Perspectives on Ethical Issues in the Publication of Health Research

A Casebook for Reflecting on Publication Ethics

Forum for Ethical Review Committees in Asia and the Western Pacific (FERCAP)

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Introduction

In line with the celebration of its 20th anniversary, the Forum for Ethical Review Committees in Asia and the Western Pacific (FERCAP) developed this Casebook for reflecting on publication ethics. While FERCAP is focused on ethics committees (ECs) and ethical review of health research, it also gives due importance to publication ethics, which is considered as an integral part of research ethics (Figure 1).

Given that health research continues to face publication controversies involving *research*/*scientific misconduct* [*fabrication*, *falsification*, and/or *plagiarism* (FFP)] and *questionable research practices* (QRPs),[1] there is a persistent need to ensure the publication of health research that is both scientifically valid and ethically sound.

Embodying this need, *publication ethics* can be defined as fair and just practices and standards of public accountability for authors, editors, publishers, referees or reviewers, and other stakeholders in the publication of research.

For this Casebook, the focus is on the authors. The contributors of this Casebook looked at selected issues in publication ethics related to authorship and author responsibilities. In the Case Studies, which were modified from actual cases, the contributors discussed the four criteria for authorship, types of inappropriate authorship, and other authorship issues. They also examined author responsibilities with regards to disclosing author contributions, conflict of interest, study design, statistical analysis, ethical approval, and originality; avoiding FFP and QRPs; ensuring ethical treatment of animals; ensuring ethical treatment of human participants; registering clinical trials; and sharing data.

In looking at these ethical issues in the publication of health research, the perspectives used in this Casebook were based on contextualizing and harmonizing international ethical guidelines in research (*e.g.* CIOMS Ethical Guidelines 2016,[2] ICH-GCP Guidance 2016,[3] WMA Declaration of Helsinki 2013,[4]

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[1] Daniele Fanelli, "The Black, the White and the Grey Areas: Towards an International and Interdisciplinary Definition of Scientific Misconduct," in Tony Mayer & Nicholas Steneck (editors), *Promoting Research Integrity in a Global Environment*, Singapore: World Scientific Publishing Co., Pte. Ltd., 2012, 79-90.

[2] Council for International Organizations of Medical Sciences (CIOMS), *International Ethical Guidelines for Health-related Research Involving Humans*, Geneva: Council for International Organizations of Medical Sciences, 2016.

[3] International Council for the Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), "Harmonized Guidance: Integrated Addendum to ICH E6(R1): Guidance for Good Clinical Practice (GCP) E6(R2)," November 2016.

[4] World Medical Association (WMA), "Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects," October 2013.

WHO Standards and Guidance 2011,[5] FASS Guide 2010[6]) and publication (*e.g.* ICMJE Recommendations 2019,[7] CSE White Paper 2018,[8] WAME Recommendations 2012,[9] COPE Code 2011,[10] ARRIVE Guidelines 2010,[11] IAVE Guidelines 2010[12]) with specific cultural backgrounds and social settings in the Asia-Pacific region.

This Casebook is dedicated to Dr. Juntra Karbwang Laothavorn, a pillar in promoting research ethics in the Asia-Pacific region. Dr. Juntra is the Coordinator of the Strategic Initiative for Developing Capacity in Ethical Review (SIDCER) and the President of the SIDCER-FERCAP Foundation. As she embarks on new challenges after her retirement from the Institute of Tropical Medicine, Nagasaki University, Japan, this Casebook is presented to her in appreciation of her distinguished career as University Professor.

With the publication of this Casebook, FERCAP hopes to provide a useful training material for authors as they tackle ethical issues in the publication of health research.

Atoy M. Navarro
Program Manager, FERCAP

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[5] World Health Organization (WHO), *Standards and Operational Guidance for Ethics Review of Health-related Research with Human Participants*, Geneva: World Health Organization, 2011.

[6] Federation of Animal Science Societies (FASS), *Guide for the Care and Use of Agricultural Animals in Research and Teaching; Third Edition*, Champaign, IL: Federation of Animal Science Societies, 2010.

[7] International Committee of Medical Journal Editors (ICMJE), "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journal," December 2019.

[8] Council of Science Editors (CSE), *White Paper on Promoting Integrity in Scientific Journal Publication*, Wheat Ridge, CO: Council of Science Editors, 2018.

[9] World Association of Medical Editors (WAME), "Recommendations on Publication Ethics Policies for Medical Journals," 2012.

[10] Committee on Publication Ethics (COPE), "Code of Conduct and Best Practice Guidelines for Journal Editors," March 2011.

[11] Carol Kilkenny, William Browne, Innes Cuthill, Michael Emerson & Douglas Altman, "Improving Bioscience Research Reporting: The ARRIVE Guidelines for Reporting Animal Research," *PLOS Biology* 8, Issue 6 (June 2010): 1-5.

[12] International Association of Veterinary Editors (IAVE), "Consensus Author Guidelines on Animal Ethics and Welfare for Veterinary Journals," July 2010.

