Responsible Research Practices to Learn from Cases

– A Casebook to Instill Awareness and Learning –

Japan Agency for Medical Research and Development

AMED

Introduction

Research is the act of developing a new system of knowledge by adding the research results onto the history of science built by the efforts of many predecessors. In other words, if we cannot guarantee responsible conduct of research, it will not only distort the history of science and undermine the trust in science as a whole that had been built up with effort, but also significantly damage public trust in scientists.

Hence, code of conduct for researchers states that researchers not only have a duty to comply with the laws and regulations, but to also conduct responsible research with high ethical standards. All who are involved in scientific research need to have a thorough understanding of what responsible research is.

This casebook is to serve as an effective educational material that can be utilized in researcher-participation educational programs (such as a discussion format), by introducing practical cases on research misconduct, bioethics violation, and conflict of interest that have been recorded in Japan and the rest of the world, and presenting the issues and problems. In addition, this casebook is not complied just for researchers; it also aims to provide excellence in education on responsible conduct of research in research institutions, as well as serve as a reference for those in charge of improving the research environment and for those in the position to judge whether the act was a research misconduct or not, by deliberating and discussing various types of practical cases and their responses.

There is an old saying of “Wise men learn by other men’s mistakes, fools by their own”. But it is too late for those who was judged as engaging in research misconduct to learn from their mistakes. It is my earnest desire that through this casebook, all who are involved in research will become wise persons who learn from the mistakes of others and carry out responsible research.

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1. What is research misconduct?

Research misconduct is defined as fabrication, falsification, and plagiarism in various countries around the world with the acronym of FFP.

In Japan, the Ministry of Education, Culture, Sports, Science and Technology (MEXT) has also formulated a new "Guidelines for Responding to Misconduct in Research" (hereinafter "new Guidelines") in August 2014, which defined FFP as specific research misconduct. The new Guidelines defined the specific research misconduct in research as follows. However, note that this does not mean that the other kinds of research misconduct are justifiable.

3. Responding to Specific Research Misconduct

1. Applicable types of misconduct in research, etc.

The research activities, researchers, and misconduct to which this section applies are as follows.

(omission)

(3) Applicable misconduct (specific research misconduct)

The misconduct to which this section applies is the fabrication, falsification, or plagiarism of data or research findings, etc., indicated in a submitted research paper or other published research results (hereinafter "specific research misconduct"), either willfully or due to gross neglect of the basic duty of care expected of a researcher.

(a) Fabrication

Making up data or research results, etc.

(b) Falsification

Manipulating research materials, equipment, or processes to change data or results obtained from research activities.

(c) Plagiarism

Appropriating the ideas, analysis, analytical methods, data, research results, research paper (s), or words of other researchers without obtaining the permission of the researchers or giving appropriate credit.

"Guidelines for Responding to Misconduct in Research", Ministry of Education, Culture, Sports, Science and Technology, page 11 (adopted on August 26, 2014)

Fabrication and falsification are explained in “For the Sound Development of Science –The Attitude of a Conscientious Scientist–” (Japan Society for the Promotion of Science Editing Committee “For the Sound Development of Science”) (hereinafter, “Green Book”) as follows.

> Fabrication and falsification are fundamentally serious acts of betrayal against the very objective of scientific research: to pursue truth. One must recognize that such acts cause society to lose its trust in the scientific community, potentially even affecting the health and safety of the people. This type of misconduct wastes the time, efforts, and research funds of other scientists who try to replicate an experiment under the assumption that the data published by the scientist is trustworthy. When one scientist announces a new idea, other scientists try to verify and validate that result as well as to advance the idea together, even further. Fabrication and falsification are, therefore, acts that undermine the foundation of the community of scientists who, even while competing with one another, strive to work together to amass research advances toward the progress of science.

Japan Society for the Promotion of Science Editing Committee “For the Sound Development of Science”, “For the Sound Development of Science –The Attitude of a Conscientious Scientist–”, May 31, 2015, Maruzen Publishing Co., Ltd.(hereinafter “Green Book”) , page 54.

Plagiarism is explained in Green Book as follows.

> Research presented by an author is his or her original work, and it is assumed that all its contents, i.e. information, ideas, and sentences, are those of the author. “Plagiarism” is an act that betrays this trust. Plagiarism is one type of false authorship; it suggests a lack of the ethical character “honesty” of the infringing scientist and is a serious violation of occupational ethics. Plagiarism can lead to a penalty as a violation of the Copyright Act.

Green Book, page 54.

1.1 Examples of fabrication and falsification

Case I-1: Fabrication of experimental results

A whistleblower complaint was filed about the suspicion of duplicated images in papers on genetic analyses on uterine and ovarian cancers that were published over the last ten years by Lecturer A of the Department of Obstetrics and Gynecology at Faculty of Medicine, University X. After this allegation, Lecturer A made a self-assessment that he found image duplication in his 22 papers. University X then set up an investigative committee to conduct investigation into the papers that were mentioned in the self-assessment, as well as 77 other papers where Lecturer A was listed as either the author or coauthor.

The investigative committee judged that Lecturer A had fabricated the data in 19 papers as there were no objective evidence such as materials or documents to prove that the reported experiments were really conducted. In addition, they confirmed that experiments were actually conducted for the remaining papers, but determined that data was falsified in two papers as there were discrepancies between the materials and the papers. Out of a total of 21 papers judged as engaging in research misconduct, Lecturer A was listed as the first author for two and corresponding author for 19 papers. Some of these papers were highly cited and even published in internationally renowned scientific journals in cancer research.

The investigative committee identified the following background that have invited the research misconduct.

- **Significant lack of moral responsibility for researchers**
  The investigative committee identified 94 parts of research misconduct, and this alarming number implies that misconduct was usual act for Lecturer A. Lecturer A also exhibited a complete lack of awareness of the code of conduct for researchers, as evident in destroying laboratory notebooks and materials and falsifying data in the preparation of manuscripts.

- **Excessive competitive rivalry**

  Since scientists are evaluated by accumulating the number of their publications and their impact factors nowadays, Lecturer A focused on how to produce papers more efficiently rather than to pursue scientific truth under the extreme pressure to "publish or perish".

- **Environment and system not favorable for detecting research misconduct**

  Most of the papers judged as engaging in research misconduct were submitted as manuscripts without being checked by other researchers. Lecturer A had also committed such misconduct for the last ten years, and his manuscripts were not cross-checked by other researchers in the same department or his co-authors.

Explanation

In this case, the research misconduct that had been ongoing for over ten years brought moral responsibility of Lecturer A into question. A Declaration on "Measures to Prevent and Deal with Research Misconduct: Toward the Healthy Progress of Science" issued by the Science Council of Japan noted the duties of researchers as follows.

> Science and scientific research exist both with and for society. Therefore, research activities based on scientific freedom and the subjective judgments of scientists only gain social recognition once they are premised upon public trust and the mandate of the people. Therefore, in order for science to contribute to realizing a more affluent human society through its own sound growth and development, there is a need for researchers to establish ethical norms to strictly control their own conduct. Hence, scientists always have to make judgments and act with honesty and integrity, endeavoring to maintain and improve their own expertise, abilities and skills, and have to make the utmost effort to scientifically and objectively demonstrate the accuracy and validity of the knowledge they create through scientific research.

The Science Council of Japan, Declaration on "Measures to Prevent and Deal with Research Misconduct: Toward the Healthy Progress of Science", page 1 (December 26, 2013)

Questions

The investigation report points out that research misconduct by Lecturer A may have far-reaching implications in the broad field of cancer research.

1. What kind of implications do you think research misconduct have?
   - On researchers themselves
   - On coauthors
   - On laboratories or affiliated institutions
   - On research field or society as a whole

Case I-2: Data fabrication and falsification due to lack of awareness of misconduct

In October 2013, a university received an insider complaint alleging that there was research misconduct in papers involving Professor A. The university set up an investigative committee to look into the 90 papers that were published by Professor A between 2004 and 2011, and found evidence of research misconduct in four papers regarding molecular reaction in stress-induced cells.

The results of the investigative committee indicated that data falsification was found in one paper with Professor A as the first author, as well as two cases of fabrication and one case of falsification in three other papers with Professor A as the corresponding author, where the images of certain bands and lanes were manipulated and the aspect ratios were altered. The investigative committee judged that these were intentionally committed by Professor A, as it involved a too complicated process to assume that they were caused by accidents or errors. The committee also confirmed that these acts of misconduct did not affect the results reported in the papers.

Professor A subsequently admitted to the investigative committee that he had committed these acts of misconduct alone and explained that he had "wanted to make the images clearer" and did not think that "it was a misconduct". The committee also found that the other first authors only used the images as instructed by Professor A, and were cleared of their involvement in the misconduct.

The investigative committee concluded that Professor A manipulated the images so as to clarify the logical reasoning, get his papers accepted by internationally renowned scientific journals, and boost his research achievements.

Explanation

As indicated in the new Guidelines, the applicable types of misconduct include fabrication, falsification, and plagiarism that arose "either willfully or due to gross neglect of the basic duty of care expected of a researcher".

In this case, Professor A was not aware that his acts were construed as misconduct; the misconduct was therefore caused by a “gross neglect of the basic duty of care expected of researcher”.

Questions

1. Professor A insisted that he did not regard his act as research misconduct. What kind of problems do you think he has as a researcher?

Case I-3: Fabrication and falsification of experimental results

A complaint was filed in April 2015 with an institution where Researcher A was working on regenerative abilities of dental pulp stem cells, alleging that some of the data published in a paper with Researcher A as the first author were cut and pasted. The affiliated institution investigated and identified misconduct in the paper.

Researcher A explained that he/she did not think that it was a problem since the image was processed in order for readers to fully understand the contents of the paper. Since the image processing did not affect the experimental results, Researcher A recognized it unnecessary to mention it in the paper. The image was processed as follows.

- In the RT-PCR images, some parts on the left of the gel were cut and moved to the right;
- A large number of non-specific bands were removed.

When the investigative committee of the affiliated institution asked Researcher A to submit the laboratory notebooks and original data, they found that the images posted on the paper were different from the original data. Moreover, for an experiment that was said to be performed three rounds in the paper, the investigative committee could only confirm two rounds in the laboratory notebooks, and no new materials or documents were submitted. The investigative committee also subsequently discovered that Researcher A did not perform the claimed experiment but added experimental results produced elsewhere.

The investigative committee judged that the data had been fabricated and falsified because Researcher A could not provide enough evidence due to sufficient basic materials to overturn the allegation of misconduct. The investigative committee also pointed out that such research misconduct occurred because Researcher A lacked the basic knowledge about the evaluation method of experimental results that researchers should have.

Explanation

It is said that as to research misconduct practiced in the field of life sciences most of them are fabrication or falsification of data by manipulating electrophoretic images (e.g.

removing or cutting and pasting specific bands, or using images from different experimental results). Scientists should understand the rules on handling digital images so as to avoid exciting suspicions on their research results.

Questions

In this case, Researcher A processed the digital images of the experimental results so that readers could easily understand the experimental results.

1. What are the points to consider when processing digital images to make the experimental results clearer? (What kind of processing would not be problematic, and how is it accountable?)
2. Is it fine to process the data if it does not affect conclusions of the paper? If not, explain why.

Case I-4: Plagiarism, fabrication, and falsification of data from other papers

Professor A and Associate Professor B were studying the functions of insulin-like proteins using mice models, and conducting research that would contribute to hair growth, anti-aging, and improvement of cognitive functions. In March 2011, the university received allegations from an outside whistleblower of image plagiarism and falsification in their research activities.

Investigative committees were set up both at their currently affiliated university X and their formerly affiliated university Y. The investigative committee in University X confirmed that images were falsified and plagiarized from other papers in eight of their papers—six were written as the first author by Associate Professor B, and two by their then-students. The investigative committee in University Y also confirmed plagiarism, fabrication, as well as falsification of data in ten papers—all were written as the first author by their then-students. The corresponding author of all these misconducted papers was Professor A.

Associate Professor B maintained throughout the investigations that he accidentally used what he had tentatively created while writing up the papers, but the investigative committees judged his statements as unreliable. Professor A commented on these acts of misconduct by saying: “I know nothing”. While the investigations did not turn up any evidence of direct involvement of Professor A in the misconduct, he was the only person engaged in all these papers. As the same image was used in the papers that listed Professor A as the corresponding author, the investigative committees also concluded that it was unlikely for Professor A to be unaware of the misconduct, and he should be called to account the responsibility for his supervision.

Explanation

The scope of sanctions for specific research misconduct prescribed in the new Guidelines applies to all research activities carried by funding from the MEXT budget or by special budgetary measures. In addition to imposing sanctions prescribed by the affiliated institutions, research funding organization would also impose penalties (e.g. return of

competitive funds) and restrictions on applications for competitive funding and eligibility to receive such funding.

In this case, the measures and penalties would apply to authors who bear prime responsibility for content of any research paper(s) connected with the research in which specific research misconduct was identified, authors found to have been committed in specific research misconduct, and persons who were not authors of any research paper(s) but who were found to have been involved in the specific research misconduct,

1.2 Examples of plagiarism

Case I-5: High degree of similarity in English phrases led to verdict of plagiarism

Associate Professor A at a pharmaceutical university submitted a manuscript to Journal P that listed himself as the first author, Assistant Professor B as the corresponding author, and Professor C (department head) as well as six other graduates and graduate students as coauthors. The manuscript was accepted and published in March 2012.

In July 2013, 16 months after the paper was published, Company E (publisher of Journal P) informed Associate Professor A of an allegation that some text may have been lifted from a 2004 paper published by the same author (Associate Professor A) in Journal D. While Company E accepted originality of the paper in defense of Associate Professor A, the complainant Journal D was not convinced due to the high degree of similarity in the English phrases in both papers. Then, Associate Professor A retracted the suspected paper from Company E to settle with Journal D in September 2013.

