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Research projects in Obstetrics and Gynecology in France:

How is functioning the Ethical Review Board « Comité d’Ethique pour la Recherche en Obstétrique et Gynécologie » (CEROG) ?

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Abstract

Introduction: The French College of Gynecology and Obstetrics (CNGOF) has created an Ethical Review Board called the CEROG that aim to ensure the research projects are in conformity with the regulation and the laws, as well as to allow their publication in international scientific journals. The aim of this work was to analyze the work of this committee through the application received and to review the ethical procedures required by type of research project.

Methods: We conducted a national retrospective study of all applications from 2018 to 2021 received by the CEROG Ethical Review Board. Each application must contain a verification of conformity with the MR004 regulation, a submission form and an information form to the patients involved. At reception, the documents are anonymized and then addressed to the members of one of the two independent sections (Obstetric and Prenatal diagnosis or Gynecology and Assisted Reproductive Therapy).

Results: Two hundred and sixty applications were received, including 52% in the Gynecology section and 48% in the Obstetrics' section. Only 10% (14/136) and 8% (10/124) were disapproved, respectively. In total, 35% of the applications to the Gynecology section led to publications in scientific journals but only 23% did so in the Obstetrics section. Most publications (60.8%) were in low impact factors journals (rank D and E).

Conclusion: The Ethical Review Board CEROG is essential to ensure the conformity of the research projects with French regulations and allow fast publication in international journals.

Keywords: Ethic ; Research ; Regulations ; Jardé

Introduction

"In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests" [1]. Inhumane research that marked the 20th century contributed to the development of codes and laws as we know them. Some of the most major abuses include the experiments of the Nazi Doctor Mengele and his colleagues on Jews [2], the syphilis injections in underprivileged black populations [3], and the multiple experiments of radiation on humans (e.g., radiated cereals for children, radiation for pregnant women). These scandals call for strict regulation of biomedical research. In response, the World Medical Association's Helsinki Declaration sets standards of ethical practice for doctors and participants involved in research as well as for personal data and identifiable biological samples [1]. Specifically in France, the Jardé law, promulgated on March 6th 2012 [4], expanded the "Huriet – Serusclat" law of 1988 [5] by defining legal restrictions for all types of research, medical or not. These law enforcement decrees have led to significant modifications of ethical procedures including two distinct categories of research: Research Involving Human Subjects (RIHS) and Research that Do Not Involve Human Subjects (RNHS). These are summarized in Figure 1. The "Comité d'Ethique pour la Recherche en Obstétrique et Gynécologie" (CEROG) can evaluate research projects that falls within this latter category and do not require formal evaluation by a "Comité de Protection des Personnes" (CPP) [6]. From a legal perspective, the CEROG has a role similar to local committees but it has a determinant role for research evaluation in projects regarding obstetrics and gynecology by being the most used. It has the authority to deliver the US Institutional Review Board (IRB) number required for scientific international publications. Briefly, two main types of projects are eligible to the CEROG assessment: (i) Research on data (with no patient involvement) exploiting data collected without human implication;

Those are the retrospectives but also prospective collection of data (including images, biological samples or medico – economics) usually collected during “usual care” (ii) Research whose aim is not to produce biological or medical knowledge such as cosmetics, satisfaction survey, human and social experiment or survey on practice and habits in practice.

The RIPH type gather 3 categories from 1 to 3, from the more to the less interventional. RIPH category 1 is for interventional research with risk for participants and not justified by standard practice. For example, medications clinical trials, but also surgical trials, medical devices, or genetical / cellular therapy are categorized as RIPH category 1. RIPH category 2 is for interventions with minimal risk and low constraint, that could include interventions or acts invasive like blood test, a questionnaire to modify clinical guidelines, a radiological exam. The complete list of these interventions was determined by a law decree (May 3rd 2017 published in the JORF n°0107). RIPH category 3 also called “non interventional research” include observational research without any additional contact with the patients included. This include the pharmacovigilance studies, practices comparison across different hospitals or departments, all of those are also detailed in a law decree. Whichever the category of the RIPH study, it is submitted to strict rules to respect prior initiation. A promoter is responsible with the course of the study: he must verify that all legal aspects have been fulfilled, and that all good clinical practices are always applied. The “Agence Nationale de Sécurité du Médicament” (ANSM) must deliver a clearance for the category 1 projects. For the other categories (2 and 3), the ANSM must only be informed prior the study begins. Then, the “Commission Nationale de l’Informatique et des Libertés” (CNIL) must also provide a clearance with a firm commitment to respect the conformity MR001 (category 1) or MR004 (category 2 or 3). Eventually, an agreement from a “Comité de Protection des Personnes” (CPP) must be obtained. The research is conducted under the

direct supervision of an investigator, in charge with the information delivered to the patients involved and with the collection of all written consents.