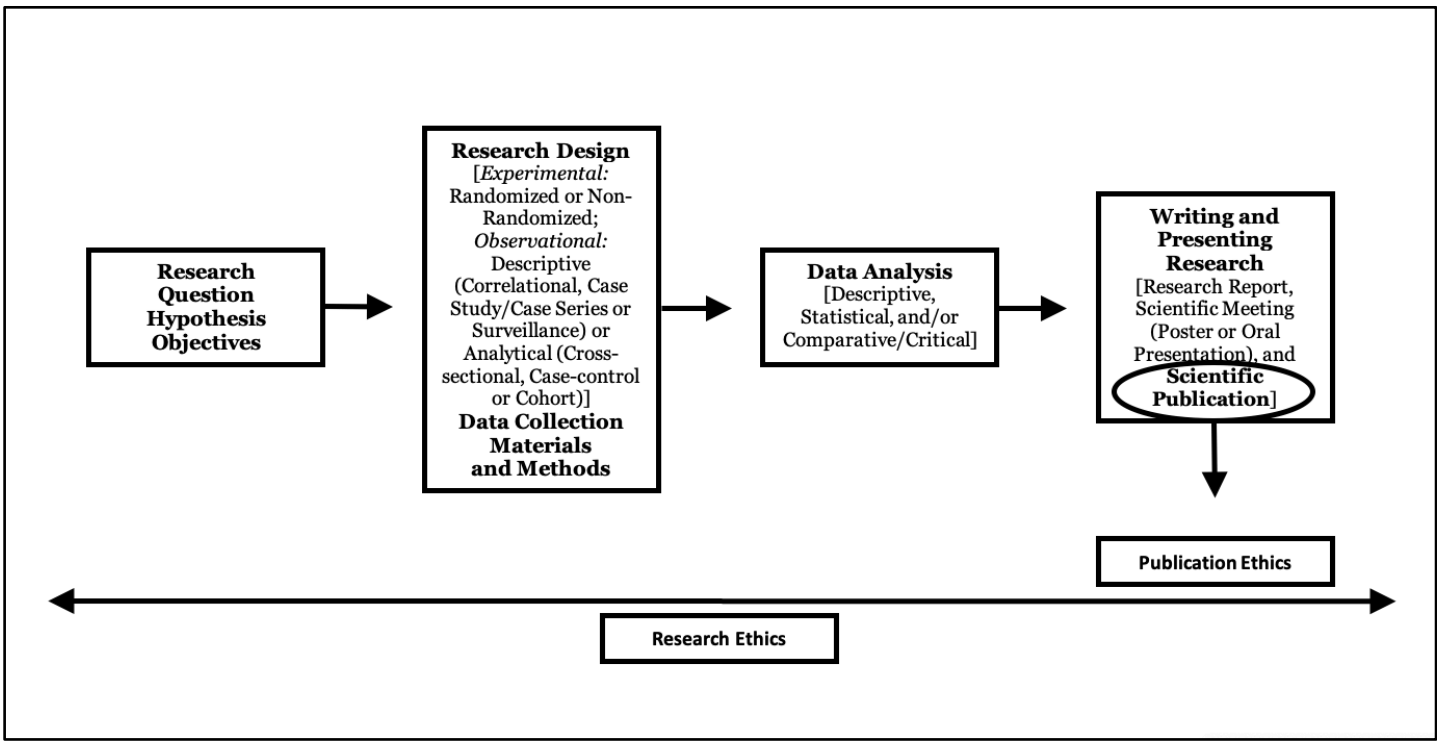

Figure 1. Process from Research to Publication.

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Case Study 1: Thesis Adviser as Author

A dermatology professor, who served as the thesis adviser of a graduate student, published a journal article based on the student's thesis that analyzed the safety and efficacy of using several types of topical herbal cosmetics and remedies. In the article, the professor was designated as the primary author, while the student was listed as the secondary author. The student gave the professor permission to be the primary author of the article. Even though the student was the one who actually implemented the research and wrote the whole article, it was the professor who thought of the topic and even served as the student's thesis adviser. As thesis adviser, the professor gave valuable comments and suggestions in the drafting, revision, and finalization of the article. Both the professor and student agreed to be accountable for all aspects of the article.

Ethical Issues

Considering international ethical guidelines on authorship, answer the following questions:

1. *Does the dermatology professor qualify as author? Explain your answer.*
2. *Does the dermatology professor qualify as primary author? Explain your answer.*
3. *Would you consider the arrangement as described above ethical? Explain your answer.*

Perspectives

In this case, the dermatology professor qualifies as *author* because he/she met all four criteria for authorship: "1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND 2) drafting the work or revising it critically for important intellectual content; AND 3) final approval of the version to be published; AND 4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved."[1] According to the International Committee of Medical Journal Editors (ICMJE), "[a]ll those designated as authors should meet all four criteria, and all those who meet the four criteria should be identified as authors. Those who do not meet all four criteria should be acknowledged.[2]

But the dermatology professor does not qualify as *primary author* since the bulk of the work was done by the student ("the student was the one who actually implemented the research and wrote the whole article"). In this case, the professor can only qualify as *secondary author*.

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[1] International Committee of Medical Journal Editors (ICMJE), "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journal," December 2019.
[2] ICMJE Recommendations 2019.

Overall, the arrangement as described above was unethical. Even though "[t]he student gave the professor permission to be the primary author of the article" (which may highlight the *vulnerability*[3] of the student), the basis for primary authorship should be the quantity and quality of contribution to the article. In line with this, the student should have been the primary author.

[3] World Health Organization (WHO), *Standards and Operational Guidance for Ethics Review of Health-related Research with Human Participants*, Geneva: World Health Organization, 2011; World Medical Association (WMA), "Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects," October 2013; International Council for the Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), "Harmonized Guidance: Integrated Addendum to ICH E6(R1): Guidance for Good Clinical Practice (GCP) E6(R2)," November 2016.

Case Study 2: Group Authorship of a Genome Study with a Deceased Author

A regional genome study on human genetic diversity in Southeast Asia was conducted by a 30-institution consortium. The study revealed that genetic ancestry is associated with geography and ethnolinguistic affiliations, and most Southeast Asian populations are related within ethnolinguistic groups even with widespread gene flow among populations. The study was eventually published as a journal article with the consortium's name, *SEAGen Consortium* as author. All 57 individual authors and their affiliations were listed at the end of the article. No *contributorship disclosure* was provided. Not long after the publication of the article, one of the readers complained that her deceased husband was not listed as one of the individual authors. After consulting with the affiliated institution, *SEAGen Consortium* conceded that the late husband of the complainant qualified as author. The consortium asked the journal for its policy on *deceased authors*. In response, the journal asked *SEAGen Consortium* for a contributorship disclosure and provided them with excerpts of an international ethical guideline on deceased or incapacitated authors.