Although the two companies had come to an agreement, the paper was not retracted immediately. In April 2014, an article about plagiarism of Professor A from his/her own paper was posted on the Internet. The university then set up an investigative committee to examine the paper published in Journal P that listed Associate Professor A as the first author. The investigation revealed that Associate Professor A did not think that he/she was self-plagiarizing or recycling his/her own text; he/she asserted that he/she wrote the paper based on the insights and knowledge he/she had gleaned, which unfortunately led to a high degree of similarity in the text between the new and old papers. The investigative committee had confirmed the originality of the data of the new paper, but judged that the extremely high degree (more than 90%) of conformity with the paragraphs in the old paper published in Journal D clearly indicates a recycling of large proportions of text. They concluded that even if the text was recycled from own paper, it still fell under the definition of plagiarism, and was an act of research misconduct.

Explanation

In this case, Associate Professor A only focused on the originality of his/her paper and was indifferent to the possibility of plagiarism of the English text. Once we can utilize online search, it becomes easier to lift (copy and paste) ideas and text from papers that are uploaded or posted on websites. This is why some undergraduates and graduate students carelessly lift some sentences or text verbatim.

However, as a number of software services to detect plagiarism become popular, lifted or copied parts in manuscripts are now more easily identified. Some research institutes have even installed such software for scientists to check their manuscripts for potential plagiarism before submission.

Case I-6: Plagiarism from a master thesis of student

In June 2015, the contents of a single-authored paper of Professor A published in a scientific journal was alleged to be plagiarized and falsified since it was remarkably similar to the master thesis of a graduate supervised by Professor A.

Upon the receipt of this allegation, the university conducted a preliminary investigation and set up an investigative committee to analyze (compare and check) both the paper in question and the master thesis. At the same time, the investigative committee conducted interviews with the persons involved and Professor A, along with a written inquiry. The results of the investigation showed that Professor A had clearly plagiarized the master thesis and falsified the suspected paper that Professor A had supposedly wrote.

The argument and numerical data in the suspected paper and the master thesis were almost the same. In total, 373 lines from 31 parts in the master thesis as well as three lines from two parts in its draft submitted to Professor A were plagiarized.

In addition, the graduate single-handedly collected and analyzed the data for the master thesis. Yet Professor A submitted the manuscript as a single-authored, original paper, despite the fact that he/she did not substantively committed to the research.

The investigative committee also confirmed that Professor A had changed the study period in the suspected paper, and discovered discrepancies in the conclusion based on the results of the original multiple regression analysis; Professor A had deleted the results of the most important regression analysis published in the master thesis from the paper, and created a diagram based on the results of the correlation analysis instead.

The investigative committee determined that Professor A did not only respect the hard work that the master student put into the master thesis, but also ignored the rules of authorship on publishing research results. Professor A asserted that he/she had plagiarized the thesis of the student and published it as own original work in the interest for the public so that the research findings could be made available to all. The committee also judged that Professor A not only strayed from the standards of responsible conduct of research expected to researchers, but also committed ethical violation and lost his credibility as an educator whose duty was to provide research guidance to graduate students.

Explanation

In this wicked case, Professor A plagiarized the idea and research data from the master thesis and the corresponding draft of the student. Despite the fact that the student single-handedly collected and analyzed the data for own research, Professor A modified some of the results from the original analyses and deceitfully published it as an original paper of Professor A.

Green Book drew attention in the explanation of plagiarism as follows.

> In experimental research, a different type of problem exists: not citing sources of published papers when documenting materials and methods used in one's own experiments. Furthermore, original sources should be cited not only when using someone else's original description but also when adding changes and modifications to original descriptions.
>
> (omission)
>
> When citing sources, a scientist must clearly specify which parts belong to him/her, the author, and which parts belong to other scientists.
>
> At times only citing a source is not sufficient. For example, suppose scientist A uses, without modification, a paragraph written by another author, scientist B, citing him only as reference. In this case, B is properly credited for the content, but the reader does not know whether the entire paragraph belongs to scientist A or B. When using just a part of some other scientist's paragraph without modification, the author must use quotation marks or different margins and clarify the source so that it will be obvious whether or not the entire paragraph belongs to another scientist.

Green Book, page 55.

Questions

1. While it is clear that copying or lifting of multiple parts of other papers as if they are one's own descriptions without proper referencing or citation is plagiarism, what are the other cases to be regarded as plagiarism?

   For example, are the following acts considered plagiarism?

- No description of the source of previous research.
- Recycling of contents or data from one's own papers without clear citations.
- Publishing papers in Japanese that were previously published in English (or vice versa)

2. Data collection, management, and processing

2.1 Data and its significance

Case I-7: Data falsification caused by a lack of awareness of the importance of control experiments

In August 2012, the Medical Center of University Y in the United States submitted an allegation of research misconduct against Lecturer A (from University Hospital X in Japan) regarding the falsification of data in five papers based on the research performed at University Y. In the allegation, the Medical Center was asked for the retraction of these five papers as they confirmed that the data was intentionally falsified.

Upon the receipt of this allegation, University X set up an investigative committee and identified that a total of 18 digital images (including the eight images stated in the allegation) were plagiarized and falsified in ten papers—the suspected five as well as the other five. The investigation further revealed that Lecturer A participated in misconducts in the processing of 11 images in four papers.

The investigative committee confirmed that the experimental results (electrophoretic images) in the three papers, in which Lecturer A was listed as the first author and one paper as the corresponding author, were published using experimental results in the same paper or from other paper by Lecturer A. The committee also identified cut-and-paste, vertical flipping, and enlargement of 12 images. Lecturer A recognized that all of these acts were conducted single-handedly.

At a hearing, Lecturer A explained that he/she had conducted control experiments but the obtained image data were mixed up, and that he/she was unable to find the correct data when preparing the manuscripts. Lecturer A therefore resorted to “using the data from other experiments”. However, when the investigative committee checked the raw data, they could not find the data of all the control experiments that were supposed to be conducted for the main experiments. The later testimony suggested that Lecturer A did not realize the necessity of a control experiment for each experiment. The investigative

committee pointed out that Lecturer A falsified the data because he/she did not recognize the importance of control experiments.

Explanation

In this case, the investigative committee judged that lack of awareness of the importance of control experiments led Lecturer A to falsify data.

The importance of data is explained in Green Book as follows.

> To assure the reliability of data in scientific research, one must make sure
> (1) that the data are obtained based on appropriate methods,
> (2) that the data collection does not involve intentional wrong-doing or mistakes due to negligence, and
> (3) that the data obtained are properly stored and their originality is maintained.
>
> With the exception of few special circumstances, the quality of all scientific research is determined upon the assumption that the "data" were obtained using the utmost care and rigor available at the time. Accordingly, scientists must handle "data" with integrity in every phase of their research activities.
>
> Collection of data differs depending on the research field, theme, objective, and other factors, so the procedures established for handling them in one's own field of specialization should be followed. However, at least in research involving experiments, there are some common factors on "record-keeping and the strict handling of research and investigation data." … (omission)

Green Book, page 45.

Questions

Accumulating experimental data in the appropriate procedure in daily research activities helps you to produce a highly reliable paper.

1. Does your laboratory provide guidance on experimental procedure as well as the handling and management of data?
2. Do you understand the appropriate experimental procedure, and the handling and management of data? Are you able to put them into practice as well?

3. Do you know how to appropriately handle data at the overseas institution where you are going to study, or have studied?

Case I-8: A case judged as misconduct because of lack of evidence

In March 2011, a university received a document alleging that some of the data in a paper (Paper 1) published by Assistant Professor A as the corresponding author in Journal A of the American X Association may have been fabricated or falsified. The university set up an investigative committee to look into the other publications that listed Assistant Professor A as the corresponding author, and confirmed that some of the data reported in two other papers (Paper 2 and Paper 3) published in Journal B and Journal C of the American X Association may also have been fabricated or falsified. In addition to hearing from the persons involved in these papers, the investigative committee also examined the records of the lab equipment, investigated whether there was any misconduct involved in his earlier papers, scrutinized the laboratory notebooks (that would form the basis of the paper) and the data, and checked whether any public research funds were used.

As a result of the investigation, the data reported in Paper 1 and Paper 2 did not match the data recorded in the laboratory notebooks of Assistant Professor A and technical assistants; some of the data in the papers were not found from laboratory notebooks of Assistant Professor A. By checking the lab equipment record, the committee also discovered that Assistant Professor A did not use the equipment, and the data used for the papers did not exist. Furthermore, even the data in the laboratory notebooks, to be served as evidence for conduct of experiments, was also falsified.

As to Paper 3, the investigative committee could not find any evidence of the paper from the laboratory notebooks of Assistant Professor A and the technical assistants. Assistant Professor A did not express that the data was not fabricated or falsified while explaining that all the evidence data had been deleted from his/her computer and it is impossible to replicate the experiment. As there was no evidence of these papers, Assistant Professor A could not dispel the suspicion of research misconduct.

According to a hearing from his/her coauthors, Assistant Professor A mostly wrote up the papers by himself/herself, and that the coauthors were not involved at all in the data creation for these three papers. In addition, the technical assistants only submitted the experimental data under the instructions of Assistant Professor A, and did not read or

check the manuscripts before submission.

Explanation

In this case, the suspicion of misconduct was not wiped out since Assistant Professor A was unable to show the evidence of his/her papers; the contents of the laboratory notebooks of Assistant Professor A and the technical assistants did not match the data reported in the papers; the data reported in the papers were not found from his/her laboratory notebooks.

The significance of data in scientific research is obvious, and we should guarantee the reliability of data as described earlier (page 45 of Green Book).

Questions

1. What are the important points to note in conducting day-to-day research activities so as to protect yourself in the case of unlikely allegations of misconduct?

2.2 Organizing laboratory notebooks

Case I-9: A case judged as misconduct because laboratory notebooks and raw data were not stored

A scientific society received a suspicion from overseas researchers that it is unable to replicate the experiments described in a paper on ribonucleic acid controlling the function of genes authored by Professor A and others. In April 2005, the scientific society requested the university to investigate the reproducibility of 12 papers in which Professor A and others were involved. The first author of all 12 papers was Research Assistant B.

The university set up an investigative committee to look into the reproducibility and reliability of these papers from a scientific standpoint. The committee selected four papers which were relatively easy to verify the reproducibility of the experimental results and requested Professor A to present the experimental records and other documents. However, the investigative committee discovered that Professor A did not store the laboratory notebooks and raw data for many of the suspected papers, and was unable to verify the reliability of the experimental results.

The investigative committee gave an opportunity to Professor A to dispel the suspicion of his/her misconduct. They requested Professor A to redo the experiments using the same experiment materials and samples as described in his/her papers, and to submit the results and experimental protocols in detail by a certain deadline. Although Professor A was given ample time to redo the experiments, he/she was unable to reproduce the same experimental results as reported in his/her papers even after the deadline.

In the course of the investigation, the committee also discovered that some of the raw data submitted for the experiment contained obviously fabricated data. Although Professor A claimed that there was an error in the paper, it soon became apparent that it was not possible to construct the hDicer expression vector with his/her resubmitted protocol and DNA primers. The investigative committee also revealed the possibility that the experiment materials may have never existed in the first place at all.

In a separate investigation conducted by another research institute with which Professor A and Research Assistant B were engaged, almost none of the research records for the

papers where Research Assistant B was listed as the first author were stored. Neither Professor A nor Research Assistant B could submit materials or documents to systematically support the experimental results of the papers. Furthermore, it was revealed that Research Assistant B had never discussed the raw data with Professor A (the corresponding author) in the process of writing up the papers; both researchers also gave different explanations on how to create the research materials. The investigative committee therefore judged both Research Assistant B and Professor A as engaging in research misconduct.

Note: In this case, the titles were described as they were used for the positions at that time. The updated titles are as follows.

Old “Research Assistant” → Now “Assistant Professor”
Old “Assistant Professor” → Now “Associate Professor”

Explanation

When conducting scientific research, researchers need to organize and store objective materials and data so as to fulfill their responsibility to objectively explain the validity of their papers. In this case, both Professor A and Research Assistant B neglected their responsibility and did not organize or store objective laboratory notebooks and raw data. The investigative committee concluded that the papers, in which the results could not be reproduced from replicating the experiments, were fabricated by both Professor A and Research Assistant B.

The purpose of lab notes is explained in Green Book as follows.

> In experimental fields, data are generally recorded in the so-called "lab notes" (sometimes referred to as research notes or experiment notes). Well-maintained lab notes that contain data and ideas recorded in an appropriate manner serve at least three crucial roles. First, they prove that the research has been conducted fairly and properly. Second, when the research produces a result, the lab notes can prove its originality. Third, they make the data and ideas transparent in the laboratory and in the research group, serving as a tool for sharing and effectively applying the data, i.e., a tool for "knowledge management."
>
> (omission)
>
> In conducting responsible research activities, one needs to understand that lab notes are an indispensable tool and to establish and implement related rules after discussing them among the entire research group, including joint researchers (check the policies of affiliated institutions if they already have such policies).

Green Book, pages 45-46.

For further reference, the purposes of recording in lab notes by the National Institutes of Health (NIH) in U.S.A. are also described in Green Book

Case I-10: Laboratory notebooks with insufficient information

In January 2014, Researcher A – who was working on pluripotent stem cells research at a leading cutting-edge research institute in the field of embryology – published a paper claiming they were able to reprogram blood cells from mice into pluripotent stem cells by merely subjecting them to stress; the results showed the expression of the Oct-4 reprogramming gene, where the newly reprogrammed pluripotent stem cells glowed green. The media went frenzy over the findings of this groundbreaking paper, which was reported all over the world.

However, just two weeks after the publication, it was reported that there were several electrophoretic images in the new paper looked like the images in an earlier paper written by Researcher A three years ago, but vertically flipped (the investigative committee judged that the contrast of the images was adjusted so that the cut-and-paste traces would not be visible), as well as there were many reports by other scientists that they were unable to reproduce the results. In addition, there were other allegations that Researcher A had used about 20 lines from a paper published by a research team in Country X without citation (Researcher A explained "I had forgotten to do so"), and that an image posted on the new paper was extremely similar to an image of a teratoma found in the doctoral thesis of Researcher A submitted three years ago (Researcher A explained "I added the wrong image by mistake"). One of the coauthors eventually asked for the paper to be retracted.

