonomy and self-determination of the participants. It is an example of major parameter to properly assess in the ethical review, notably in the frame of international research projects. Any research promoter must obtain the prior free and informed consent from the person that is expected to participate or its legal representatives, as a legal and ethical condition of involvement [112]. Consent must clearly express the will of the person to participate in the research at stake and eventually to future ones. However divergent and more or less stringent approaches and practices exist within and between countries, adding complexity to ethical reviews.

Kind of consent

In France, the law clearly requires to obtain the written participants' consent before the beginning of the research project. Where the consent cannot be obtained in written form it must be attested by a third that will be totally independent from the research promoter or investigator [113,114] that can be designated by the law. French law authorizes both opt-in and opt-out consent processes depending on the situation, but in any cases the consent must be free, specific and informed and adapted to the planned interventions on the human body and the use of personal data for research purposes. For instance, genetic studies are strictly regulated and the written consent must have been obtained. Today in France, as in other western countries, main issues on informed consent to biomedical research concern the scope of the consent, the responsibilities attached to the broadening of both the purposes of the researches for which materials could

be reused and the possibilities to let individuals select research parameters, France having a tradition of specific and fix consent. These reflections are source of ethical dilemmas surrounding the biobanking and genetic research activities [115,116]. The point is to adapt practices to the new scientific necessities and medical evolutions while ensuring understanding of the implications and participants' protection.

In China, the process of informed consent to biomedical research is detailed through the CFDA Regulations [117]. However, while the positive effects of informed consent for patient-doctor relationships start to be considered by researchers, under US bioethics influences, it is not a traditional practice in China that essentially considers social entities on the basis of communities or groups like the family, and traditionally provides authority to the elders in a Confucian way of thinking social relationships [118]. Thus, the right to individual self-determination and autonomy in research seems less important in China than in Western countries, what has an impact on the practices of informed consent and needs more attention in order to conciliate the respect of bioethical principles and Chinese traditional culture. While the relevant Chinese Regulations provides that written informed consent should be obtained before any research involvement and provided to IRB [119] it seems not to be yet a usual practice in the Chinese research settings. Given consent to participate in the research still often be given orally and are not always recorded. If it can be argued that inadequacies exist between the Chinese conception of individual rights and freedom with regard to the occidental doctrine of informed consent to biomedical researches, new ways of conceiving this process with regard to both Chinese traditions and necessary good management practices should be worked out in order to respect this principle through effective processes that will have to be reviewed by RECs.

Information prior to consent

In France, whatever the kind of interventional research the person must receive fair and objective information about the participation. Where children are involved it is important to adapt the information to their level of understanding and to gather their opinion on the participation (assent system). Any expected participant must be informed about the objectives, the methodology, the late, the benefits and constraints that can be foreseen, medical alternatives, modalities of taking in charge at the end of the research, the obtainment of a CPP approval, the interdiction to participate to other research projects (due to the health risks or bias this would cause) and an information about its rights, notably with regard to the obtainment of personal health information resulting from the research [120]. Regarding personal data, the French law requires prior information about the nature of the data, the purpose of their processing, the recipients and the existence of the rights to access, to rectify the date and to oppose to the processing [121]. This minimal information shall be completed by any other useful information for understanding the research and obtain valid consent.