Ethical Issues

Considering international ethical guidelines on authorship, answer the following questions:

1. *Was the use of SEAGen Consortium as author of the journal article justified? Explain your answer.*
2. *Was contributorship disclosure relevant for this case? Explain your answer.*
3. *What steps can be taken to prevent the exclusion of a deceased author? Explain your answer.*

Perspectives

In this case, *group authorship* was appropriate since "[s]ome large multi-author groups designate authorship by a group name, with or without the names of individuals."[4] For this case, "[a]ll 57 individual authors and their affiliations were listed at the end of the article." This was done because "it can be inaccurate and impossible to list all collaborators"[5] in the byline space. Therefore, group authorship was suitable in this case due to the large number of authors and affiliations.

Regarding contributorship disclosure, the consortium should have properly communicated credit and responsibility for the content of the article. They

[4] ICMJE Recommendations 2019.

[5] Council of Science Editors (CSE), *White Paper on Promoting Integrity in Scientific Journal Publication*, Wheat Ridge, CO: Council of Science Editors, 2018.

should have shown that all those "listed at the end of the article," qualified as authors. The journal for its part should have required this from the very beginning. According to the Council of Science Editors (CSE), "[t]he general aim of contributorship disclosure is to have authors describe, on the basis of a contributor taxonomy created by the journal editors, exactly what each author did during the course of the study from its inception to publication."[6] By having a detailed contributorship disclosure, the deceased author who "qualified as author" can be identified and recognized.

For deceased or incapacitated authors, CSE said that "[f]or cases in which a coauthor dies or is incapacitated during the writing, submission, or peer-review process, coauthors should obtain disclosure and copyright documentation from familial or legal proxy."[7] A contributorship disclosure[8] is also necessary to avoid inadvertently excluding an author. If the late author's wife had not realized the mistake, the article would not have acknowledged the contributions of the deceased author. To prevent such situation from occurring again, a contributorship disclosure should be made mandatory especially since the *SEAGen Consortium* is a "30-institution consortium" where the possibility of unaccounted for authors is much higher.

[6] CSE White Paper 2018.
[7] CSE White Paper 2018.
[8] CSE White Paper 2018.

Case Study 3: Anonymous Authorship of a Study on Young Doctors

An anonymous young doctor working in a public hospital published a journal article on the mental health issues of junior doctors while in residency. Using anonymized questionnaires and online interviews, the qualitative study identified depression and suicides, caused by burnout, emotional exhaustion, and psychological distress, as major mental health issues of junior doctors in public hospitals. Most of the respondents said that these issues were exacerbated by the brutalizing culture of medical training and poor public hospital working conditions. Respondents complained of prolonged working hours, low financial compensation, and discouragement from public hospital administrators to claim overtime pay. In its concluding section, the study criticized the new policy of the National Health Service (NHS) that took away important safeguards that prevent public hospitals from abusing and overworking junior doctors in public hospitals. Reacting to the study, the NHS Director slammed the journal editor for publishing an article with anonymous author. According to the NHS Director, *anonymous authorship* goes against the publication principles of public accountability and transparency. He felt that the NHS was unfairly criticized in the article. Calling for impartiality from the journal, the NHS Director demanded that the journal editor identify the author or retract the article.

Ethical Issues

Considering international ethical guidelines on authorship, answer the following questions:

1. *Was the journal editor justified in allowing anonymous authorship? Explain your answer.*
2. *Was the NHS Director justified in criticizing the journal editor for allowing anonymous authorship? Explain your answer.*
3. *How should the journal editor respond to the demand of the NHS Director? Explain your answer.*

Perspectives

In this case, the journal editor may be justified in allowing anonymous authorship provided that it was clearly established, based on background checks, that the author is credible, and putting the author's name will put the author at high risk (*e.g.* possible NHS retaliation). According to the Council of Science Editors (CSE), "[i]n extremely rare cases, when the author can make a credible claim and attaching his or her name to the document could cause hardship (*e.g.* threat to personal safety or loss of employment), the journal editor may decide to publish anonymous content."[9] However, the journal editor should first conduct a thorough assessment of the article to ensure public accountability of its content and its

[9] CSE White Paper 2018.

author. The impact of the publication to all parties should also be considered prior to its release.

While generally, in the spirit of "public accountability and transparency," "it is not appropriate to use pseudonyms or to publish scientific reports anonymously,"[10] in extremely rare cases, the journal editor may allow anonymous authorship. Such decision should consider existing national regulations on "public accountability and transparency." The NHS Director may be justified in criticizing the journal editor for allowing anonymous authorship if the journal editor was not able to clearly establish that it is indeed an extreme rare case. The NHS Director may also claim that sensitive issues should be reported within appropriate channels instead of being made public as it may cause institutional unrest. The journal should also have clear editorial policies on anonymous authorship. Although the NHS Director may be justified in his criticism, as a public official, he should also be open to policy criticism and respond appropriately.

Instead of identifying the author or retracting the article, the journal editor should ask the NHS Director for a written response to the article which the journal should publish. In line with fostering debate, "[e]ditors should encourage and be willing to consider cogent criticisms of work published in their journal."[11] Also, "[a]uthors of criticized material should be given the opportunity to respond."[12] Therefore, equal opportunities to publish for all parties should be considered by the journal editor as long as these are based on scientific and ethical values.

[10] CSE White Paper 2018.
[11] Committee on Publication Ethics (COPE), "Code of Conduct and Best Practice Guidelines for Journal Editors," March 2011.
[12] COPE Code 2011.

Case Study 4: The Politician and His Researcher: Who is the Real Author?