The investigative committee further found that Researcher A had almost lifted about 20 pages of text from the website of a research institute in the United States in its entirety and used it in the doctoral thesis of Researcher A.

Three months after this groundbreaking publication, the investigative committee published their investigation report, which stated that they had found evidence of misconduct and concluded that the digital images in the paper were falsified and fabrication. Researcher A commented that judgement of misconduct by the committee was unacceptable and asserted that mistakes were innocent errors.

Researcher A subsequently attempted to replicate the experiments but was unable to reproduce the pluripotent stem cells. In addition, when another research institute

performed genome analyses on the said pluripotent stem cells, they found that it was contaminated with ES cells; the paper was eventually retracted. The question of why the samples were contaminated with ES cells remains today, and inadequate laboratory notebooks of Researcher A could not provide the answer.

Explanation

In this case, it still remains unknown as to why the samples were contaminated with ES cells. The fact that the experiments were conducted without the awareness of such a severe issue (sample contamination) is problematic. Some of the contents of laboratory notebooks recorded by Researcher A were reported by press, and their sloppy descriptions were pointed out.

Excellent lab notes are explained in Green Book.

According to F. L. Macrina, et. al., useful lab notes are those in which the scientist has clearly recorded

(1) what was done, why, how, and when it was done,
(2) where the experiment materials and samples are kept,
(3) what phenomena occurred (or did not occur),
(4) how the scientists interpreted the facts,
(5) what the scientists will do next.

The best lab notes are stated to be (1) easy to read, (2) well organized, (3) recorded accurately without omission, (4) contain information sufficient for replication, (5) satisfy the requirements set by funding agencies and affiliated institutions, and (6) properly stored so that only authorized personnel can see them, and duplicates are made in case something should happen to the original notes. Macrina et. al. conclude that lab notes are the "record that will ultimately validate the scientific contributions you have made."

Green Book, pages 46-47.
For further reference, specific examples of items to record and methods of recording are described in Green Book.

Questions

1. Does your research group have rules on record and storage of laboratory notebooks? Have you also received any sort of instruction on this?

2. Do you keep writing experiment note appropriately? If not, why? How can these issues be resolved?

Case I-11: Research misconduct arising from personal mismanagement of experiment- and research-related materials

In February 2011, both University X where Associate Professor A belonged to at that time and University Y where Associate Professor A previously belonged to received allegations that 66 pieces of data (such as "several images in the same paper are suspected to have been copied from another experiment" and "there are traces of images being patched up with a software") in ten papers authored by Associate Professor A, whose expertise were molecular biology and food functional chemistry, were fabricated and falsified.

In light of these allegations, both universities set up separate investigative committees and cooperated with each other in their investigations. Their investigation results revealed that in the suspected ten papers and one another paper, there were at least 66 inadequate acts, in which the resulted images obtained from one experiment were presented as different experimental results. In detail, the investigative committees identified that the 66 images were derived from the same digital image or the same experiment, 27 of which were manipulated by means of cut-and-paste, horizontal and vertical flipping, and enlargement. Furthermore, 35 and nine of the 66 images were respectively images of more critical than those used for control experiments, and of important control experiments that affected the contents of the paper.

Associate Professor A admitted that he/she played a central role in the creation of the images. He/She explained that he/she had posted the wrong experimental results in the papers by mistake but was unable to resubmit the correct ones to the committees as he/she had lost the data. As he/she was unable to submit most of his/her experimental records, the investigative committees judged that he/she had fabricated the experimental results and fraudulently published these papers.

At the laboratory of Professor B in University Y where Associate Professor A had worked as Assistant Professor, each faculty member was basically engaged in education and research independently, and responsible for managing the experiment- and research-related materials. As Associate Professor A (then Assistant Professor) was also in charge of creating figures and illustrations, and writing and submitting manuscripts, Professor B was held responsible for his supervision.

Explanation

In this case, Associate Professor A did not submit the experimental results and experimental records that he conducted. Storage of laboratory notes is explained in Green Book as follows.

> Fundamentally, lab notes do not belong to an individual; they are considered to belong to the institution (e.g. research institution) that provides the research environment and funding. Therefore, they should be managed appropriately in accordance with the rules of that institution. Where the institution does not have a dedicated department or office that stipulates management rules, it is necessary for the principal investigator to initiate an effort to create such an office and to establish management rules by discussing them with the members of the research group. In institutions where the research members come and go frequently, such as universities, it will be necessary to create a management system that also includes training of new members. Particularly close attention should be given if the research involves data containing personal information. Access to the lab notes should be limited, and the notebooks should be kept in a locked cabinet. On the other hand, if the research is done by a team, the progress of the research could be hindered if the members' access to the data is severely limited. Therefore, discussion with the team members is necessary to obtain an appropriate balance.
>
> As discussed above, lab notes are extremely important to scientists as a record of the experiments and research they have conducted. These notes are more than just an intellectual compilation of their own research processes and ideas. As lab notes can provide validation and evidence after a paper is presented, each research institution must establish policies on the method and duration of their storage.

Green Book, pages 48, 50.

3. Authorship

3.1 Authorship and responsibility

Case I-12: Submitted manuscripts without checking with coauthors

Between July and August 2006, multiple coauthors of two papers that listed Professor A – who was highly respected in the field of DNA replication in Japan and overseas – as the corresponding author, made the following allegations:

- Professor A submitted the manuscripts without notifying the coauthors or giving them an opportunity to check the final version of the manuscripts.
- The papers contain data fabricated or falsified by Professor A.

Upon receipt of these allegations, University X set up an investigative committee to examine the publications, laboratory notebooks, raw data, e-mail records, and electronic files submitted by the persons involved, and to conduct interviews with them.

Regarding Paper 1, Professor A submitted the manuscript without showing the first author the final version of the manuscript; the other coauthors were not even aware that this happened until they found the published electronic version. As the coauthors pointed out that the data published by Professor A was very problematic and requested for paper retraction, Professor A contacted the editor-in-chief of the journal and asked for the retraction.

As to Paper 2, Professor A did not share with his coauthors the revised version of the manuscript before the submission, nor inform them of the revised points. The coauthors pointed out that data fabricated by Professor A may have been used in the revised manuscript, and subsequent investigations confirmed their suspicions.

In the laboratory of Professor A, many visiting staff came in and out. and ratio of graduate students and international students were high. On top of this, he was extremely busy with going overseas and running laboratories of other universities at the same time. He seldom had his students and younger researchers work on the same research theme or project consistently; when necessary, they would be asked to share collection of the data required. This system meant that only Professor A was privy to the overall structure of the

research, and he/she was the one who drafted the manuscripts right from the beginning. Moreover, because the first authors or coauthors transferred to other positions oftentimes when starting preparation of manuscripts, Professor A had to take the lead in these cases without sufficient contact or communication with the coauthors.

The investigation report indicated that Professor A was extremely sensitive to competition in research; he/she did not pay much attention to verifying details, but rather was focused on creating a convincing narrative that would logically draw the desired conclusions of his/her research. The report also stated that Professor A strongly wanted to avoid any disadvantage from a delay in publication of his/her papers. The investigative committee concluded that this, coupled with his/her neglect in verifying details and conducting the corresponding experiments, might have led Professor A to commit such acts of research misconduct.

Explanation

While the data fabrication is a critical issue here, it is also problematic that Professor A did not check with the first authors or coauthors before manuscript submission.

The duties and responsibilities for authorship are explained in Green Book as follows.

> Authorship is accompanied by duties and responsibilities. Authorship also implies that the writer guarantees that the research is free of errors and falsehoods and is of good quality. In other words, it is a guarantee that the presentation of responsible research results has met all the relevant standards (omission). In other words, authorship implies responsibility to meet requirements that are “not as easy as one might anticipate.” Disclosing any conflict of interest on the part of the author is also necessary to achieve that purpose.

Green Book, page 72.

Questions

The research competition in the field of life sciences is cut-throat. Professor A was overly sensitive to the disadvantage arising from the delay in publishing papers. This led him/her to fabricate the data, and to submit the final and the revised versions of the manuscripts

without checking with the first authors and coauthors. In light of these facts, it is without doubt that Professor A had disregarded the duties and responsibilities for authorship.

1. If you are asked to be a coauthor of a paper, do you understand the obligations and responsibilities that you have to fulfill?
2. More specifically, how would you go about fulfilling those responsibilities?

3.2 Who should be the authors?

Case I-13: Fabrication of paper that misused and exploited names of coauthors

In July 2011, a university received an investigation request from an overseas journal which alleged that Associate Professor A, who had published over 200 original papers in more than 40 Japanese and international academic journals for 19 years, might have fabricated his/her papers. The university asked Associate Professor A to resign as they discovered that research for eight of his papers were conducted without the approval of the ethics committee. However, the suspicions about fabrication by Associate Professor A deepened since several journals in overseas continued to publish editorials on his research fabrication.

Taking these circumstances seriously, Scientific Society Y set up an investigative committee to examine 212 original papers published by Associate Professor A and conducted interviews with him/her and 15 coauthors. They set out to verify the reproducibility of the data posted in the papers that was based on the raw data submitted by Associate Professor A and the coauthors. In addition, the committee accessed the Anesthesia Information Management Systems from the three medical institutes that Associate Professor A used to work in, as well as reviewed the anesthesia records, number of cases by surgery types for each medical institution, number of cases conducted by Associate Professor A by surgery types, animal experiment protocols, records of retrieval of dogs from the animal experiment centers, records of retrieval of poisonous substances, and reviews of the ethics committees. The investigative committee also checked the number of subjects listed on the papers against the actual number of human and animal subjects, the usage records of the drugs purportedly used in the research, as well as the reliability of the experimental conditions (such as double-blinded studies) based on the testimonies of the human subjects.

The investigative committee confirmed that only the first three papers published were valid as the research was actually conducted on real animals and patients. However, they discovered that 172 papers were fabricated by reason that the number of subjects, experimental conditions, or records of drugs administration did not match that of the papers. Most of other papers were entirely fabricated; none of the subjects were real, no

drugs were administered, and no research was ever actually being conducted. The investigations report stated that "papers were produced from idea of Associate Professor A at a desk as if it had been writing a novel."

The investigations report submitted by the scientific society provided several reasons as to why Associate Professor A was able to continue with such research misconduct for 19 years.

(a) He/She did not specify details such as the dates of the studies and the names of the institutions where they were conducted, and conveyed the impression that the research was conducted at his/her previous workplaces.

(b) He/She listed co-authors at other institutions (although he/she had submitted most of the manuscripts without their consent).

(c) Many of the cover letters for the papers submitted were not signed by the co-authors, or signed as allographic.

While some coauthors were not even aware of these fabricated publications, some knew but leave them, and others even agreed to "lend" their names each other so as to increase their list of research achievements.

Explanation

In this case, Associate Professor A continued to publish hypothetical experimental results in his papers for many years. Despite the fact that many coauthors were listed on his/her papers, one of the possible reasons as to why Associate Professor A was able to commit such misconduct so many times is that the coauthors did not fulfill their obligations and responsibilities. The investigation report submitted by the scientific society further stated that Associate Professor A chose scientists who were not very interested to be listed as coauthors; even if they were listed as coauthors without their consent, they would not be suspicious or complain about it.

What are the criteria for a qualified person to be listed as a coauthor? They are explained in Green Book as follows.

Given the responsibilities of authorship, whose names should be listed as the authors of a paper is an extremely important question. Obviously, anyone who has made an important contribution to the research reported in the paper is entitled to be listed as an author, while those who did not are not so entitled.

The International Committee of Medical Journal Editors (ICMJE) has drawn up uniform requirements for manuscript submission, which stipulate the following four criteria for one to be listed as a paper author.

(1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work;
(2) Drafting the work or revising it critically for important intellectual content;
(3) Final approval of the version to be published;
(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.

These are the conditions that must be satisfied to be eligible for authorship; conversely, people who satisfy all of these conditions must be listed as authors.

People who do not satisfy these conditions are to be, for instance, included in the "acknowledgements." A person who was only involved in acquiring research funding, supervising a research group, or doing overall coordination does not satisfy the requirements of authorship. It is appropriate for such persons to be included in the acknowledgements.

Green Book, pages 72-73.

4. Laboratory management

4.1 Matters to consider in laboratory management

Case I-14: Research misconduct caused by excessive competitiveness and inappropriate guidance system

Suspicions were raised on the internet about images posted in papers published by Professor A, who was a world-renowned researcher in nuclear hormone receptor research. In January 2012, the university received a complaint alleging that Professor A was engaged in paper fabrication.

Research institute of the University conducted a preliminary investigation on a total of 165 papers that either listed Professor A as the corresponding author or laboratory members of Professor A as the first author when Professor A was affiliated with the university, and suspected misconduct in 60 of them. Then, the investigative committee of the university proceeded with their investigations on these 165 papers. They examined the results of the preliminary investigation, verified the digital images that were suspected to be fraudulent, and conducted interviews with the persons involved.

The investigative committee confirmed that 51 papers published in scientific journals contained incorrect images. They investigated 193 authors and judged that a total of 11 authors were involved in the fabrication and falsification of images or figures: Professor A (principal investigator), Assistant Professor B, Project Lecturer C, Associate Professor D, and seven others who were listed as first authors on these papers.

There were three research groups in the laboratory of Professor A, where most of them were working under the leadership of Assistant Professor B and Project Lecturer C, who were supervised by Professor A since they were graduate students. In the report, Assistant Professor B and Project Lecturer C insisted that the environment in the lab was one of "absolute compliance to Professor A", where one was "unable to refuse or say no, but had to try to meet his/her excessive demands and expectations". None of the other group members led by researchers from other universities were working with Assistant Professor B and Project Lecturer C, and were found to commit research misconduct.

Professor A created a culture in his/her laboratory where excessive pressure was placed on its members to publish papers in internationally renowned scientific journals, and then

to produce experimental results that would be consistent with or support such publications. The investigative committee also revealed that Assistant Professor B and Project Lecturer C – who played central roles in managing the laboratory of Professor A – as well as Associate Professor D, provided inappropriate guidance such as sloppy checking and handling of data, set schedules that were not feasible, and gave coercive instructions and directions to students over a long period of time at a particular research group.

