Issues with Ethics in Research – A Case Study of the IHU Mediterranee Infection

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Abstract

The practice of clinical research is strictly regulated by law. During submission and review processes, compliance of such research with the laws enforced in the country where it was conducted is not always correctly filled in by the authors or verified by the editors. Here we review 456 studies published by the IHU Méditerranée Infection (Marseille, France) and identify a range of issues with the stated authorization of the research, ethically and potentially legally. Of these, 248 were conducted with the same ethics committee reference, even though the subjects, samples and countries were different. Thirty-nine did not even contain a reference to the ethics committee while they contain research on human beings. With this example, we call for stricter control by publishers of the regulatory documentation related to clinical research during the publication process. All supplementary materials are available on https://osf.io/ueqf8/.

Keywords

Clinical research, ethics, scientific publications, scientific publishing, IRB.

Background

There are over 27 million scientific articles listed on the National Health Institute Platform PubMed. Previous investigations have shown that many of these papers are likely to be flawed, including numerous instances of misconduct [1]. The business of scientific publication has surged during the last decade, including a staggering growth in the number of articles submitted and finally accepted for publication [2]. The peer review process is important for assessing the quality of hypotheses, methods, reliability of the data, and legal requirements. The Covid-19 pandemic was a stress test for the academic publishing system and unveiled several failures in processes evaluating quality of scientific publications [3-7]. Neglected or non-existent review procedures, inconsistent publications and irregularities in legal permissions are among the most common concerns.

In the morass of scientific publishing, it is not uncommon for a controversial hypothesis to gain traction despite a dearth of either biological plausibility or evidence, and to remain popular even when new data contradicts the initial postulate. For instance, Professor Didier Raoult, former head of IHU Mediterranée (IHUm), vigorously promoted hydroxychloroquine (HCQ) and azithromycin association for the treatment of COVID-19 [8], after testing it in a small, poorly-controlled observational study that has been described as having “major methodological shortcomings which make it nearly if not completely uninformative” and “fully irresponsible” in an independent review commissioned by the parent publishing company Elsevier [9,10] and negative peer-review comments on PubPeer and by French authorities.[1] This regimen has remained popular in some minds despite increasingly robust evidence that it is ineffective in the treatment of COVID-19 and indeed may increase the risk of death [11].

This drew the French government’s attention, which launched legal actions in early September 2022, following a damning report on the ethics and conduct of research taking place at IHUm during the investigated period. The seriousness of the accusations reported made us question whether the current editorial processes could have caught such concerns regarding the legal framework implemented at IHUm when conducting clinical trials. This paper provides the results of a detailed review covering the work of researchers at IHUm, comparing published ethical statements related to the guidelines of the Declaration of Helsinki on human experimentation.

Investigation

After screening studies published by the IHUm, we noticed that one of the Institutional Review Board (IRB) approval numbers (09-022) appeared in several publications while topic and involved patients were significantly different. We then used "Google scholar" to identify all occurrences of this approval number. After cleaning, we noticed that the IRB number had been used 248 times over 12 years (between 2009 and 2021). Reusing approvals is allowed if results are from samples originally approved by the committee and in compliance with local laws related to clinical research. However, we found that those

[1] https://www.igas.gouv.fr/spip.php?article861

248 publications covered a large variety of samples (stool, vaginal secretions, urine, samples taken during surgical procedures), and a wide array of populations (adults, children, healthy volunteers, obese patients…) and countries (France, Senegal, Niger, Gabon, Saudi Arabia, ...) as depicted in Figure 1 (see the full data in supplementary materials "Studies_with_09-022_IRB.csv").