While employed by a politician, a public health researcher wrote a paper on the major health problems confronting the district represented in Congress by the said politician. With the permission from the researcher, the politician presented the paper in a public health conference. The paper was eventually included in the conference proceedings with the politician as sole author. Soon thereafter, the researcher resigned from the office of the politician after getting a university position as a professor. Facing publish or perish worries in the academe, the researcher published as a journal article the paper she previously wrote for the politician, but this time under her name. She argued that she was the one who actually wrote the paper so she has the right to claim authorship. The researcher did not acknowledge the politician nor cite the conference proceedings where the paper was previously published because according to her, it will only confuse the readers on who the real author of the paper was.

Ethical Issues

Considering international ethical guidelines on authorship, *research*/*scientific misconduct*, and/or *questionable research practices* (QRPs), answer the following questions:

1. *What type of inappropriate authorship was involved in the publication of the paper in the conference proceedings? Explain your answer.*
2. *What type of research/scientific misconduct and/or QRP was committed in the publication of the journal article? Explain your answer.*
3. *Would you consider these publications as ethical? Explain your answer.*

Perspectives

In this case, for the publication of the paper in the conference proceedings, *gift or honorary authorship* and *ghost authorship*—both types of inappropriate authorship, were committed. There was gift authorship because authorship was based solely on a tenuous affiliation to the paper[13] (the politician employed the researcher, who was therefore in a *vulnerable situation*[14]) and authorship was granted as a favor to someone powerful[15] (the politician). There was also ghost authorship[16] (the researcher was the ghost writer) because the "real author" of the paper (the researcher) was not disclosed in the author byline.

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[13] CSE White Paper 2018.

[14] WHO Standards and Guidance 2011; WMA Declaration of Helsinki 2013; ICH-GCP Guidance 2016.

[15] World Association of Medical Editors (WAME), "Recommendations on Publication Ethics Policies for Medical Journals," 2012.

[16] CSE White Paper 2018.

For the publication of the journal article, research/scientific misconduct of *plagiarism*[17] was done because the paper in the conference proceedings as credited to the politician was not cited by the researcher. Plagiarism refers to the "appropriation of another person's ideas, processes, results, or words without giving appropriate credit."[18] But if the researcher is considered the "real author" of the paper in the conference proceedings, QRP of *duplicate and redundant publication* or *self-plagiarism*[19] was perpetuated by the researcher since the journal article overlaps substantially with the paper in the conference proceedings, without clear reference to the latter. Self-plagiarism "usually violates the copyright that has been assigned to the [original] publisher"[20] which "may require permission of the copyright holder."[21]

Both the paper in the conference proceedings and the journal article were unethical publications. Both publications violated international ethical guidelines on authorship, research/scientific misconduct, and/or QRPs.

[17] Office of the Federal Register (OFR), "42 Code of Federal Regulations (CFR) 93.103: Research Misconduct," October 2019.
[18] OFR 42 CFR 93.103 2019.
[19] WAME Recommendations 2012; CSE White Paper 2018.
[20] WAME Recommendations 2012.
[21] CSE White Paper 2018.

Case Study 5: Oversight Failure: Research/Scientific Misconduct?

As the primary author of a journal article that introduced a revolutionary method for creating stem cells, a young biochemist was found to have committed *fabrication*, *falsification*, and *plagiarism*. The article has since been retracted by the journal. Following the retraction, an institutional investigative body ruled that for the article, she reused images from a different paper, manipulated the images of two different gels, and plagiarized parts of the methods section from a different study. But while the young biochemist was found to be guilty of *research*/*scientific misconduct*, a senior researcher, who was the secondary author for the article, was cleared by the institution because he did not have any "direct involvement" in committing the research/scientific misconduct. However, he was found to have "great responsibility" for his failure to provide adequate oversight to the stem cell research.

Ethical Issues

Considering international ethical guidelines on authorship, research/scientific misconduct, and/or *questionable research practices* (QRPs), answer the following questions:

1. *Was the decision on the secondary author justified? Explain your answer.*
2. *Do you think oversight failure constitutes research/scientific misconduct? Explain your answer.*
3. *Who was/were accountable for this publication? Explain your answer.*

Perspectives

In this case, the decision on the secondary author was justified since he did not directly commit research/scientific misconduct—he did not directly commit fabrication, falsification, and/or plagiarism (FFP) in proposing, performing, reviewing, and/or reporting research.[22] Fabrication is "making up data or results and recording or reporting them."[23] Falsification means "manipulating research materials, equipment, or processes, or changing or omitting data or results such that the research is not accurately represented in the research record."[24] Plagiarism refers to the "appropriation of another person's ideas, processes, results, or words without giving appropriate credit."[25] It was the primary author who fabricated data ("reused images from a different paper"), falsified data ("manipulated the images of two different gels"), and plagiarized texts ("plagiarized parts of the methods section from a different study").

[22] OFR 42 CFR 93.103 2019.
[23] OFR 42 CFR 93.103 2019.
[24] OFR 42 CFR 93.103 2019.
[25] OFR 42 CFR 93.103 2019.

Oversight failure (poor supervision of the research) is not research/scientific misconduct, but it falls within QRP which refers to a form of research/scientific misbehavior other than FFP.[26]

Both the primary author and the secondary author were accountable for this publication since accountability is one of the four criteria for authorship ("agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved").[27]

[26] Daniele Fanelli, "The Black, the White and the Grey Areas: Towards an International and Interdisciplinary Definition of Scientific Misconduct," in Tony Mayer & Nicholas Steneck (editors), *Promoting Research Integrity in a Global Environment*, Singapore: World Scientific Publishing Co., Pte. Ltd., 2012, 79-90.
[27] ICMJE Recommendations 2019.