The aim of our study was to investigate the recent activity of the CEROG by reviewing all applications over the past few years and by describing the outcome of the approved studies.

Material and Methods

Submission process

The ethical department of the “College National des Gynecologue – Obstétriciens de France” Gynecology (CNGOF), CEROG ensures that all research conducted within this specialty that are submitted for evaluation conform to national ethical regulations. Members of the CNGOF can contact the CEROG to evaluate a research project or to seek advice. At conception, the type of research project must fit one of the categories described in Figure 2. Then, three simple questions determine whether the project will be assessed by the CEROG or rather by any local/ institutional committee.

- 1) Is the design strictly observational? If no, the research belongs to the RIPH type, category 2 or 3, requiring formal evaluation by a CPP.
- 2) Is the design retrospective? If no, further evaluation should help determine whether the prospective project can fit the CEROG competences (or any local / institutional committee).
- 3) In case of prospective study, does the study concerns daily care not involving any supplementary patient contribution? If no, the research is part of the RNIPH type category 3 and should be evaluated by a CPP.

A prerequisite to applying for a CEROG validation is to be member of the CNGOF and to pay the submission fees (40 euros) online. Confirmation of payment will be asked prior the delivery of the Committee response. Of note, none of the members of the CEROG, neither the Experts nor the two Secretary, are paid for the involvement in the CEROG. The payment is only required to sustain the operability of the CEROG. The applicant must fill a form confirming the project is within the CEROG field of competency, a conformity form of the MR004 methodology, a CEROG - submission form and a notice for patients informing them they are included in the research project. The MR004 methodology is the legal reference for

RNIPH studies that strictly defines the kind of data researchers are allowed to collect on patients included. All demands are transmitted by e-mail to one of the two Secretaries, depending on the matter of the study (ART – Gynecology or Prenatal diagnosis – Obstetrics section). From upon receiving the demand, the Secretary assigns a submission number and a date of process' initiation. Then, he fully anonymizes the different forms, including for the place the study will be conducted to ensure the evaluation will focus on the hypotheses and the methods while preventing conflicts of interest. The Secretary then send the application to the reviewers of the section, which are practitioners selected for their expertise in both research and ethic's rules. The list of the members of the CEROG committee in 2021 is displayed in Annex 1. The members of the CEROG volunteers for this task and a month (except during vacations periods) is usually necessary to evaluate an application. The reviewers will have to determine whether the project is in accordance with the CEROG competency as aforementioned. Final decision is delivered following a synthesis by the Secretary of the reviewers' answers. A minimum of 5 reviewers' answer is required prior a decision can be reached. In discordant cases (at least two reviewers against the validation) a general meeting is planned to discuss all together the demand. Three type of decisions can be returned to the applicant: Favorable (no restriction) : (i) an Institutional Review Board number is delivered, (ii) Specifications are required prior final decision (temporary decision) (iii) Rejected: a CPP is required for formal evaluation.

Retrospective survey of the applications

Based on aforementioned submission process, a retrospective analysis of all applications received between January 1st 2018 and June 1st 2021 was undertaken. All the applications were gathered from the two Secretaries in charge of the CEROG functioning and the following data were analyzed: Date of submission, section it was submitted to (Gynecology and ART / Obstetrics and prenatal diagnostic), validation or not by the committee. Then, the

PubMed database was searched using the following terms “authors’ name”, “title of the project” “mesh term included in the application” and Boolean operators “AND” and “OR”. The aim was to investigate whether the project had been published yet. Last consultation of the PubMed database was on September 15th 2022. Each publication identified was then classified using journal’s name and official rank of the journal (from A to E)