Explanation

In this case, the acts of research misconduct that happened in the laboratory of Professor A – once recognized as a world-renowned researcher in his field of research – was due to the inappropriate culture and environment that placed an extreme emphasis on producing results. Assistant Professor B, Project Lecturer C, and Associate Professor D, who played central roles in managing the laboratory of Professor A, have provided inappropriate guidance, set unreasonable schedules, and gave coercive instructions to their students over a long period of time.

The responsibilities of the principal investigator are listed in Green Book as follows;

- responsible for ensuring that all procedures are carefully followed according to various ethical policies and guidelines.
- responsible for managing personal information, data, and intellectual properties.
- responsible for achieving the project's goals (obtaining the desired results) while carrying out the research according to its plan as much as possible

The other responsibilities are also explained.

In most research projects, at some stage a problem or an unforeseen situation will occur, and whenever this happens, the hypothesis or research method may be modified. Meanwhile, graduate students and young scientists may be doing research under tremendous pressure because they are required to produce a certain level of work, such as giving a presentation at a conference or publishing a journal article, within a fixed period of time in order to receive a degree or get a job. If joint research with a company is carried out, the company may try to find results that can be immediately applied to a patent. The principal investigator is required to conduct the research with a comprehensive understanding of all these demands and financial implications.

When research is conducted as a team, often the members will include young researchers and graduate students. The principal investigator needs to be aware that his/her conduct on the team can have a powerful influence on them, including influence in an educational sense. While it is important to maximize the research results of the team, the principal investigator should recognize that publishing a paper is not the only result/goal to be sought, but that fostering principled scientists and building a sound environment for scientific research are also honorable outcomes. Hence, the principal investigator should refrain from excessively rushing or pushing the team members.

Green Book, pages 60-61.

Questions

1. What actions do you think you should take if you are being forced to comply with unreasonable demands? Do you know who you should consult or check with?

4.2 Research guidance

Case I-15: Research misconduct caused by a lack of guidance on the rules for research practice

In May 2013, MEXT and University X received a formal complaint alleging that Professor A had committed misconduct in his research on pharmacological actions in genetically modified animals. As some of the papers mentioned in the complaint were written by Professor A when he was affiliated with University Y, both University X and University Y conducted a joint investigation on works of Professor A.

The investigative committees of both universities examined over 200 papers and identified acts of misconduct (such as fabrication and falsification) in ten papers. Most of these papers listed Professor A as the corresponding author, and members of the research group presided by Professor A at University Y (five graduate students and one researcher) as the first authors.

The investigative committees judged that the first authors were directly involved in the research misconduct found in these papers and commented on their "significant gross neglect of the basic duty of care in the creation of papers which led to such acts of misconduct like fabrication as a result". The committees did not accept their excuse of oversight since "there were no raw data, and there is no rational explanation for plagiarizing other images even if the raw data did exist", and explicitly stated that they were "extremely responsible" for their acts of research misconduct.

Explanation

In this case, the investigative committees indicated that these acts of research misconduct happened because Professor A did not provide sufficient guidance on the rules required in writing papers. The committees further stated that because Professor A neglected his duties in providing the guidance required and performing the checks that he should had, his research group members were extremely careless in data management and the creation of figures and images, which in turn created an environment where they could easily

fabricate, manipulate, and plagiarize images that led to the occurrence of these acts of misconduct.

Questions

1. Do you understand what are the rules formulated in your laboratory or research institute?
2. Are you conducting research according to the formulated rules? If not, what is preventing you from doing so?

Case I-16: Inadequacy of research progress management

Professor A and his colleagues at a laboratory famous for obesity research published a paper in an American medical journal in October 2004, where they genetically engineered mice in which the expression of obesity-related enzymes was suppressed. They reported that the mice decreased weight and that their blood sugar levels were lowered, and alluded that this enzymatic suppression might lead to treatment for lifestyle diseases such as diabetes. The first author of this paper was Student C in the Faculty of Medicine, who was in charge of the actual experiment.

Several months later, a researcher in the same university raised suspicions about the existence of the genetically engineered mice that were reported in the paper. In response to this, the university set up an investigative committee, which then confirmed that Student C had fabricated data. He/She excused that he/she was not able to reproduce the experiment since he/she no longer had the mice used in the experiment, and he/she also did not keep any laboratory notebooks. The investigative committee also discovered that data in several other papers authored by Student C was suspected to have been fabricated or falsified.

Up till then, Student C was an active researcher with several English publications under his/her belt, and was regarded as a rising star with great potential in his/her field of research. Although the experiment was conducted under the guidance of Professor B who was an expert in developmental engineering, investigations revealed that Student C had conducted experiments without training in recording laboratory notebooks or basics of experimental techniques.

Explanation

The investigative committee concluded that the causes of this case were the inadequate guidance and supervision provided by Professor A and Professor B and pointed out as follows;

“If (Professor A and Professor B) had personally checked the research capability (experimental ability) of the student and circumstances of the research by their own eyes,

and joint guidance such as discussing the raw data was conducted, they would have had enough opportunities halfway through the research and during the revision of the manuscript to realize that the data was actually fabricated, and be able to prevent the student from fabricating it. In the first place, they should have been more careful about the research progress as researchers,"

5. Prevention of research misconduct and whistleblowing

Case I-17: A case of a researcher accused three times

A university received three separate allegations that Professor A – who specializes in pharmacology – had violated the responsible conduct of research and committed research misconduct such as falsification and fabrication in 27 papers that listed Professor A either as the first or the corresponding author. The university set up an investigative committee with each allegation received, and through investigations on the incriminated papers and interviews with the persons involved, it confirmed that Professor A had committed misconduct (such as data falsification) and engaged in unfavorable behavior in multiple papers.

The investigation on the first allegation received in December 2009 identified errors in the contents of the incriminated papers and concluded that Professor A had falsified the data.

Investigation on the second allegation received in May 2012, however, did not reveal or turn up any acts of research misconduct. When the third allegation was made in December 2013, the university reinvestigated and confirmed that different experimental data and images were used in two papers, data of control animals were used in seven different papers but yet not cited in subsequent papers, and data was reused in five papers. These investigations confirmed that experimental data was inappropriately handled in papers that listed Professor A as the first author as well as papers that listed a number of his graduates as the first authors. In the end, seven papers were retracted.

Explanation

What actions should be taken if one discovers potential fraudulent acts or behaviors? They are explained in Green Book as follows.

When there is misconduct suspicion or behavior, only scientists can recognize it, so as scientists they need to deal with and correct the situation. As a place of contact for such scientists, research institutions need to establish a contact desk where research misconduct can be reported. Organizations that provide research funds, such as MEXT and JSPS, also have contact desks. When at a research site one encounters a situation where misconduct is suspected, ideally one should first bring it to the attention of a member of that research team or discuss it with other researchers. However, there are cases where such an action may be difficult to take, and may not work to resolve the issue. In such a case, one should not just leave the problem unresolved but should at least consult with the person at the contact desk.

Green Book, page 122.

Questions

1. Are you aware of the specific actions you need to take if you suspect that misconduct has been committed during your research activities?
2. Who you can consult with when you find research misconduct in practice? If you have none, why?

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Ⅱ Cases with questionable research practices

1. What is conflict of interest and how to manage it
2. Ethical issues in clinical studies: Human subjects protection and informed consent etc.
3. Reliability in research data and research reproducibility issues

1. What is conflict of interest and how to manage it

"Conflict of interest" is currently a matter of some concern at universities and research institutes in Japan. A literal interpretation of "conflict of interest" is simply a situation where there is a clash of interests. It can occur not only in the activities of universities and research institutes, but also of companies and our social lives. In addition, the severity of a problem with conflict of interest can vary according to its situation.

Why are conflicts of interest at universities drawing attention now? In fact, between 1985 to 2000, conflicts of interest were often regarded as problematic in the finance and securities sectors, and they were not escalated to the status of "social issues" so often. However, since 2001, the issue of conflicts of interest at universities has often been pointed out. Behind this background, it all started with the collapse of the bubble economy in the early 1990s. The Japanese government created a system to promote industry-academia collaborations in a bid to escape the long-lasting economic stagnation. This resulted in a huge flow of funds from the private sector into the universities which are public entities, and consequently raised doubts about the integrity and objectivity of research at universities.

What exactly are the conflicts of interests here? The "Guidelines on Conflict-of-Interest Management in Health and Labour Sciences Research" (Chief of Health Science Division Decision Number 0331001 on March 31, 2008) (partially revised on April 1, 2015) defines the conflict of interest (COI) as follows.

COI specifically refers to a situation where a third party may express concern that the impartial and proper judgment required in conducting or reporting public research is, or may be, compromised from the financial benefits that one receives from external parties.

In other words, it refers to a situation where the actual, apparent or potential interest has distorted the impartial judgment of a person in his/her position, and may compromise the interests of third parties or broader citizens through the execution of his/her job; a conflict of interest has occurred here. In particular, if the person in the middle of this scandal holds an accountable position such as a government official or a corporate executive, or an authoritative position where strong credibility is required such as physicians, attorneys,

bankers, etc., suspicions or doubts raised about the impartiality of their judgments and/or decisions can lead to grave problems.

In the first place, scientists who belong to universities and research institutes are naturally expected to report or publish objective and responsible research findings. Yet there have been many reports that indicated that when there is a financial stake in research, not only would doubts be cast on the research outcomes, but the researcher's judgement would have also been affected by a positive bias towards the sponsor.

One might think that the problem of conflict of interest would rarely occur if all financial interests that cast questions on the impartiality of public sector research were eliminated. But it is not so straightforward. The national finances are tight, and the funds that support basic research at universities and other institutions are steadily decreasing year by year. In particular, for medical research, this is even more apparent; scientists are not able to conduct clinical studies at universities without external funding such as research funds commissioned by pharmaceutical and other companies. Moreover, it is natural to have an idea that the party who uses or benefits from the intellectual property developed in the university ought to pay a certain amount in exchange.

In light of the national policies, the government does not necessarily want to put the brakes on the industry-academic collaboration; they are also not going to stipulate prohibitive regulations like "research funding by corporations of xx yen or over are prohibited". Rather than limiting financial interests (i.e., provision of funds) from the beginning – even if such a relationship did exist – it should be dealt by appropriately managing it. What does the appropriate management mean here then?

The first step is to disclose the interest so as to ensure transparency. It is necessary to examine the interests disclosed by each institution (such as universities), determine whether it is appropriate for the relevant parties of interest to engage in research, and draw conclusions. In some cases, measures such as monitoring, abandonment of interest, and change of the principal investigator may be required. Another way of the appropriate management would be to publicly disclose the interest on the Internet or the other media. Such a public disclosure would have the effect of limiting excessive provision of benefits to scientists, and provide materials for third parties – who are then made aware of the

interest(s) – to judge the research results produced.

When the stake later becomes visible, it often turns into a big social problem. From a researcher's standpoint, disclosing such stake in advance and having a third party manage it will create an environment for securely conducting research.

Case II-1: A clinical study of a technology licensed out from a professor to a biotech company – A case where both the university and the professor were shareholders of the company

In September 1999, patient X died after participating in a gene therapy clinical study conducted at Institute Z in University A in the United States. Although patient X suffered from a genetic disorder which sometimes causes neonatal death, he had a mild form of the disorder and kept it under control with diet and medication. The cause of death for patient X was due to acute respiratory distress and multiple organ failure caused by an injection with an adenoviral vector that carried the normal gene.

Bereaved family of patient X filed a civil suit seeking damages against University A, Professor Y and other related faculty members, as well as Company B that sponsored this research in Institute Z. According to the plaintiff, the defendants used a vector for gene transfer that was known to be more toxic than others, and some monkeys fell sick and died in earlier experiments using the same vector. The plaintiff also added even though some patients who participated in the same clinical study suffered serious adverse effects, it was not disclosed to patient X.

In addition, there were many financial connections between Company B and Professor Y, Institute Z, and University A. Company B was a biotech company founded in 1992 by Professor Y during his years at University C; the patent of Professor Y was licensed to Company B on the use of adenovirus-derived vectors for gene transfer. In addition, Professor Y and his immediate family had a 30% nonvoting equity stake in Company B. In 1993, Professor Y was recruited to the University A to be the director of Institute Z. In 1995, the clinical protocol of Institute Z was approved, and enrollment of patients in the gene transfer protocol has begun in 1997. The principal investigator was a surgeon at University A, and the collaborative principal investigator was a researcher at Medical Center D, a separate organization. Professor Y was a joint researcher in this clinical study. Company B agreed to provide Institute Z with over US$ 4 million annually for a period of five years until 1999 to conduct genetic research and experiments, and University A held 5% of shares in Company B as an alternative to advance payments. Patient X was only informed that University A, Professor Y and Company B had a financial interest in the outcomes of this study, but not the specific details and scale of it. In the late 1990s,

University A was actively pursuing the benefits of the discoveries of the research conducted by the faculty members.

The lack of factual explanation and inadequate disclosure of information led patient X and his/her family to believe that the clinical study posed minimal risks, and that participation of patient X in the study would greatly benefit and contribute to the future treatment of other patients affected with the same genetic disorder

This case became a quite shocking case because press reported that both Professor Y and University A owned shares in Company B, and that the patent for the vector of the professor might have affected the clinical study. In 2002, Professor Y announced that he would step down as director of Institute Z, which was also forced to close. The case was settled out of court in November 2000, so there was no judgment from the court.

Questions

1. The process for getting informed consent was deemed to be inadequate in this case. Which parts do you think were especially inadequate?

2. In this case, who is involved in the conflict of interest?

3. How do you think University A should have handled the conflict of interest when this clinical study was conducted? Please pay special attention to the financial interests.

4. What are the possible problems associated with conflicts of interest other than the risks that the subjects themselves receive in clinical study?