Case Study 6: Questionable Research Practices and Research/Scientific Misconduct in Human Embryonic Stem Cell Research

In two breakthrough journal articles, a veterinarian claimed to have generated human stem cell lines from cloned embryos (therapeutic cloning), creating potential source of versatile, therapeutic cells that would be genetically matched to any patient. But after an investigation by the university research integrity office, it was found out that the veterinarian committed *questionable research practices* (QRPs) and *research/scientific misconduct*. It was exposed that the egg donors received huge payments, and two laboratory members of the research team provided the human oocytes. There was no *informed consent* obtained from the donors as well. Furthermore, four microscopic photographs were duplicated in different panels and designated as different human embryonic stem cell (ESC) lines. Deoxyribonucleic acid (DNA) fingerprint comparison of designated donor and derived human ESC lines did not match and were in fact performed on the same DNA fingerprint profile. In addition, generated ESC lines were destroyed after the research. Because of these findings by the university research integrity office, the journal retracted the two articles. The veterinarian lost his job, and his reputation was forever damaged.

Ethical Issues

Considering international ethical guidelines on research/scientific misconduct and/or QRPs, answer the following questions:

1. *What type of QRPs were committed by the veterinarian? Explain your answer.*
2. *What type of research/scientific misconduct was committed by the veterinarian? Explain your answer.*
3. *What is the difference between research/scientific misconduct and QRPs? Explain your answer.*

Perspectives

In this case, the QRPs committed were *undue inducement* ("egg donors received huge payments"), exploitation of *vulnerable subordinates* ("two laboratory members of the research team provided the human oocytes"), lack of informed consent ("no *informed consent* obtained from the donors"), and improper collection, storage, and use of human biological materials ("generated ESC lines were destroyed after the research"). "[P]ayments should not be so large… as to induce prospective participants to consent to participate in the research against their better judgement or to compromise their understanding of the research."[28]

[28] WHO Standards and Guidance 2011; Council for International Organizations of Medical Sciences (CIOMS), *International Ethical Guidelines for Health-related Research Involving Humans*, Geneva: Council for International Organizations of Medical Sciences, 2016.

With regards to vulnerable subordinates, they are often exploited because they have "insufficient power… to protect their own interests."[29] There should be complete, comprehensible, and freely-given or voluntary informed consent from the donors.[30] There should also be clear "governance system" in the ethical collection, storage, and use of human biological materials and related data in research.[31]

The research/scientific misconduct committed was *fabrication*. Fabrication refers to "making up data or results and recording or reporting them."[32] The veterinarian fabricated data ["four microscopic photographs were duplicated in different panels and designated as different embryonic stem cell (ESC) lines" and "[d]eoxyribonucleic acid (DNA) fingerprint comparison of designated donor and derived ESC lines did not match and were in fact performed on the same DNA fingerprint profile"].

Research/scientific misconduct means *fabrication*, *falsification*, and/or *plagiarism* (FFP) in proposing, performing, reviewing, and/or reporting research[33] while QRPs refer to forms of research/scientific misbehavior other than FFP.[34]

[29] WHO Standards and Guidance 2011.
[30] WHO Standards and Guidance 2011; WMA Declaration of Helsinki 2013; ICH-GCP Guidance 2016; CIOMS Ethical Guidelines 2016.
[31] CIOMS Ethical Guidelines 2016.
[32] OFR 42 CFR 93.103 2019.
[33] OFR 42 CFR 93.103 2019.
[34] Fanelli 2012.

Case Study 7: Conflict of Interest and Falsification in Publication?

A biochemical engineer published a journal article that reanalyzed government data used in a previous paper that showed no correlation between measles-mumps-rubella (MMV) vaccination timing and autism incidence. For his article, he reanalyzed the previous study's case control data as a cohort data. Instead of employing conditional logistic regression as used in the previous paper, Pearson's chi-squared test was utilized. He concluded that there's an elevated risk of autism for the male population of an ethnic minority group who received the MMR vaccine prior to 24 months or 36 months of age. The article was heavily criticized and was retracted by the journal which argued that the biochemical engineer did not fully disclose his *conflict of interest* which compromised the peer review process. To review his article, the biochemical engineer recommended a colleague from *Combat Autism*, an antivaccine foundation. Issues were also raised about the validity of his study design and statistical analysis. The biochemical engineer disagreed with the decision of the journal. He argued that although he did not disclose that he has an ongoing court case claiming vaccine injury for his son, he did declare in the article that he has been "involved in vaccine litigation." In the article, he also acknowledged *Combat Autism* for funding his research. Regarding the reviewer, he vouched for the expertise of his colleague and placed the blame squarely with the journal for not choosing a different reviewer. Finally, regarding his study design and statistical analysis, he insisted that analyzing the data differently is the essence of reanalysis.

Ethical Issues

Considering international ethical guidelines on conflict of interest, *research*/*scientific misconduct*, and/or *questionable research practices* (QRPs), answer the following questions:

1. *Do you agree with the biochemical engineer that his declaration of conflict of interest was adequate? Explain your answer.*
2. *Who was/were accountable for compromising the peer review process? Explain your answer.*
3. *Would you consider inappropriate study design and misuse of statistics as examples of falsification? Explain your answer.*

Perspectives

In this case, although the biochemical engineer declared in the article that he has been "involved in vaccine litigation," it was inadequate since he has clear personal and professional interests in autism. He should have disclosed that he has an "ongoing court case claiming vaccine injury." He should have disclosed as well that he works ("colleague") at/with *Combat Autism* which is funding his research. This is especially important since *Combat Autism* is "an antivaccine

foundation." As author, the biochemical engineer was "responsible for disclosing all relationships and activities that might bias or be seen to bias his work."[35]

Both the biochemical engineer and the journal were accountable for compromising the peer review process. While the biochemical engineer should not have recommended "a colleague from *Combat Autism*," the journal has the responsibility to ensure that reviewers don't have conflicts of interest. Journal editors are "accountable for everything published in their journals."[36] They should "ensure that peer review in their journal is fair, unbiased and timely."[37]

Inappropriate study design ("reanalyzed the previous study's case control data as a cohort data") and misuse of statistics ("Pearson's chi-squared test was utilized" which does not consider all matching factors as covariables and allows more confounders) are not examples of *falsification*, which refers to "manipulating research materials, equipment, or processes, or changing or omitting data or results such that the research is not accurately represented in the research record."[38] Inappropriate study design and misuse of statistics fall within QRPs.[39]

[35] ICMJE Recommendations 2019.
[36] COPE Code 2011.
[37] COPE Code 2011.
[38] OFR 42 CFR 93.103 2019.
[39] Fanelli 2012.