Results

Between January 1st 2018 and June 1st 2021, the CEROG received a total of 260 applications, 136 for the Gynecology – ART section and 124 for the Obstetrics and Prenatal Diagnostic section. Among those, following evaluation by the reviewers, 14 (10%, 14/136) were rejected in the Gynecology – ART section and 10 (8%, 10/124) were rejected for the Obstetrics and Prenatal Diagnostic section. The number of applications monthly was very variable and ranged between 0 to 14 (gynecology – ART section) and between 0 to 8 (obstetrics and prenatal diagnostic section). The number of applications kept increasing over the last 3 years with respectively for the Gynecology – ART section and Obstetrics – Prenatal diagnosis sections 16 and 20 applications (2018), 26 and 37 applications (2019), 42 and 45 applications (2020). On August 10th 2021, among all applications during the inclusion period that received a favorable answer, respectively 43 (35%; 43/122) and 26 (23% ; 26/114) led to publications in scientific journals for the Gynecology – ART and Obstetrics – Prenatal diagnostic sections. Most publications were in journals ranked D and E (60.8%, 42/69). The most represented journal was the Journal of Gynecology Obstetrics and Human Reproduction (JOGO). Scientific publications of the projects validated by the CEROG classified by journal and rank for each section are displayed in Figure 3 and 4. No project that was rejected by the CEROG was ever published.

Discussion

The constant evolution of the strict regulations that define ethic for research might constitute a brake to research publications of young residents. Indeed, most of their work is retrospective (in up to 60% cases) using data registered during clinical – daily practice, also called “usual care research”. As this is currently considered as RNIPH, it can be assessed by the CEROG committee. We found that among project that was rejected by the CEROG committee, none was ever published, highlighting the importance of the CEROG committee and. This also highlight the breaks to research publication when the project does not fit the CEROG competency as the steps to obtain clearance from a CPP are expensive, long and require most of the time the involvement of the institutional research department.

In our evaluation of all the application received and their outcomes once granted with a favorable answer, two elements are particularly singular: the low rate of negative responses on one hand, and the high rate of projects that did not leaded (so far) to scientific publications. The low rate of negative response might reflect the good knowledge by the applicants of the current regulations and an experience of the project that require a CPP evaluation and those that could be assessed by the CEROG. As for the unexpected low proportion of projects that leaded to publications in scientific journals, it could be explained by the submission process that can last for several months (for just one journal attempt). Besides, if the application was filled prior the initiation of the study (as it always should be), the delay before publication is necessary increased. As this low rate of publication could be perceived as a negative elements, it should been seen a the CEROG fulfilling its role by providing rapid ethical opinions for non-interventional and most often unfunded clinical work.

A strength of this work is to highlight that some works that did not require more than evaluation by a local committee could achieve publications in highly ranked journals which should encourage young residents and researchers to conduct and publish their work.

Perspectives for the CEROG development include the complete digitalization of the process to improve traceability for the applicants while making easier for the reviewers. Communication to residents, midwives and researchers about the role of the CEROG and its function could increase the proportion of projects submitted for evaluation and contribute to research dynamism.

Conclusions

. The CEROG is competent in many cases for the evaluation of the ethical aspect of research projects conducted in France but also to promote French research to international publications in English – written journals. CEROG fulfills its full role by providing rapid ethical opinions for non-interventional and most often unfunded clinical work.

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Figures Caption

Figure 1: Research categories and regulations associated

Figure 2: Algorithm decision for the type of ethical committee required

Figure 3: Scientific journals that published the CEROG – validated projects in the Obstetric and Prenatal Diagnosis section (left) and Gynecology – ART section (right).

Abbreviations: JOGOH: Journal of Gynecology, Obstetrics and Human Reproduction ;

Gynecol Obstet Fertil Senol: Gynecologie Obstétrique Fertilité Sénologie; Eur Journal Obstet

Gynecol Reprod Biomed : European Journal of Obstetric, Gynecology and Reproductive

Biomedicine; Arch Gynecol Obstet : Archives of Gynecology and Obstetrics; J Clin Med:

Journal of Clinical Medicine; Ann Surg Oncol: Annals of Surgical Oncology; Eur J Surg

Oncol: European Journal of Surgical Oncology.

Figure 4: Publications from the CEROG – validated projects, classified by the rank of the journals in the Obstetric and Prenatal Diagnosis section (left) and the Gynecology – ART section (right)