References

1) Gelsinger v. Trustees of the University of Pennsylvania. (Phila. Cnty. Ct. of CP filed September 18, 2000)
2) Steinbrook, R.: The Gelsinger Case, The Oxford Textbook of Clinical Research Ethics, pp. 110-120, Oxford University Press, 2008
3) Tomoko Mise: “Medicine and Conflict of Interest”, pp. 42-53, Koubundou Publishers Inc., 2007
4) Sheldon Krimsky: “Science in the Private Interest: Has the Lure of Profits Corrupted Biomedical Research?” (translated by Yukio Miyata), pp. 136-139, Kaimeisha, 2006

Case II-2: Donations by a pharmaceutical company and the safety review of their drugs conducted by the researchers who accepted the donations

There were a series of reports that patients who took the influenza drug X exhibited severe abnormal behavior such as "dashing" and "jumping", which became a social problem. For the while, a research group commissioned by the Ministry of Health, Labour and Welfare (MHLW) to investigate the relationship between drug X and abnormal behavior, compiled their findings in a report in October 2006 that showed no difference in the rate of abnormal behavior between drug X users and non-users. However, a news report in March 2007 revealed that the pharmaceutical company that imports and markets drug X had made donations to a research laboratory ran by Professor A – the principal investigator of the aforementioned research group – at a city university that totaled to an amount of ten million yen over a period of six years since 2001; this turned into an issue of public concern[5]. In addition to Professor A, other members of the same research group also received donations from the pharmaceutical company: Professor B from a national university received a total of six million yen in 2003, 2004, and 2006, while Professor C at an Inter-University Research Institute received 60 million yen in 2006[6,7]. The Minister of MHLW at that time revealed his decision at the Committee on Health, Labour, and Welfare of the House of Representatives to exclude these three researchers (out of a total of eight) who received donations from the pharmaceutical company that imports and markets drug X from the MHLW-commissioned research group to investigate causal relationship of the drug with abnormal behavior. The Minister of MHLW explained that "I will rightfully exclude (the researchers who took donations) and create a new organization to build an impartial system that would be free from all suspicions and doubts[8]".

The following comments of stakeholders were published in the newspaper.

○Professor A: "It is regretful that it caused this misunderstanding, but I am sure that the research is fair. I wanted to continue to complete the research too[7]"

○Professor B: "I have been so impartial that those donations did not compromise my scientific judgement[9]"

○MHLW: They had talked to Professor C and others since last year to understand the whole situation. They apologized for their negligence in providing guidance such as not accepting donations so as not to impair the credibility of the research, and that "the majority of responsibility lies with MHLW"[7].

Questions

1. Why did this case turn into such a big problem that it had to be addressed in the National Diet?
2. In this case, who is involved in the conflict of interest?
3. How would you judge the comments of Professor A and Professor B?
4. For this case, the MHLW research group conducted a second round of investigation and review of drug X and declared in June 2009 that "It is now clear that abnormal behavior may occur with influenza, regardless of administration of drug X[10]". Even though they have stipulated that careful measures need to be taken if patients or users are teenagers, the updated report is basically the same as the one published by the research group in 2006. What specific actions do you think MHLW needed to take before this problem came up?

References

5) The Asahi Shimbun, Mar 14, 2007 Morning edition
6) The Asahi Shimbun, Mar 14, 2007 Evening edition
7) The Asahi Shimbun, Mar 31, 2007 Morning edition
8) Minutes from the 166th National Diet's Committee on Health, Labour, and Welfare No. 7 (Mar 23, 2007)
9) The Asahi Shimbun, Mar 24, 2007 Morning edition
10) MHLW "Q&A on Influenza (Q.14)"
http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou01/qa.html (see Jan 17, 2017)

Case II-3: Clinical study conducted by private equity shareholders of a university spinoff

It was revealed that five people, including a professor at University Hospital A who was in charge of a clinical study on gene therapy drugs developed by Spinoff B from University A, had acquired private shares of the university spinoff before listed. The following table summarizes the major events reported in the press in chronological order.

Month/Year	events
1998	Professor X et al. submitted applications with University A to conduct clinical studies
Dec 1999	Spinoff B from University A (Former Assistant Professor Y at University A held the major patents)
Dec 2000	Out of approximately ten clinical study members, two professors (including the clinical study leader) and three physicians acquired several to twenty shares at 50,000 yen per share through a third-party allotment of shares by Spinoff B (the number of shares held by them subsequently increased through shareholder allocation; the two professors each held 320 shares while the physicians held dozens of shares)
Jan 2001	Announcement of partnership with a major pharmaceutical company regarding the development of gene therapy drug at Spinoff B
May 2001	Clinical study approved
Jun 2001 to Mar 2003	Conducted a clinical study with 22 patients
Sep 2002	Spinoff B was listed (stock price temporarily exceeded 1 million yen per share), Professor X sold half of his shares (160 shares) back to Spinoff B at its request when it was listed and acquired about 32 million yen

Key points of the case

The press[11] published comments by Research Environment and Industry Cooperation Division at MEXT: "We do not think there's an issue at this stage" and "It is important for university spinoffs to properly disclose to the public how their profits are distributed and the sources of their income so that the neutrality and impartiality of the university would not be subjected to any doubts or suspicions". The press also published an opinion of chairman of NPO Z, who was familiar with drug evaluations: "If this drug becomes a blockbuster and generates enormous profits, the researchers will be motivated. But in this case, since we know that the price of the acquired private shares would skyrocket once the

company gets listed, it is a big problem. Researchers or scientists should not be allowed to hold shares of related companies. Clinical studies of new drugs are not conducted in the interests of companies or individuals, but for public interest; to test and see whether these drugs can be administered or not". Even if it does not violate laws and regulations, it raises ethical issues from the point of conflict-of-interest management.

References

11) The Asahi Shimbun, Jun 12, 2004 Evening edition
12) The Nikkei, Jun 12, 2004 Evening edition

Case II-4: Donations and clinical study from a pharmaceutical company – A case that was brought to the conflict-of-interest committee

The following clinical research proposal was submitted to the conflict-of-interest committee established at the University Hospital A.

In the clinical study, it planned to administer two types of hypertension drugs with different mechanisms of action that were manufactured and marketed by Pharmaceutical Company B to patients. The purpose of the clinical study was to establish optimal administration and dosage of these two drugs for hypertensive patients suffering from a type of kidney disease that is supposed to develop with hypertension as an underlying disease. Therefore, in the clinical study, the drugs are planned to be administered to the hypertensive patients who may have high risk of developing this kidney disease. As the drugs used in this clinical study are covered by health insurance, patients are asked to pay for the drugs. The principal investigator of this clinical study received donations amounting to ten million yen from the Pharmaceutical Company B in the previous year.

Key points of the case

The donations of ten million yen necessitates an assessment of its impact in clinical studies, particularly from the following perspectives.

1. The amount of money; purpose and timing of the donations, etc.

2. What should they do to the subjects if it is judged that the possibility of affecting scientific objectivity in this case is extremely small? What should they do when presenting the outcomes of the clinical study in a paper or at an academic conference?

3. If it was judged that the possibility of the impact on the scientific objectivity could not be ruled out, the conflict-of-interest committee should consider how meaningful the clinical research is, and how important it is for the principal investigator to carry out the clinical study. There is also a need to look into future procedures according to the results of their review.

References

13) Office of Conflict of Interest and Security Export Control, University of Tsukuba “Q&A on Cases of Conflict of Interest and Measures for Them, Extended 2nd Edition”, p. 44, 2014

Case II-5: Clinical studies and their papers conducted with donations from a pharmaceutical company

Research misconduct was discovered in publications on clinical studies conducted after 2002 that sought to investigate the efficacy of hypertension drug X, which was launched in Japan in November 2000 by Pharmaceutical Company A[14]. These clinical studies were conducted in five national, public and private universities that enrolled over 8,000 patients in total. The published papers stated that drug X not only lowers blood pressure, but also has the effect of reducing stroke and angina compared to other antihypertensive drugs[15]. Pharmaceutical Company A used these papers to demonstrate the efficacy of drug X as their promotional materials; the drug recorded domestic sales of over 100 billion yen in 2012 alone and became the flagship product of the company[16].

However, several opinions were reported on an English Medical Journal L and others that questioned the results of the papers published by four universities between 2007 and 2012 [14]. In July 2013, two universities admitted and apologized that they had manipulated the data in the papers, such as changing the incidence of stroke and intentionally altering the blood pressure data[15,16]. Several papers, including those published by the other two universities, were retracted between December 2012 and August 2016[14,17-21].

The following facts were revealed during the investigation process.

Fact 1: Investigations revealed that Pharmaceutical Company A had made donations exceeding 1.1 billion yen in total to these five universities between 2002 and 2012 [22].

Fact 2: Employee Y at Pharmaceutical Company A was found to be in charge of statistical analyses, and creating charts and diagrams for these papers. He/She also sat in the review meeting that laid down the implementation plans for these clinical studies, as well as the Clinical Endpoint Committee (an independent committee comprising physicians from other universities or institutions that reviews the clinical data to determine if the diagnoses provided by investigators of the clinical study were appropriate or not)[22,23].

In addition, employee Y at Pharmaceutical Company A worked as a part-time lecturer (on an annual renewal basis) in City University B from April 2002 to March 2013. He/She was listed in the papers as one of the authors with only the title of “part-time lecturer in City University B”, concealing his/her affiliation with the pharmaceutical company[14,24,25].

Key points of the case

It is pointed out with regards to Fact 1 that during the conflict-of-interest management meetings for the discussion on the submission of self-declaration of financial interests that were held when the clinical research proposals were submitted to each university, they could have examined the facts and looked into the details of the large amount of donations provided by a company with interests, and might have taken some measures to mitigate or eliminate the conflict(s) of interest. Moreover, it is also needed to consider why the donations were provided as research funding instead of sponsored research contracts. There are a couple of matters to consider with regards to Fact 2: Should employee Y be involved in clinical studies? And even if involvement of employee Y in the clinical studies is deemed to be necessary, what should be the scope of his involvement, and how should this be managed? Furthermore, employee Y ought to disclose his interests when the papers are published.

References

14) The Mainichi Shimbun, Jul 30, 2013 Morning edition
15) The Mainichi Shimbun, Jul 31, 2013 Morning edition
16) The Mainichi Shimbun, Jul 12, 2013 Morning edition
17) Kyoto Prefectural University of Medicine "Investigation Report on the Clinical Study 'Kyoto Heart Study'", p. 1, Jul 11, 2013
18) MHLW's Committee on the Clinical Study Cases of High Blood Pressure Medications "Response & Recurrence Prevention Measures Based on the Clinical Study Cases of High Blood Pressure Medications (Report)", Apr 11, 2014
19) The Japanese Circulation Society "On the Manipulation of Data in Kyoto Heart Study", Jul 12, 2013
20) The Japanese Society of Hypertension "Our Society's Response Regarding the Alleged Research Misconduct in 'VART Study' Clinical Studies", Mar 27, 2015
21) The Japanese Society of Hypertension "On the Retraction of Papers Published in Hypertension Research", Aug 15, 2016
22) The Asahi Shimbun, Aug 10, 2013 Morning edition
23) The Mainichi Shimbun, Jun 15, 2014 Morning edition
24) The Mainichi Shimbun, Jul 12, 2013 Evening edition
25) The Asahi Shimbun, Aug 8, 2013 Morning edition
26) Yukiko Shinya "Conflicts of Interest in Theory & Practice – How to Rebuild Public Trust in Scientific Research", pp. 64-69, University of Tsukuba Press, 2015

Case II-6: Joint research agreement and purchase of goods agreement between a university and a university spinoff

Professor X at University A has established a university spinoff B that develops and markets medical devices based on his invention to which University A owns the patent P, and Professor X has become its representative director. As Company B has just been established, the equipment necessary for further research on patent P are only available in the laboratory of Professor X which also holds the know-how to it. Company B therefore wants to enter a joint research agreement with University A for further research and development (R&D).

Company B is subsequently outfitted with R&D equipment and has begun to manufacture medical device Z. Medical device Z is a new and novel treatment device highly appraised by medical institutions and patients. Professor X now wants to purchase medical device Z from Company B with university research funds and conduct further research on it.

Key points of the case

Technology transfer from universities to industry is often so difficult that it is sometimes referred to as the "Valley of Death". Rejecting all joint research between universities and university spinoffs may therefore jeopardize the existence and development of university spinoffs. When allowing joint research, it is necessary to be in a situation where a third party can judge it as inevitable. It is also critical to lay down the conditions for contract procedures and, in some cases, conditions for conducting research as well. Even if Professor X is to purchase medical device Z of Company B at University A, it is necessary to examine if there are any potential unavoidable circumstances and to take measures such as conditioning in the contract procedures. In other words, the crux of the issue is the extent of involvement of Professor X as a stakeholder. Either way, cases like this can only be accepted as an exception if the medical and social significance of the joint research is exceedingly large, and if it is imperative for the faculty members to participate in this joint research. While this can be said of all side business, Professor X should also specify

whether he was carrying out his activities on behalf of University A or Company B so as to avoid future trouble.

References

27) Office of Conflict of Interest and Security Export Control, University of Tsukuba "Q&A on Cases of Conflict of Interest and Measures for Them, Supplementary Revision 2nd Edition", pp. 1, 9, 2014

Case II-7: Using the name of a university for the outcome of university-industry research collaboration

University A conducted joint research with Company B. Company B now wants to use the name and photos of University A for a promotion of the product that was developed based on their joint research outcome, as well as to publish comments from the faculty members involved in the joint research. Should restrictions be imposed on such requests? If so, what kind of conditions would such restrictions necessitate? Consider the following two cases separately.

Case 1: When a faculty member at University A is substantially involved in the joint R&D → (Ex.) Jointly developed medical device X with Company B by using the patent rights held by University A.

Case 2: When involvement of University A was only verification of the efficacy of a product (such as measurement, analysis, or validation) → (Ex.) University A verifying the effects of health foods manufactured by Company B.

Key points of the case

In Case 1, if Company B wanted to include the description of "This product was developed in collaboration with University A" on the package of medical device X for its sales promotion, there would be little cause to keep that fact a secret. However, careful attention must be paid to the possibility that the social credibility of University A and the involved faculty member may be undermined depending on how the name is used. Take for example Case 2 where only the product's efficacy was verified; in most cases, this could have been performed by any general company without involving a university that is expected to come up with innovations through new discoveries. Nevertheless, such a company has asked a university to participate in joint research with the intention of increasing product sales by exploiting the brand power of the university. For those cases, more stringent measures are required, and the contents of the description and how it would be used must be carefully examined. In any case, the point of contention is whether the university is able to take responsibility for its name being used in the product description.