Case Study 8: Animal Cruelty in Research

A group of biomedical researchers published a journal article on the association between depression and variations in gut microbiota. By using a chronic variable stress (CVS)-induced depression rat model, the researchers were able to show that gut microbiota was altered in association with fecal metabolism in depressive conditions. Without showing the details of the sample size calculation, the researchers used 48 healthy male Wistar rats (24 rats in the experimental group and 24 rats in the control group) for the study. After the article was published, members of the *3Rs International*, a non-governmental organization (NGO) dedicated to promoting ethical treatment of animals in research, filed a complaint with the journal and asked the journal to retract the article. The complainants argued that there were too many rats used and that the treatment of the rats in the experimental group was too cruel. The rats received several "stimuli" every day for 28 days. The rats were exposed to loud sounds or stroboscopic lights, forced to swim in ice cold or hot water, received multiple electric shocks within a minute, and denied food or water for 48 hours. There was also incomplete reporting of this *in vivo* experiment. In response to the complaint, the researchers, without showing their sample size calculation process, explained that the use of a high number of rats was necessary to achieve their scientific objectives. They also said that their institution's human research ethics committee (HREC) reviewed and approved their study. They also followed the reporting requirements of the journal. Satisfied with the response from the researchers, the journal did not retract the article.

Ethical Issues

Considering international ethical guidelines on animal research, answer the following questions:

1. *Was the use of a high number of rats by the researchers necessary? Explain your answer.*
2. *Was the approval of the study by the human research ethics committee appropriate? Explain your answer.*
3. *Do you agree with the journal in their decision not to retract the article? Explain your answer.*

Perspectives

Without showing the sample size calculation process [based on power analysis that depends on the "(1) effect size of interest, (2) standard deviation…, (3) chosen significance level, (4) chosen power, (5) alternative hypothesis, (6) sample size"[40]], it is difficult to determine if the use of a high number of rats was necessary. Although the researchers specified the "total number of animals used

[40] Michael Festing & Douglas Altman, "Guidelines for the Design and Statistical Analysis of Experiments Using Laboratory Animals," *ILAR Journal* 43, Number 4 (2002): 244-258.

in each experiment and the number of animals in each experimental group"[41] ["48 healthy male Wistar rats (24 rats in the experimental group and 24 rats in the control group)"], they did not "[e]xplain how the number of animals was decided"[42] and they did not "[p]rovide details of any sample size calculation used."[43]

The researchers should have submitted their study to "an active Institutional Animal Care and Use Committee (IACUC)"[44] for review and approval. While approval from an HREC may also be required in some instances (HREC and IACUC are merged in some institutions), a clear IACUC approval is paramount. IACUC ensures the humane use of animals in order to avoid animal cruelty in research as described in the study.

Since the study was not clearly reviewed and approved by an IACUC,[45] did not adhere to the guidelines for the design and statistical analysis of experiments using laboratory animals,[46] and did not comply with the guidelines for reporting animal research,[47] the journal should have retracted the article. It was not enough to follow the "reporting requirements of the journal," the researchers should have complied with international ethical guidelines for reporting animal research[48] that are guided by the "3Rs" framework: *Replacement*, *Reduction*, *Refinement*.[49] "Animals should be *replaced* by less sentient alternatives… Experimental protocols should be *refined* to minimize any adverse effects for each individual animal… The number of animals should be *reduced* to the minimum consistent with achieving the scientific objectives of the study…"[50] Further guidance on animal research ethics is available from the International Association of Veterinary Editors (IAVE).[51]

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[41] Carol Kilkenny, William Browne, Innes Cuthill, Michael Emerson & Douglas Altman, "Improving Bioscience Research Reporting: The ARRIVE Guidelines for Reporting Animal Research," *PLOS Biology* 8, Issue 6 (June 2010): 1-5.
[42] Kilkenny *et al*. 2010.
[43] Kilkenny *et al*. 2010.
[44] Federation of Animal Science Societies (FASS), *Guide for the Care and Use of Agricultural Animals in Research and Teaching; Third Edition*, Champaign, IL: Federation of Animal Science Societies, 2010.
[45] FASS Guide 2010.
[46] Festing & Altman 2002.
[47] Kilkenny *et al*. 2010.
[48] Kilkenny *et al*. 2010.
[49] William Moy Stratton Russell & Rex Leonard Burch, *The Principles of Human Experimental Technique*, London: Methuen, 1959.
[50] Festing & Altman 2002.
[51] International Association of Veterinary Editors (IAVE), "Consensus Author Guidelines on Animal Ethics and Welfare for Veterinary Journals," July 2010; ICMJE Recommendations 2019.

Case Study 9: Inclusion of Actual Names in Publication

A social science researcher published a journal article on the perceptions of national athletes regarding common sports-related health issues that they face and the effectiveness of the national government's delivery of health services addressing these issues. The article included the actual names of high-profile and popular retired national athletes that were interviewed for the study. The researcher obtained written informed consent for publication from the national athletes according to national laws and regulations. The national athletes were also shown the manuscript before publication. The researcher hoped that with the inclusion of the actual names of the national athletes, sports-related health issues will receive better attention from the national government and other sports stakeholders.

Ethical Issues

Considering international ethical guidelines on *privacy*, answer the following questions:

1. *Was the inclusion of the actual names of national athletes justified in this case*? *Explain your answer.*
2. *When is the inclusion of actual names in published work justified? Explain your answer.*
3. *In what situations can you consider national athletes as vulnerable? Explain your answer.*

Perspectives

In this case, the inclusion of actual names of national athletes was justified since the study met the criteria for the disclosure of identifying information: 1) Essential for scientific purposes; AND 2) participant (or parent or guardian) gave written informed consent for publication; AND 3) identifiable participant was shown the manuscript to be published; AND 4) local laws and regulations were followed with respect to the receipt and archiving of written *informed consent*.[52]

The inclusion of actual names in published work is only justified when it meets all four criteria for the disclosure of identifying information.