In China, Art. 14 of the CFDA GCP requires that the researcher, or that any representative nominated by the researcher, must explain to the expected participant the detailed condition of the clinical trial. The expected participant shall be informed that the participating of trail is voluntary, and he/she has the right to withdraw from any phase of the trial without any discrimination or reprisal, the this medical treatment and benefit shall not be influenced by the withdraw. All the personal information of the participant in the trail is confidential. In case of necessity, the CFDA, the ethical review board, or the sponsor, may exam the data of the participant according to regulations. The aims, procedure and period, methods, the anticipated benefits and potential risks of the study, shall be informed to the expected participant. And the expected participant shall be informed that they are subject to be distributed into different groups. The information shall be given in the oral or written language that is understandable to the expected participant. According to Article 17 of the Regulation on the Ethic Review for Biomedical Research Involving Human Participants of the Ministry of Public Health of 2007, if people from ethnical minor groups are involved, all the information shall be given in their native language(s), or in the language understandable to them. The expected participant shall be given sufficient time for consideration. For those unable to express themselves, legal representatives shall be informed instead. During any phase of the trial, the participant has the right to require further information. Additionally, the expected participant shall be informed that in case of damage caused by the trial, he/she is entitled for treatment and compensation. In case of minors involved in the trial, the CFDA GCP requires that the informed consent of his/her guardian shall be granted. The minor shall also assent if he/her is able to do so.

Potential exceptions to prior informed consent

French CPPs are competent to approve exception to prior informed consent where the provision of the

information or the obtainment of consent proves impossible or would involve disproportionate efforts with regards to the risks and benefits of the research for the participants and society, like where the person cannot be contacted anymore or where the protocol includes resources from deceased person. This does not apply to genetic research where written specific informed consent must be obtained [122]. The exceptions' applicant must document these insurmountable hurdles. In case of urgency, where the person is incapable to provide consent, biomedical research protocol must be submitted to a CPP that could exceptionally allow the research to begin provided that a family member or a confident person consents.

In China, some legal provisions also plan exception to participants' informed consent, mainly in case of emergency. Indeed, the Tort Law [123] of 2010, Article 56, states that "where the opinion of a patient or his close relative cannot be obtained in the case of an emergency such as rescue of a patient in critic condition, with the approval of the person in charge of the medical institution or an authorized person, the corresponding medical measures may be taken immediately". In research, according to CFDA GCP [124], in case of emergency when is not possible to have the written form of the informed consent from the patient or his/her legal representative, and there is no current proven treatment, whereas the medicine for trial is most likely to save the life, restore the health and release the pain, the patient may be considered to be accepted as a research participant. However, in this case, the method of the acceptance for the participant shall be clearly verified in the study protocol, and shall be authorized by the REC in advance. The process for approving researches including available resources coming from deceased persons remains to be specifically worked out.

Management of documentation

In France, the information notice must be separated from the consent form, usually they are two different documents that can be signed by the participant. The information notice and the consent form have to be provided to the CPPs, in French language, for assessing their appropriateness with regard to the research protocol and the population concerned. All the assessed documents during the ethical review are archived by the CPP services for 10 years after the end of the research for the purpose of proof.

In China, the last CFDA Guidelines of 2010 for Ethical Review Work of Drug Clinical Trials, Annex 2 point 2.1, includes specific rule to archive the informed consent documentation within the dossier concerning the application. There is no mention of a late of storage.

CONCLUSION

The 1980's have been a crucial period in France and in China in the process of establishing RECs. France and China have both interdisciplinary RECs capacities in place reviewing biomedical research protocols before their implementation according to international recommendations as benchmarks. However, each country developed very different systems. France developed a system of RECs based on strict legal statute and mandatory procedures while China, widely influenced by the US system, established IRB system and mainly regulates RECs through soft law and Guidelines from Administrative bodies. Thus, Chinese RECs suffer from a lack of legal certainty. While the last CFDA Guidelines of 2010 bring a lot of best practices recommendations and insists on the need of independence of RECs' members and on the need for developing written informed consent process, they only apply to clinical drug trials. Coordinated actions and ongoing studies will be necessary to measure their implementation. While the substantial content of the rules does not fundamentally differ, challenges remain in both countries regarding economical sustainability, independence, informed consent and the legal protection of research participants. While China progressively engages in the development of health law, one of the main foreseeable common challenges will be to ensure that RECs will be able to absorb an increasing number of applications which are complexifying due to the use of new health technologies and methodologies including wider international dimensions. Regular training of the RECs' members and international exchanges of experiences will be essential to ensure best practices. ■

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