References

28) Office of Conflict of Interest and Security Export Control, University of Tsukuba “Q&A on Cases of Conflict of Interest and Measures for Them, Supplementary Revision 2nd Edition”, pp. 14-15, 2014

Case II-8: The review of a national project by a review board including a stakeholder

MHLW, who was in charge of National Project Z that conducted research on disease X, appointed Professor Y at University A, who retired University B in 2007 and then became emeritus professor at University B and was leading the research as the chief advisor of the project, as one of the board members to review the expenditure of grants-in-aid to the project. National Project Z was carried out over a period of six years from 2007; it received a total of 2.4 billion yen in grants-in-aid from MHLW, Ministry of Economy, Trade and Industry (METI), and MEXT, as well as 900 million yen in funding from 11 pharmaceutical companies. Professor Y was instrumental in the launch of National Project Z in 2007 and served as the chief advisor throughout the project. He was also guiding Professor W at University B, the representative researcher of the national project. Professor Y was the only researcher from National Project Z to have received "guidance fees" amounting to 2 million yen from MHLW in 2007; his laboratory at University A also received approximately 120 million yen from METI for "related technology development expenses" from 2007 to 2012.

In 2010, MHLW appointed Professor Y as one of the 11 board members that review expenditure of grants-in-aid to National Project Z for the latter three years. The scores given by each board member were not disclosed but according to media reports, Professor Y gave a high score of nine out of ten for National Project Z. The decision to continue National Project Z was passed, and the project continued to receive more grants-in-aid.

Key points of the case

What should Professor Y – who had received grants-in-aid related to National Project Z – have done when he was asked to be one of the board members to review the project? Another issue lies with MHLW and METI: What kind of measures should they have adopted in such a situation? It is essential to consider the amount and timing of the subsidies that Professor Y received and his relationship with the representative researcher of National Project Z, and to find specific measures to address these issues.

References

29) The Asahi Shimbun, Jan 10, 2014 Morning edition
30) The Asahi Shimbun, Aug 20, 2014 Morning edition

2. Ethical issues in clinical studies: Human subjects protection and informed consent etc.

The following are the laws and regulations that researchers must comply with under the jurisdiction of the Ministry of Health, Labor and Welfare (MHLW) in conducting research.

1. Clinical Trial Act

2. Overview of Guidelines for Medical Research

A. Ethical Guidelines for Medical and Health Research Involving Human Subjects

Chapter 1 “General Provisions”, Chapter 2 “Obligations of Investigators, etc.”, Chapter 3 “Research Protocol”, Chapter 4 “Ethical Review Committee”, Chapter 5 “Informed Consent, etc.”, Chapter 6 “Personal Information, etc.”, Chapter 7 “Response to Serious Adverse Event”, and Chapter 8 “Ensuring of Reliability of Research”.

B. Ethical Guidelines for Human Genome and Genetic Analysis Research

Part I “Basic Ideas”, Part II “Responsibilities of Researchers, etc.”, Part III “Basic Stance Toward Donors”, Part IV “Ethics Review Committee”, Part V “Handling of Human Specimens”, and Part VI “Protection of Personal Information”

Others include:

C. Guidelines on Clinical Research on Gene Therapy, etc.

D. On Research and Development Utilizing Human Tissues Removed by Surgery and Other Procedures

E. Basic guidelines for the conduct of animal experiments in implementing agencies under the jurisdiction of MHLW

F. Public Health Guidelines on Infectious Disease Issues in Xenotransplantation

G. Ethical Guidelines for Research on Assisted Reproductive Technology to Develop Human Fertilized Embryos
H. Ethical Guidelines for Epidemiological Research
I. Ethical Guidelines for Clinical Studies
J. Guidelines on Clinical Research Using Human Stem Cells

Please refer to “About Research Guidelines” page that is published in the homepage of MHLW for more details on each guideline.
(http://www.mhlw.go.jp/stf/seisakunitsuite/bunya/hokabunya/kenkyujigyou/i-kenkyu/index.html)

In this casebook, we have shown various cases on violation of ethical guidelines, as well as the relevant key points.

In order not to violate these ethical guidelines, it is necessary to pay consistent attention at the researcher level, course and/or clinical department level, hospital and/or university headquarters level, as well as to build relevant system to educate and train researchers. Since these would inevitably differ according to the size of the organization, we would like to ask individual researchers to put in their utmost efforts according to the size of their organization. In order to develop and advance clinical studies in Japan, we would also like them to respond with a sense of morality and responsibility from their own position. We therefore hope that this casebook would be used as a teaching material for group discussions.

Case II-9: Violations of ethical guidelines for clinical studies

The clinical study for pediatric liver cancer was conducted before the national Ethical Guidelines for Clinical Studies were formulated. After the guidelines were formulated, this study was purportedly re-conducted again in 2006 with the following changes made.

1) To conduct the study after obtaining the approval from the ethics committee of the institution;
2) To conduct the clinical study after obtaining the consent of the patients or their medical proxies;
3) To use samples of patients in research based on the consent of the patients or their medical proxies;
4) The study using samples include liver cancer-related genetic analysis research.

However, researchers in Institution A participated in this study without the approval of the ethics committee because they thought as follows; firstly, while the treatment provided to the patients was based on a treatment protocol, the protocol is considered to be a standard one by a group of specialists; secondly, the research plan did not prevent treatment that deviates from the treatment protocol according to the condition of the patients; lastly, human subjects were not divided into two or more groups for comparison. In these reasons, they did not consider it as an intervention study. As a result, the implementation plan prepared for the provision of advanced medical care was carried out from July 2010 to February 2013 without the review and approval of the ethics committee of Institution A. Moreover, the data management and monitoring necessary for quality control and quality assurance required in the current advanced medical care were not properly implemented.

Investigation method and research findings

Institution A set up an investigative committee that collected and checked the materials related to the clinical study, and that conducted interviews with the persons involved. The investigation revealed that while the research plan was revised in 2006 and every institution was required to obtain the approval of the ethics committee of each institution,

however, Institution A did not make an application with the ethics committee. The first patient registration was carried out for this study in 2010, but investigations revealed that the physician in charge considered it not to be a clinical study, but just a pediatric cancer patient registration. In addition, the data and results of the 2006 study were not introduced due to various reasons such as the transfer of the institution manager.

In this study, treatment must be provided after explanation and consent from the patients or their family members, and the informed consent for treatment from the patient or family was obtained in all cases. Although Institution A had registered five cases with the research office, consent about participation in the clinical study were obtained from only three cases. Of the remaining two cases, consent was not obtained from one, and it was unclear whether consent was obtained or not from the other one. The pathological samples, tissue samples, and blood samples of all five cases were sent to the research office.

In response to this, the following points were requested; Institution A should be stripped of its status as a research-participating institution; all information, including the personal information of the patients that were registered with the research office, should be erased; the samples of the registered patients should discarded. The five patients, who were the human subjects of this study, as well as their guardians or parents, were provided with an explanation and apology. After a report about this case was submitted to the MHLW, the full text was published on the website of the Institution.

Questions

1. This case seems like one that may often occur in other institutions as well; why do you think this is so? What factors come to your mind from considering the following perspectives?

   1) From the perspective of the system of the clinical department
   2) From the perspective of educational system
   3) From the perspective of type of clinical studies

2. What preventive measures can you think of when considering the following perspectives?

1) From the perspective of ethics training
2) From the simplified application to the ethics committee and sharing of information on ongoing research
3) About the check system regarding the appropriateness of clinical studies

3. What do you think the investigative committee of the institution should focus on during their investigations?

1) On the investigation subjects
2) On the investigation method
3) On how they handled the patients and their guardians or parents, and participants

Case II-10: Violation of the ethical guidelines for human genome and genetic analysis research

In 2012, Faculty Member B at University A submitted an application for approval to the Ethical Review Committee to conduct a "Study on postoperative nausea/vomiting and genetic polymorphism by general anesthesia". But as the approval process took time, Faculty Member B requested the cooperation of Professor C at the Anesthesiology Department in University Hospital A. As Professor C did not think that it would raise any ethical issues and expected that the study would gain the approval of the ethics committee, he started collecting blood samples with the consent of the patients. Meanwhile, Professor D, who was the direct supervisor of Faculty Member B, was initially unaware that this was happening. After Faculty Member B had collected blood samples from 20 patients, Professor D realized that blood samples were collected from patients before the approval of the ethics committee. He/She instructed Faculty Member B to suspend the study, but eventually allowed him/her to continue collecting blood samples. In the end, they had obtained the informed consent from 391 patients, and collected and stored blood samples from 362 patients between April and June that year. They did not perform any genetic analysis on these collected samples. The initial application submitted to the Ethical Review Committee was reviewed on May 23 and given a conditional approval, but that was subsequently revoked due to the violation.

Investigation method and research findings

The investigative committee collected and checked the materials related to this clinical study, and interviewed the persons involved. The act of collecting patient samples before gaining the approval of the ethics committee is a violation of the ethical guidelines. The investigations discovered that some of the faculty members instructed their subordinates to collect blood samples as they had mistakenly thought that the clinical study would start after collection of blood samples. Furthermore, since the Ethical Guidelines for Human Genome and Genetic Analysis Research clearly states that all researchers must not obtain personal information and materials through deception or other dishonest means when

conducting human genome and genetic analysis research, this case has also violated the Ethical Guidelines for Human Genome and Genetic Analysis Research.

This case is the act that neglected the kindness of the patient due to the lack of recognition and the lack of teaching ability of the faculty members who are in a position to guide research ethics. The persons involved were punished, the approval of this research application was revoked, and the samples and related materials collected in this study were discarded. In addition, all studies that were using human-derived samples in the faculty where Faculty Member B belonged to were temporarily suspended. They were asked to submit a written explanation and apology to the patients and their guardians or parents, as well as a report to MEXT, MHLW, and METI. This report, along with the penalties that were handed out to the persons involved, were also published on their websites.

Questions

1. After looking at the problems of this case from the perspectives of Faculty Member B, Professor C, and Professor D, why do you think this case was happened?
2. What do you think can be done to prevent such cases from happening in future?
3. Which topic about the Ethical Guidelines for Human Genome and Genetic Analysis Research do you think requires special attention with regards to its training?

Case II-11: Violations of ethical guidelines for clinical studies

At School of Medicine in University A, two clinical studies were conducted by Clinical Department B: Clinical Study 1 was on the detection of peripheral blood cancer cells in lung cancer (approved in June 2009 and to end by March 2010), and clinical study 2 was on the detection of circulating tumor cells in lung cancer (approved in December 26, 2011). The department head was Professor C and the researcher in charge of conducting the clinical studies was Faculty Member D. In the second clinical study, aspiration of 2 mL of bone marrow from patients that underwent surgery was different from the first clinical study. In January 2012, the department received reports of unethical behavior during respiratory surgeries, and subsequently conducted an investigation to look into this matter. The investigation results revealed that bone marrow aspirate was collected from the ribs of patients with bone marrow aspiration needles during their lung cancer surgeries before the researchers had obtained the approval from the ethics committee.

Investigation method and research findings

The investigative committee collected and checked the materials related to this clinical study, and interviewed the persons involved. The committee also investigated if there were any conflict-of-interest management with the company that sold the equipment used in this study, but no management violation was found. The investigations revealed that they had conducted clinical Study 1 beyond the study period – which was supposed to end by March 31, 2010 – approved by the ethics review, and had collected peripheral blood from 90 patients. On top of this, the investigative committee could not confirm or find the written informed consent of 27 subjects, out of a total of 136 subjects in this study. The investigative committee also found that the researchers had collected bone marrow aspirates from 26 lung cancer patients during their surgeries for clinical Study 2 before it was approved (January 11, 2012) by the ethics committee without informed consents from the patients. In addition, peripheral blood and bone marrow aspirates were collected from five patients with benign diseases (to serve as control data) without their informed consent that were not listed in their ethics approval application. Moreover, Faculty Member D

admitted that he/she had submitted a deceitful application: He/She had put down the names of faculty members of other clinical departments as research members under the research team, as well as the name of his/her coworker as the personal information manager, in the ethics approval application without obtaining their consent.

The background to this case occurred is that the doctor in charge of the ward is responsible for obtaining informed consent, and the surgeon or assistant is responsible for collecting bone marrow fluid, and no one confirmed or checked with the others during the study period. The surgeon was instructed by Professor C and Faculty Member D to collect the peripheral blood and bone marrow aspirates, and only found out that informed consents from the patients were not obtained when the investigation was launched. Information on the ethics approval application, including the research protocol, was also not shared within the faculty, and no research procedures could be found.

In the end, the approval for this research application was revoked, and all samples and related materials collected for this study were discarded. In addition, all the studies that were using human-derived samples in the faculty where Faculty Member D belonged to, were temporarily suspended. They were asked to submit a written explanation and apology to the patients and their guardians or parents, as well as a report to MEXT, MHLW, and METI. This report, along with the penalties that were meted out to persons involved, was also published on their websites.

Questions

1. What are the specific problems in this case? Please describe each problem from multiple aspects (perspectives).
2. What do you think can be done to prevent such cases with the aforementioned problems from happening in future?

Case II-12: Violations of ethical guidelines for clinical studies (mistaking it as usual medical care)

In November 2011, University A received a report from an anonymous but stating one of employees of University Hospital A; it was pointed out in this report that informed consent of patients for the clinical study on anesthetic management in surgery were not obtained, and a presentation at an academic conference without obtaining the approval of the medical ethics committee was done. A preliminary investigation was then mounted, which revealed that out of the 52 subjects that were presented at the academic conference, written informed consent was obtained from only eight subjects. While anesthesia consent forms for the remaining 44 cases were confirmed, the investigation found no informed consent regarding their participation in the clinical study. University A decided to set up an investigative team.

Investigation method and research findings

The investigative team comprised two physicians, one nurse, and two administrative employees. The chairman of the medical ethics committee also conducted a separate investigation at the same time.