National athletes are considered as *vulnerable* since their dependence on the national government may affect their decision-making.[53] Such dependence may also "increase the likelihood of being wronged"[54] by the national government. Compared to the national government, they have "insufficient power… to protect

[52] ICMJE Recommendations 2019.
[53] ICH-GCP Guidance 2016.
[54] WMA Declaration of Helsinki 2013.

their own interests."[55] If the national athletes are critical of the national government in their interviews, they might receive a retaliatory response from the national government. For active national athletes, the national government may not select them for national and international competitions and/or their government salaries may be withheld. For retired national athletes, their government pensions and other benefits may be withheld. In these situations, national athletes are considered as vulnerable.

[55] WHO Standards and Guidance 2011.

Case Study 10: Reporting Ethical Approval of an International Health Research

A group of post-graduate biomedical students from the United States of America (US) undertook a university sponsored study on the incidence, prevalence, and control of dengue in one of the Association of Southeast Asian Nations (ASEAN) countries. The students were able to publish in an international journal using publicly available government data on the epidemiology of dengue in the ASEAN country. After the publication of the article, the National Health Research Ethics Committee (NHREC) of the ASEAN country discussed in the article pointed out to the journal that the study did not secure any ethical approval. Because of this concern, the journal editor called the attention of the students. In response, the students said that they only obtained permission to use the government data from the National Dengue Agency (NDA) of the ASEAN country discussed in the article. They did not submit their study to an institutional review board (IRB) in the US and in the ASEAN country (which they did not disclosed in the article), because according to US regulations, as a secondary research, their study is exempt from ethical review. For their study, the students recorded the data of anonymized human participants. They also said that they did not think they needed ethical review since the journal does not have clear reporting instructions on ethical approval.

Ethical Issues

Considering international ethical guidelines on ethics committee review, answer the following questions:

1. *Does the study require ethical review from an IRB in the US and in the ASEAN country? Explain your answer.*
2. *Should the journal editor consider retraction of the journal article because of lack of ethical approval? Explain your answer.*
3. *In the future, should the journal editor refuse the publication of articles that do not report ethical approval? Explain your answer.*

Perspectives

In this case, the study does not require ethical review from an IRB in the US because it falls under "secondary research for which consent is not required,"[56] which is exempt from ethical review. Data were recorded by the students "in such a manner that the identity of the human subjects cannot readily be ascertained directly."[57] While "[s]ome studies may be exempt from review,"[58] exemption "depend[s] upon the nature of the research and upon applicable law or

[56] Office of the Federal Register (OFR), "45 Code of Federal Regulations (CFR) 46.104: Exempt Research," October 2019.
[57] OFR 45 CFR 46.104 2019.
[58] CIOMS Ethical Guidelines 2016.

regulations."[59] As stated in the US Code of Federal Regulations (CFR), this policy does not affect any foreign laws or regulations and therefore this study has to comply with local law or regulations.[60] With regards to ethical review in the ASEAN country, if the ASEAN country does not allow exemption or requires a certificate of exemption, the students should have applied for ethical approval or ethical review exemption. This is especially important since "[i]n externally sponsored research, ethical review must take place in both the host and the sponsoring institution,"[61] unless the study qualifies for an exemption from ethical review.

Related to this, the International Committee of Medical Journal Editors (ICMJE) recommends that "[a]ll authors should seek approval to conduct research from an independent local, regional, or national review body."[62] Given such premise, the journal editor may consider retraction if the ASEAN country does not allow exemption or requires a certificate of exemption. But if the regulations on exemption from ethical review of the ASEAN country are similar with US regulations, a correspondence letter explaining these regulations should be published in the journal.

The journal should first develop clear reporting instructions on ethical approval ("the journal does not have clear reporting instructions on ethical approval"). It has been shown that ASEAN journals with clear reporting standards had a higher percentage of articles that adequately reported ethical approval.[63] Once these reporting standards are in place, the journal can advocate the importance of reporting ethical approval by enforcing these reporting standards and refusing the publication of articles that do not report ethical approval.[64]

[59] CIOMS Ethical Guidelines 2016.
[60] OFR 45 CFR 46.104 2019.
[61] CIOMS Ethical Guidelines 2016.
[62] ICMJE Recommendations 2019.
[63] Junjira Laothavorn, Pantipa Wongwai, Shyam Prakash Dumre, Panida Kongjam, Kesara Na-Bangchang & Juntra Karbwang, "Ethical Approval and Informed Consent Reporting in ASEAN Journals: A Systematic Review," *Current Medical Research and Opinion* 35, Number 12 (2019): 2179-2186.
[64] Laothavorn *et al*. 2019.

Case Study 11: Retrospective Ethical Approval and Retrospective Clinical Trial Registration

Several readers sent a number of concerns about a journal article on a multinational, randomized, double-blind, Phase 2a study of Drug ABC in pulmonary hypertension patients. The concerns sent to the journal were largely around retrospective ethical approval and retrospective clinical trial registration of the study. Because of these concerns, the journal editor conducted a comparison of the national clinical trial registry record of the study and the published paper. The journal editor found several inconsistencies. The trial received national ethical approval in April 2018, as reflected in the documentary submission of the corresponding author, but the article stated that the execution of the study was from August 2017 to July 2019. On the other hand, the trial registration materials were first submitted in May 2018 but were only posted at their national clinical trial registry system in December 2018.