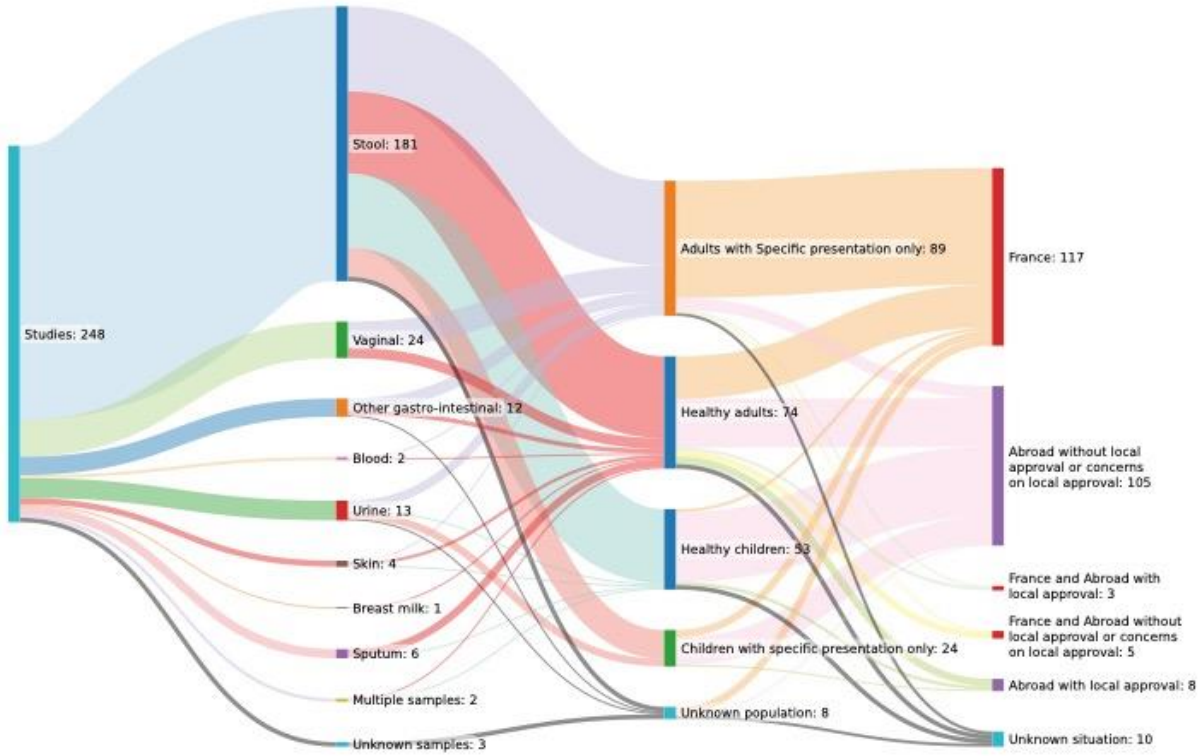

Fig. 1. Various subjects, samples, and countries for the 248 studies with the IRB number 09-022.

Moreover, the French legislation changed in 2016 with the Jardé Law on good practices in clinical research [12]. Any experimentation on human beings must be approved by an independent ethics committee and depending on the complexity of the protocol, additional authorizations are required, especially regarding the collection of body fluids such as stool, vaginal secretions or urine). Among the 248 studies identified, we have found at least one that was conducted after the Jardé Law was implemented [13], as well as many more published after 2016 with no dates of patient enrollment identifiable.

Could a single IRB approval cover such a wide breadth of clinical research? We could not access the original file with the IRB number 09-022, even after requesting this document from the IRB. However, we obtained a copy of the outline of the document (see supplementary materials "Outline of IRB approval.png"). Based on our analysis, this form does not allow such a wide variety of samples, clinical conditions, and geographical origin to be documented. There is no reasonable explanation for such a multiplicity of occurrences in the literature. The original document might mention all of those samples, conditions and countries or amendments could have been made and validated without explicitly being mentioned in the published literature. We cannot exclude that this number has been misused to publish unauthorized clinical research.

Further investigation in the bibliography from IHUm showed 456 studies that could have ethical and legal concerns of the same type: multiple and different studies with the same IRB, absence of legal authorization, recruitment start before authorization, etc (see supplementary materials "Clinical_Research_Papers_With_Ethical_Concerns.csv").

The ethics of biomedical research is generally governed by the Declaration of Helsinki,[2] adopted in 1964 by the World Medical Association to ensure respect for people who entrust their time and safety to

[2] https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/

scientific researchers. It highlights how "researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research". Most, if not all, scientific publishing companies have subscribed to this declaration,[3,4,5] which is also recommended by COPE.[6]

Conclusion

Editorial practices in verifying ethics and lawfulness of clinical research are still very heterogeneous despite most publishers having signed the Declaration of Helsinki. We wish to initiate a conversation for a more global and homogeneous implementation of ethical controls at the editorial level. We argue that submission processes should be amended to require the potentially confidential upload of ethical documents linked to clinical research, and that editorial procedures should ensure that international (and potentially local) laws are being rigorously respected. This responsibility should absolutely not be placed on reviewers whose primary mission is to ensure the scientific robustness of the research as well as its relevance for publication. Indeed, much of this process could be easily automated by publishing companies such as Elsevier to avoid precisely the issues identified in this review. Converging towards an editorial responsibility would also further facilitate verification. Indeed, as we have ourselves experienced, independent researchers investigating the adequacy of ethical documents are not likely to obtain an answer from IRBs or ethical committees, while editors and publishers would have an easier and more legally anchored claim to request those documents. In conclusion, there is an urgent need for publishers to require clinical research approvals. This could be done by requesting validation from the sponsoring organization or from the authority that issued the IRB number.

Supplementary materials

All supplementary materials are available on https://osf.io/ueqf8/

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Authors contribution

Conceptualization: FF, NF, LB
Methodology: FF, NF, LB
Investigation: FF
Writing – original draft: FF, NF, EB
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