The title of the clinical study was “Pain Reduction with Sedatives and Analgesics at the Epidural Anesthesia Puncture & Verification of Anterograde Amnesia Effects”. Assistant Professor B at the Anesthesiology Department was the principal investigator of this study, which received an approval by expedited review from the ethics committee in August 2011. Assistant Professor B subsequently presented the results of this study in an academic conference in November 2011. The investigations, however, revealed that aside from the eight patients to which informed consent had been obtained, the study was performed on 44 patients before the ethics approval. They also found that in May 2011, the medical director of the Anesthesiology Department commented that the research conducted by Assistant Professor B was “problematic”. during the medical office conference. The professor asked Assistant Professor B that the study had to be reviewed by the medical ethics committee, and then Assistant Professor B submitted an application in July 2011

that stated himself as the principal investigator of the study. The submitted research application, however, did not state that the study had already been conducted in 44 patients prior to obtaining approval. Assistant Professor B also made no mention of this when he was asked to brief explanation at the ethics committee on his study. In addition, all the physicians in the Anesthesiology Department, including the professor, were not aware that the study – which was already conducted before approval was obtained – would not receive a "backdated approval" from the ethics committee because it was an intervention study. The research protocol approved by the ethics committee stated that informed consent would only be obtained from patients who are competent to make a voluntary decision about whether to undergo the intervention. Despite this, the families of two subjects – one before approval, and one after approval – gave consent on behalf of the patients. Assistant Professor B indicated that he was under the misunderstanding that interventions of the study were "conducted within the scope of general anesthesia", and therefore he obtained the usual anesthesia consent forms from the subjects. He also did not understand that according to the ethical guidelines, the usual anesthesia consent form alone did not suffice for intervention studies like his, where several drugs were administered as placebo and compared between groups.

Assistant Professor B was asked to submit a "Report and apology for a clinical study that violated ethical guidelines", which was published on the website of University A, as well as to submit a written explanation and a report to MHLW and MEXT. He was also to submit a written explanation and apology to the patients and their guardians or parents.

Questions

1. In this case, Assistant Professor B claimed that he did not understand the difference between providing patients with usual medical care and conducting a clinical study on them. What do you think this "difference" exactly is?

2. When the research results were presented at an academic conference using data from patients who did not provide informed consent, how do you think this issue from the perspectives of the responsibility of the presenter, and the responsibility of the

coauthor, especially of the professor?

3. What factors do you think may have contributed to the contradiction presented in this case?

4. What perspectives should you consider regarding the circumstances which caused the aforementioned problem and countermeasures for prevention of recurrence from happening in future? What specific measures can you think of from each perspective?

Case II-13: Violation of ethical guidelines and implementation procedures in advanced medical care

This case occurred in a clinical study, which was conducted at the University Hospital A and a professor and an associate professor at Department B were listed as the principal investigator and the study leader respectively, to an advanced medical care. The researchers administered patients that were undergoing endoscopic surgeries for cancer with a chemical compound (a fluorescent dye for tissues that was not yet approved by Pharmaceutical Affairs Law) and used a fluorescence camera (a device that was also not yet approved by Pharmaceutical Affairs Law) to observe the cancer lesions fluoresced. This clinical study was conducted with the aim of photodynamic diagnosis to improve diagnostic performance of cancer and surgical outcomes, and was approved by the ethics committee in 2004 and 2006. The researchers submitted an application for advanced medical care and got approvals from both the evaluation committee for investigational medical care and expert committee on advanced medical care. But before the approval in both committees, the research plan had to be revised many times that the final plan was different from the original one that was submitted to the ethics committee. The clinical study that had been carried out for some time at the start of the approval was confused with the clinical study that was supposed to be carried out to implement advanced medical care. Due to this confusion, the final implementation plan created for advanced medical care was not resubmitted to the ethics committee for review or approval. Under these conditions, University Hospital A used this technique in 60 cases, from July 2010 to February 2013. Regarding their medical practices, the researchers obtained the informed consent from the human subjects as detailed in the research implementation plan.

Investigation method and research findings

The investigation was conducted in a rigorous manner by involving external committee members. The investigative committee stated that this case should not be viewed as one where the researchers and administrative staff committed minor administrative errors in their advanced medical care application procedures. They added to state that as a medical

school that conducts clinical research, it was considered that it failed to adhere to the principle of obtaining approval from the ethics committee of the medical school when conducting clinical research using unapproved diagnostic agents. The crux of the problem lay in the fact that for a clinical study using unapproved diagnostics, first and foremost, they should respond in accordance with the general principles of human subject protection.

Questions

1. Unlike other medical care, patients who are receiving advanced medical care may be eligible to receive benefits. What are the differences?
2. A feature of advanced medical care is that it is implemented in a clinical study according to a research implementation plan that also includes quality control and assurance measures that equivalent to that of clinical trials. With this in mind, please consider what was lacking in this clinical study.

Case II-14: Leakage of personal information

In February 2015, a hospital discovered that information about 126 patients, including their medical interview sheets, consent forms, and patient referral documents, were lost. They later confirmed that some of the medical interview sheets of some clinical departments that were kept during a three-day period in February 2015 were lost after they were saved as electronic documents. The hospital immediately conducted a search within its premises to locate these documents as well as checked with all involved persons, but was unable to find it. They suspected that the lost documents were most likely accidentally incinerated together with other waste when they were sorted or handled. At present, no reports or inquiries suspected of information leakage have been confirmed.

Response and recurrence preventive measures

The hospital is to notify and send a written apology to every inconvenienced patient whose documents were lost, as well as a written apology to the medical institutes involved. The hospital also needs to explain since the documents were eventually saved as electronic documents, the patients would not receive any detrimental or unfavorable medical care or treatment.

The hospital is to enforce and thoroughly implement measures such as reviewing the paperwork process (including methods of delivering documents and storage) so as to strive to prevent such recurrence.

Questions

1. From the perspective of protection of personal information, what kind of other leakages may occur?
2. What are the possible ways to prevent the aforementioned leakage when considering a) from perspective of an individual, and b) from perspective of an organization?
3. Penal provisions have been stipulated when the protection of personal information is violated, but if direct damages incurred, what are the penal provisions of individuals and hospitals?

Case II-15: Violation of the Cartagena Act

University A received an insider report describing an eyewitness account of recombinant E. coli being discarded without inactivation. The report stated that Faculty Member B at University A has dumped the recombinant E. coli culture in the laboratory sink in the laboratory of his research department once or twice a month on average over a period of three years (from April 2013 to March 2016), without inactivating it as stipulated in the Cartagena Act (Act on the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms). Faculty Member B asserted that he/she was aware that these disposals violated the Cartagena Act. He/She used K12 strains of E. coli which do not produce toxins like the pathogenic E. coli, and by his/her selfish judgement he/she discharged recombinant E. coli from the laboratory sink to the public sewer system via the drainage channel of the university.

Investigation method and research findings

Faculty Member B submitted a written statement to the investigative committee and admitted to the disposals that were described in the eyewitness account. The committee judged that this case was a violation of the Cartagena Act; under this Act that regulates the use of living modified organisms, it is illegal to dispose them without autoclaving. The investigative committee submitted their first report to MEXT Research Promotion Bureau, Life Sciences Division that was in charge of this case. They subsequently interviewed and surveyed all the managers, researchers, and employees in University A, including those that belong to the same laboratory as Faculty Member B but were in other institutions, that were conducting recombinant experiments, as well as conducted sampling survey and verification experiments on the wastewater in the drainage channels. From their results, they judged that the K12 strains and the recombinant E. coli did not survive in nature and did not affect the surrounding environments for the following reasons. 1) A sampling survey on wastewater in the drainage channels confirmed that all the recombinant E. coli found were negative. 2) The E. coli K12 strains, which are widely used in recombination experiments, are not toxic and would not be able to transfer its plasmid to other strains. 3)

Their experimental results reconfirmed that the recombinant E. coli was rapidly eliminated in nature. 4) Their verification experiments confirmed that the recombinant E. coli was killed at the chlorination concentration at the second purification center in Prefecture C, which was the last sewage treatment plant.

In addition, MEXT conducted investigation on the site and subsequently sent a letter of strict caution disposal notice to University A.

Questions

1. The "containment measures" of the Cartagena Act describe the measures when using genetically modified organisms. What are those measures?
2. Why did such a violation of the Cartagena Act take place over a long period of three years? What can you think of from the perspectives of education for researchers, responsibility of managers, and awareness of researchers?

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3. Reliability in research data and research reproducibility issues

In recent years, many cases of research misconduct have been brought up as social issues. The "new Guidelines" revised by MEXT in 2014 redefined the three most important issues of research misconduct, namely fabrication, falsification, and plagiarism, as "specific research misconduct". If specific research misconduct is simply perceived as "misconduct that was intentionally committed based on malice", then one might be led to think that "obvious misconduct" (such as specific research misconduct) – if it was not committed maliciously – would not even happen to begin with. However, many of the past examples of penalties that have been handed out in reality for specific research misconduct were cases where it has nothing to do with the person's malicious intent, or where the misconduct occurred due to a lack of understanding in the handling of research data and inadequacies in managing and conducting research. In order for researchers to properly address and tackle research misconduct, they need to understand "Questionable Research Practices" (QRPs) that may unintentionally lead to specific research misconduct, to think about research habits and behaviors that may cause them to commit misconduct, and to adopt an attitude toward responsible conduct of research by introspectively looking at their own research practices.

The National Academy of Sciences of the United States indicated that "A questionable research practice is a practice that violates the traditional values of research activities, potentially resulting in harmful impacts on research process. These practices could damage trust in the honesty of the research process, threaten a variety of traditional customs of science, affect research results, waste time and resources, and weaken the education of young scientists." (excerpt extracted from Green Book, page 57). While it is difficult for researchers to predefine the scope of QRPs when engaging in their daily research practices, a review of their research habits with the aim of ensuring data reliability in their activities would allow them to understand appropriate and commendable behaviors as well as the aspects they need to pay attention to in research practices.

This section therefore sets out to present hypothetical cases with QRPs that may affect

data reliability. It might be helpful to look back on one's research practices through these hypothetical cases by considering "the types of activities that may lead to the types of misconduct" as one switches between the different position of a mentor and a mentee.

Hypothetical Case 1

The laboratory to which Graduate Student A belongs is known for their laissez-faire guidance; it is customary for students to proceed with their own research after they have learned the basic experimental techniques from faculty members. As Student A is busy conducting a lot of experiments every day, he/she records the experimental conditions on a memo pad and saves all the photographs such as electrophoretic images as electronic data. When he/she has to make a progress report for an experiment, he/she creates the presentation materials with his/her personal computer while looking at the memos that he/she made for the past experiments and has regular discussions with others through oral presentations. The supervising faculty member then gives a general direction to Student A about the next step he/she should take in his/her research based on the presentation materials he/she created. Student A is very satisfied with the current laidback research environment because the students can proceed with their research at their own pace without interference from each other.

Questions

In the aforementioned research environment, point out the issues that might affect the reliability of the research data. If you were the supervising faculty member, describe the measures you would take to increase the data reliability and prevent unintended research misconduct.

An example of a viewpoint

The potentially problematic research habits include “laboratory notebooks were not appropriately recorded”, “raw data was not adequately checked during research guidance”, and “lack of discussion with others”. It is advisable for the principal investigator to manage the research so as to resolve these issues. It also needs to understand that inadequate management system of the laboratory may cause unintended research misconduct.

Hypothetical Case 2

Researcher B has been required by the editor of the journal to revise the manuscript that he/she submitted as a reviewer indicated that an immunostaining image in one figure was unclear. But Researcher B discovered that the primary antibody used in this experiment had already been used up, and it would take several months before the order for this antibody would be delivered to him/her. Researcher B then decided to check the photo files he/she had taken for the past experiments and was able to find a photo with just the right field of view. Although it was extremely likely that the photo was taken under the same experimental conditions, it was taken during a preliminary experiment, there was no clear description of it in the laboratory notebooks, and there was no information in the file name. Due to the impending deadline, Researcher B used this photo to replace the figure and addressed the revision, and the paper was successfully published in the journal. Afterwards, Researcher B found an old memo while he/she was cleaning up the laboratory and was able to confirm that the photo used in in revised manuscript was the appropriate photo.

Questions

Describe how behavior of Researcher B might be problematic. Also, what do you think Researcher B should have done instead to conduct responsible research practices?

An example of a viewpoint

The problem here is “using a photo that Researcher B himself could not fully confirm for a publication”. Even if the data is possibly authentic or correct, it is dangerous to judge based on assumptions in a time-pressed situation. It is important to carefully annotate and record all electronic data, and to cultivate a habit of recording down all experimental results (including results of preliminary experiment) in laboratory notebooks so as to avoid concerns like this. In addition, reagents used in experiments should be managed and stored such that researchers would not run out of them as much as possible in case they need to reproduce the experiments.

Hypothetical Case 3

To conduct detail analysis of the functions of a gene, Graduate Student C spent much effort to create and design a complex gene expression plasmid, and also created a polyclonal antibody using the protein encoded by this gene as an antigen. However, after Student C had gotten the cultured cells to express this gene and analyzed its interaction with the nuclear factors, he/she was disappointed as he/she did not obtain the expected outcomes. Nevertheless, he/she managed to compile these outcomes and publish them as a short paper. Student C graduated the very next year and the laboratory was closed at the same time. Student C cleaned up the laboratory, and after making sure that the laboratory notebooks were properly recorded, entrusted all of them to the retiring supervising faculty member. Since Student C heard that no one would be continuing his/her research from the supervising faculty member and the deadline for clearing the refrigerator was approaching, he/she discarded all the plasmid DNA and polyclonal antibodies used in the experiments.

Questions

Describe how behavior of Student C might be problematic. Also, if you were the supervising faculty member, what instructions would you give to a student in such a situation?