Ethical Issues

Considering international ethical guidelines on ethics committee review and clinical trial registration, answer the following questions:

1. *Should the journal editor consider retraction of the journal article because of retrospective ethical approval? Explain your answer.*
2. *Should the journal editor consider retraction of the journal article because of retrospective clinical trial registration? Explain your answer.*
3. *Is a national registry for clinical trials adequate for this study? Explain your answer.*

Perspectives

In this case, the journal editor should retract the journal article because of retrospective ethical approval. According to the Declaration of Helsinki, "[t]he research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins."[65] This means that "research should be subject to prior ethical review."[66] Furthermore, independent ethics review is essential to ensure that research participants exercise their right to self-determination and adequate protection of their welfare are in place during the implementation of the research (*i.e.* privacy[67]).

As for the retrospective clinical trial registration, the journal editor may consider retraction of the journal article if the inconsistencies are not adequately explained. While it should be clear that "[e]very research study involving human subjects must be registered in a publicly accessible database before recruitment

[65] WMA Declaration of Helsinki 2013.
[66] WHO Standards and Guidance 2011.
[67] ICMJE Recommendations 2019.

of the first subject,"[68] it is not clear in the study when the first subject was actually recruited. Although the article stated that "the execution of the study was from August 2017 to July 2019," the recruitment of the first subject might have occurred before "May 2018." With regards to "the substantive delay between the submission of registration materials and their posting at the trial registry"[69] ("May 2018" vs. "December 2018"), the journal editor "may inquire about the circumstances that led to the delay."[70] If the responses to the journal editor's queries are satisfactory, a correspondence letter explaining the retrospective clinical trial registration should be published in the journal.

While the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) and ClinicalTrials.gov are preferred,[71] a national registry for clinical trials is adequate as long as it is "publicly accessible"[72] and "include[s] the minimum 24-item trial registration dataset… at the time of registration and before enrollment of the first participant.[73] It is critical that clinical trials are duly registered to ensure public accountability of clinical research.[74] This also serves as a platform and an opportunity for potential human participants to engage in ongoing clinical trials.[75]

[68] WMA Declaration of Helsinki 2013.
[69] ICMJE Recommendations 2019.
[70] ICMJE Recommendations 2019.
[71] ICMJE Recommendations 2019.
[72] WMA Declaration of Helsinki 2013; ICMJE Recommendations 2019.
[73] ICMJE Recommendations 2019.
[74] CIOMS Ethical Guidelines 2016.
[75] ICMJE Recommendations 2019.

Case Study 12: Post-Publication Data Sharing

A group of biomedical researchers would like to replicate the findings reported in a journal article based on a multinational, randomized, double-blind, Phase 3 study of Drug XYZ in human immunodeficiency virus (HIV) patients with pulmonary tuberculosis. Through the journal editor, they asked the corresponding author of the article for some raw data including randomization codes, information about confounders, numbers of concomitant drug use, and amount of CD4. The corresponding author denied the request of the researchers saying that the pharmaceutical company that sponsored the study refused to provide the raw data requested. The corresponding author relayed to the journal editor that the sponsor wants to protect commercially confidential information and their intellectual property against competitors. The journal editor reminded the corresponding author that the authors signed a data sharing agreement with the journal. In response, the corresponding author said that while they would like to adhere to the signed agreement, they don't have control over their sponsor.

Ethical Issues

Considering international ethical guidelines on data sharing, answer the following questions:

1. *What are the different author considerations in data sharing? Explain your answer.*
2. *Was the refusal of the pharmaceutical company to share data justified? Explain your answer.*
3. *Should the journal editor consider retraction of the journal article because of refusal to share data? Explain your answer.*

Perspectives

Authors should consider the privacy and informed consent of the study participants as well as having a data sharing agreement that is cleared not only with the authors but also with their institutions and sponsors. The information in a data sharing agreement should mention to whom the data are shared and under what specific conditions they are shared. In addition, the institution should appoint an independent panel to review any data sharing request. According to the Council for International Organizations of Medical Sciences (CIOMS), "[w]hen sharing data, researchers must respect the privacy and consent of study participants."[76] The Council of Science Editors (CSE) adds that "[a]uthors should be aware of their data sharing responsibilities imposed by their funding agencies… authors should consider where they will submit their data and should consider the journals they may want to submit their study and review the data sharing policies for each journal."[77] The goal of data sharing policies is "making data used for scholarly

[76] CIOMS Ethical Guidelines 2016.
[77] CSE White Paper 2018.

research available to other investigators" in order to "promote reproducibility and availability of underlying data sets."[78] This builds up transparency that increases public trust in research results because these results can be independently verified. Further guidance on data sharing policies is available from the International Committee of Medical Journal Editors (ICMJE).[79]

In this case, the refusal of the pharmaceutical company to share data was not justified. While it is understandable for the sponsor to "protect commercially confidential information and their intellectual property against competitors," the pharmaceutical company also has a responsibility to "share information about and data from past research."[80] "Data sharing requires careful balancing of these competing considerations."[81] The sponsor should contribute to "a culture of responsible data sharing and mutually reinforcing incentives for sharing."[82] The sponsor may ask for a data sharing agreement to mitigate risks of data sharing by controlling with whom the data are shared and under what specific conditions they are shared, without compromising the scientific usefulness of the shared data and to request for additional privacy protections beyond de-identification and data security.

The journal editor should retract the journal article because of refusal to share data. This is in line with international ethical guidelines on research[83] and publication[84] as well as the journal's own policies on data sharing ("the authors signed a data sharing agreement with the journal"). In particular, ICMJE also requires that clinical trials "must include a data sharing plan in the trial's registration."[85]

[78] CSE White Paper 2018.
[79] ICMJE Recommendations 2019.
[80] CIOMS Ethical Guidelines 2016.
[81] CIOMS Ethical Guidelines 2016.
[82] CIOMS Ethical Guidelines 2016.
[83] CIOMS Ethical Guidelines 2016.
[84] ICMJE Recommendations 2019; CSE White Paper 2018.
[85] ICMJE Recommendations 2019.

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