An example of a viewpoint

The problem here is the “disposal of experimental samples without checking with the supervising faculty member”. Even if they are samples reproducible by referring to the recorded laboratory notebooks, the samples are owned by the research institute and should not be discarded without permission. The samples used in the experiments for the published paper should also be stored for a certain period of time to serve as proof that the experiments were indeed conducted. And even if the laboratory would be closed down, the principal investigator has a duty to check the regulations of his/her institution regarding the storage system for these samples and indicate the scope of items to be retained. The principal investigator should also consider the point whether the samples to be retained can be reproduced by looking at the data or not.

Hypothetical Case 4

Researcher D has been administering a Chemical Compound P to a disease mouse model and investigating its effect. It took Researcher D a considerable amount of time to conduct these experiments in the beginning as it was necessary to orally administer the solution of Compound P to a large number of mice using a special instrument. But once Researcher D got used to it, he/she was able to do it in less than one-fifth of the time originally required per mouse. While the results from concluding all the experimental data did confirm the efficacy of Compound P, Researcher D reviewed his/her data and realized that his/her crude handling of the mice during the experiments in the beginning subjected them to stress, which might have biased the results. However, as the results were consistent with that of another experiment that was conducted in parallel, Researcher D decided that the possibility of the bias was low, and not to record the possibility of influence of the stress in laboratory notebook. In fact, the efficacy of Compound P was subsequently demonstrated in another study as well.

Questions

Describe how behavior of Researcher D might be problematic. Also, what do you think Researcher D should have done instead to engage in responsible conduct of research?

An example of a viewpoint

Some of the problems in this case include “starting the main experiment without being proficient in the procedures”, “design mistakes in the experimental plan”, “intentionally not recording down the possibility of bias despite one’s awareness”, and “lack of discussion with others”. If there is a possibility of bias, one needs to record it down honestly, and try to eliminate the possibility by discussing with other researchers or replicate the experiments.

Hypothetical Case 5

A laboratory to which Researcher E belongs is conducting research using a stem cell called α. Researcher E learned the experimental methods from his/her supervisor, Faculty Member F, made a new purchase of the same α stem cells, and began his/her research using the differentiation culture conditions of stem cell α that took Member F five years to establish. However, Researcher E could not obtain the same results despite the fact that he/she had independently conducted the experiments using the protocol established by Member F. Researcher E then suspected that the data may have been fabricated and discussed this with Faculty Member R at the neighboring laboratory. Faculty Member R reviewed experimental records of Member F – which were intact and complete – and found no signs of misconduct. Faculty Member R also found that the experimental data can be reproduced by using the retained samples of Member F.

Questions

Describe the possible reasons as to why Researcher E could not obtain the same results despite using experimental conditions established by Member F. Also, what advice would you give both Researcher E and Member F regarding responsible conduct of research if you were Member R?

An example of a viewpoint

Some of the possible reasons are "Researcher E is not proficient in techniques of Member F", "there might be some knacks required in techniques of Member F but they are not detailed in the protocol", and "Member F had been culturing the α-strain stem cells for many generations; the properties of the stem cells may have changed from the newly purchased stem cells by Researcher E". Even if experiments are conducted faithfully and honestly, results may not always be consistent; it is not appropriate to immediately conclude that misconduct was involved with a lack of reproducibility. An honest attitude in reviewing and handling data would, in this case, recommend Researcher E to raise his/her suspicions candidly with Member F, while Member F should also be encouraged to consider the possibility of a technical bias in his research results.

Hypothetical Case 6

The laboratory of young Faculty Member G is a popular laboratory where many students work in. Research field of Member G is highly competitive; he/she publishes a large number of papers every year, and his/her students are required to conduct experiment efficiently. Member G therefore provided his/her students with careful and thorough research guidance by explaining the current research trends, hypotheses, as well as giving concrete examples such as the desired experimental results. As Member G wanted to accomplish both goals of educating the students and increasing productivity by quickly using the experimental data in papers to be submitted, his/her students were required to summarize the data for regular progress reports in his/her laboratory in the format of figures according to the submission guidelines of manuscripts, even the data or results were from preliminary experiments. To ensure that the experiments proceed smoothly with no delays, Member G also prepared a detailed protocol (including the minimum time required for the experiments) for his students, and set clear rules such that they must submit the experimental results/data in the prescribed format on the scheduled end date of the experiments. On top of this, Member G declared that he/she would give incentives to students who produced excellent outcomes ahead of schedules, such as employing them as RA (research assistant), to motivate them.

Questions

Identify the issues that may affect the reliability of the research data in the aforementioned research environment. Also, what kind of advice would you give to Member G, including plans to improve the situation, if you were the head of the department to which Member G belongs to?

An example of a viewpoint

The issues that one should pay attention to include “Being too specific about the desired experimental results”, “Asking students to create figures for hypothetical manuscript submissions based on data that has not been sufficiently validated”, and “Inciting students

to compete with each other with financial rewards, even if indirectly". Researchers who are in a supervisory or mentoring position need to be aware of the psychological impact of their own teaching and communication methods on students. While a competitive environment can increase productivity, one should appropriately anticipate and deal with the risks that may occur in data reliability under such a high-pressure environment.

Hypothetical Case 7

Graduate Student H learned about research ethics in class and decided to be very careful so as not to commit research misconduct. Student H carefully recorded down his/her laboratory notebooks, cautiously repeated his/her experiments, and was able to produce enough data to write a paper after about two years. When Student H was creating the figures during preparing the manuscript for submission, he/she checked the photos used in the figures and realized that there were two parts in the electrophoretic gel image of the control that were extremely similar. Student H reexamined his/her past laboratory notebooks and electronic data, and confirmed that he/she did not mix up the images. But he/she was afraid that he/she might be suspected of committing misconduct if the paper was published, and decided to partially redo the experiment and selected and replaced it with new images that would not arouse any suspicions. To be doubly sure, he/she also replaced the original gel images in his/her past laboratory notebooks with the new ones.

Questions

Describe how behavior of Student H might be problematic. Also, what do you think Student H should have done instead to engage in responsible conduct of research?

An example of a viewpoint

One potential issue here is the “replacing of images or photos in past laboratory notebooks”. Even if by chance there was indeed another figure that looked remarkably similar, one should present the paper as it is if there are evidence to prove the authenticity of the data. If one was to redo the experiment, then it should be noted down as a new experiment. One should refrain from modifying or revising past laboratory notebooks in a way that no one else can notice, even if the results are scientifically authentic.

Hypothetical Case 8

Faculty Member Q discovered in a preliminary experiment that a specific cellular factor ε has a new function that will overturn the established scientific theory, and he/she wanted to announce this result as soon as possible. Member Q then invited a Graduate School Student J, who was enthusiastic about research with highly evaluated abilities in terms of conducting precise experiments, to participate in this research topic. After explaining the results of the preliminary experiment to Student J, Member Q instructed Student J to promptly and quantitatively analyze changes in the expression level and binding amount of multiple target factors in dozens of samples, to evaluate the effect of the functional inhibition of this factor ε on mouse cells and individual mice. Student J finished the experiments ahead of expectations of Member Q, and summarized the results in easy-to-understand figures to Member Q. Faculty Member Q was very pleased because the change in the expression level of the target factor was consistent with the hypothesis derived from the result of his/her preliminary experiment. He/She then immediately prepared a manuscript based on the figures submitted by Student J, which was eventually published in the journal he/she had hoped for. When Member Q later went through the laboratory notebook of Student J, he/she realized that experimental records of Student J indicated that Student J had only conducted the first control experiment to ensure the quantification of the amount of RNA derived from the sample. When he/she checked with Student J, Student J replied that he/she was not aware that he/she was required to conduct a control experiment every time. Faculty Member Q immediately re-conducted the experiments himself/herself and was able to reproduce the same results, and he/she confirm that the experimental facts shown by the data in the publication remained correct. Member Q regained a peace of mind and decided to leave the publication as it was.

Questions

How are the actions of Member Q and Student J problematic? Also, describe the actions that Member Q and Student J should have taken from the perspective of responsible conduct of research.

An example of a viewpoint

When students conduct experiments based on instructions from faculty members, they may not be given detailed instructions in advance regarding specific matters such as control experiments. If so, students should take the initiative to update the faculty members or mentors with the progress of the experiments, and check if there are any problems with their work. Even if the faculty member believes the student to be excellent, he/she should not be overconfident in the student and take care to convey his/her instructions carefully and correctly. The faculty member should also regularly check the progress and results of the experiments based on raw data from the laboratory notebooks, and to personally scrutinize all the data again before submitting the manuscript. In addition, if one knows in advance that the experiment is complicated, or that it would be repeated on many samples, it is useful to document down the procedures in a detailed protocol, including the flow of experiment process (such as how to create control experiments), and give instructions based on this so as to properly manage the research. If any doubts arose in the publication, it is also advisable for the corresponding author to ask the editor at his/her own discretion whether or not to revise the paper, even if there are no substantial changes.

Hypothetical Case 9

A young Faculty Member K is conducting research as a principal investigator (PI) in collaboration with Associate Professor S at another university, who is an active researcher that is famous as a pioneer in the research field of Member K. Member K intends to obtain valuable suggestions on experimental methods and how to proceed with research by asking the experienced Associate Professor S to be his/her collaborator. Member K took the initiative and approached Associate Professor S for a joint research, hoping that the credibility of his/her research results would increase, and that name value of Associate Professor S would bring more publicity to outcomes of the study. Member K had a research meeting with Associate Professor S, and it came to an agreement on the experiments that would be conducted by Associate Professor S, and the joint research started. On his/her side, Member K proceeded the research and tasked a Graduate School Student L in his laboratory as the main person in charge of the experiments on this topic. Based on the experimental results provided by Associate Professor S according to the initial allocation of research work, Member K asked Student L to be the first author, and Student L started to write the paper with guidance from Member K. When Student L was finishing up the paper, he/she asked Member K that he/she would like to include Graduate School Student M and N as coauthors because "Student M taught me the experimental techniques when I was first assigned to the laboratory" and "Student N is a classmate who helped me with my experiment when I was busy" respectively. Member K readily agreed to requests of Student L. In addition, Member K sent the draft of the paper to Associate Professor S for his review and corrections, and he improved the draft through discussions. After that, Associate Professor S asked Member K to add two more coauthors, including Professor U (the PI of the laboratory where Associate Professor S belongs to) and Student T (a student who was actually contributed to the experiments); Member K also agreed to requests of Associate Professor S. As Member K thought that advice from Associate Professor S was extremely vital to this research, he/she changed the last author to Associate Professor S as a sign of his/her gratitude just before submitting the final manuscript via the online manuscript submission system, while Member K listed

himself/herself as the fourth and corresponding author.

Questions

Recalling the customs in your own research field, are the behaviors of the Member K, Student L, and Associate Professor S problematic in this case from the perspective of responsible conduct of research? If so, how? Also, what kind of preventive measures can one take to avoid issues with authorship in this case?

An example of a viewpoint

In determining the authorship and its order, not only respecting the customs of each research field, but the corresponding author's fair understanding of actual contribution of the coauthors is important. In recent years, there have been many demands for the clarification of the substantial contribution (also in terms of responsibility for its experimental results) by each author. For authorship, it is desirable that the coauthors understand what each author has contributed, including the importance of the contribution, and that the corresponding author should manage this appropriately.

In this case, Member K should be clear which students in his laboratory participated in the research from the stages of planning and conducting the experiments. Based on the importance of the contribution, Member K should decide who should be the authors, and who to mention in the Acknowledgements section. To make that decision, Member K should discuss with his/her coauthors to ensure that there is common understanding before finalizing the draft for the paper, and to notify the coauthors in advance when the author order is finalized before submitting the manuscript. Student L should have consulted with Member K before letting others help with his/her research. During the joint research meetings with Member K, Associate Professor S should have checked with Professor U (the PI of the laboratory where Associate Professor S belongs to) first regarding who will participate in this research, including the authorship, before conveying his thoughts to Member K. At the same time, Member K. who is the researcher leading this project, should make common consensus about coauthors with Associate Professor S.

In order to avoid issues concerning authorship, it is helpful for the PI to clarify the

concept of authorship in his/her laboratory in advance and to let everyone in the laboratory know. Especially in the case of joint research, one should check the list of participants of other party as well as the specific parts they are in charge of before submitting the manuscript, and one should make adjustment to alterations as they arise. This is important measure to avoid potential problems and issues.

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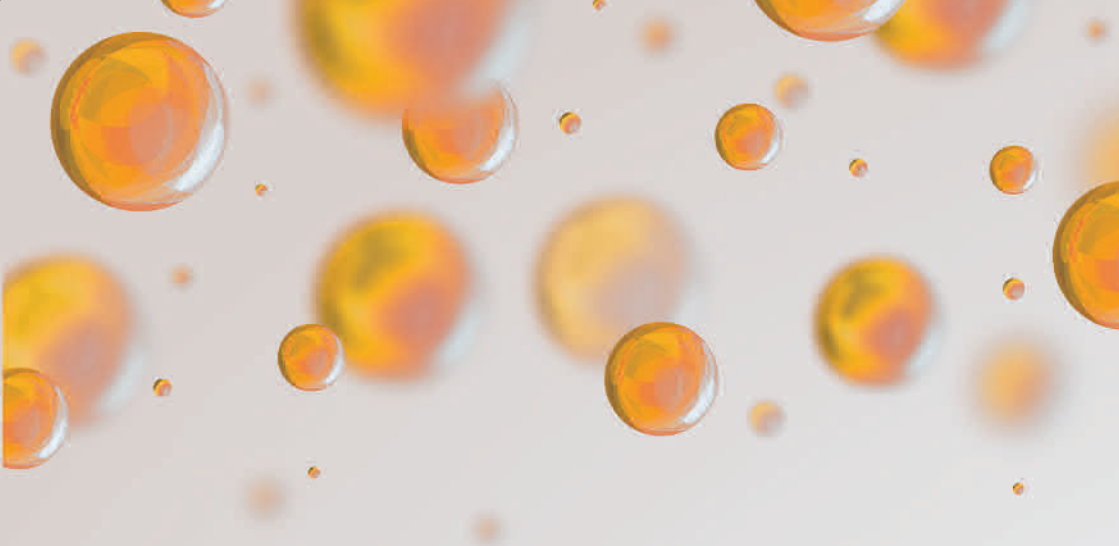

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