SCOPE OF RESEARCH MISCONDUCT

The Office of Research Integrity (ORI), Department of Health and Human Services (HHS), has oversight authority for institutional investigations of possible research misconduct when U.S. Public Health Service (PHS) funds are involved. ORI relies on the institutions to investigate allegations of research misconduct. The purpose of this document is to provide information to assist institutional officials who are responsible for addressing allegations of possible research misconduct with fulfilling their obligations under 42 C.F.R. Part 93, Public Health Service Policies on Research Misconduct (Final Rule). The contents of this document do not have the force and effect of law and are not intended to bind the public in any manner. This document is intended only to provide clarity to the public regarding existing requirements under the law or agency policies.

An important issue that has arisen in the course of investigations conducted by institutions into allegations of research misconduct is the determination of what the scope of such investigation should be. The scope of research misconduct refers to an institution diligently pursuing all significant leads discovered to be relevant to an investigation (42 C.F.R. § 93.310(h)).[1] It is possible that the scope of the research misconduct is limited to the initial allegation(s). It also is possible that the allegation(s) may be an indication of widespread research misconduct that can be identified only by expanding on the leads discovered during the examination of the allegations.

The determination of the scope of the research misconduct follows the research misconduct proceedings. For example, if during the inquiry the allegation is determined to be credible and specific, the scope is often limited to evaluating papers and grants that are directly related to the initial allegation. Prior to the institution making a determination that investigation is not warranted, the institution should perform a cursory review of other papers and grant applications within the six-year time limitation (§ 93.105(a)) to eliminate the possibility of any additional instances of potential misconduct. At the investigation stage, the scope of research misconduct should include: (1) examining all relevant underlying raw data/documents to validate/support the research findings or to make a determination of research misconduct; (2) examining additional papers and grant applications of the respondent(s) that contain similar data elements as that of the initial allegation(s); (3) if more questionable data are found, then further expand the scope to include documents that come under the subsequent use exception and analyze other data elements (blots vs microscopy images vs other analytical data).

For papers with alleged questionable data that are beyond the six-year time limitation in § 93.105(a), there is a subsequent use exception (§ 93.105(b)(1)), which states:

> ***Subsequent use exception:*** The respondent continues or renews any incident of alleged research misconduct that occurred before the six-year limitation through the citation, republication or other use for the potential benefit of the respondent of the research record that is alleged to have been fabricated, falsified, or plagiarized.

An institution should determine whether the subsequent use exception applies to any papers published or grant applications submitted outside of the six (6) year period that contain potentially falsified, fabricated, and/or plagiarized data or text. The subsequent use exception does not apply to those papers of the respondent(s) that were cited in past six years by a person or a group other than the respondent(s).

An institution that does not adequately address the scope of the potential research misconduct in accordance with § 93.310(h) and perform timely sequestration of research records (§ 93.307(b) and

[1]The institutions are responsible for making the relevancy determinations that are included in the Final Rule. *See* 70 FR at 28373.

§ 93.310(d)) may compromise the effective handling of the investigational process and may allow undetected research misconduct to remain in the literature or to be used in applications for PHS funds. In some cases, ORI has requested that an institution initiate an investigation or conduct a second investigation to examine questionable data in other papers, grant applications, or research records that initially were overlooked by the institution.

Importance of Addressing the Full Scope of Research Misconduct:

- Avoid repeated research misconduct proceedings.

- Help strengthen the research misconduct findings by establishing a pattern, intent, and/or significance and, in some cases, proving culpability. Review of presentations, theses, grant applications, and research records can implicate a particular individual, which can be difficult in a publication with multiple authors.

- Determine specific research misconduct findings and implement appropriate administrative actions, as the scope of the misconduct is a consideration in this decision.

- Publish complete and detailed research misconduct findings.

Leads That May Warrant Expanding the Scope:

Expanding the scope means exploring the possibility that the potential research misconduct extends beyond the initial allegation(s). This is achieved by evaluating relevant leads that warrant expanding the scope beyond the initial allegation(s), for example:

1. Pattern of behavior:

    a. The occurrence of falsifications/fabrications in multiple figures in the same paper or multiple papers/grant applications and/or over an extended period of time

    b. The occurrence of the same type of falsifications/fabrications in several figures:

        i. reuse and relabeling of Western blot panels, microscopy images, flow cytometry graphs or reuse with or without manipulation of the same source data
        ii. reuse of a portion/section of the Western blot panel or microscopy image
        iii. reuse and relabeling with manipulation or alteration of the image or data

2. Repeated or extensive use of methodology/technique that a respondent had used to generate the questioned data:

    a. Respondent may have generated previously published data of the same type generated using the same technique/method

3. Testimony or other evidence that the experiments were not performed:

    a. Respondent rarely present in the laboratory or not utilizing the laboratory instruments necessary to conduct the experiments and generate the data

    b. No laboratory notebooks or research records

c. A paucity of original data on laboratory computers/hard drives/flash drives or experimental computer hard drives (e.g. RT-PCR, ELISA, FACS, microscopy, Excel spreadsheets, etc.).

In an effort to assist institutions with determining whether a significant issue or lead may be relevant while conducting a research misconduct proceeding, ORI has constructed several hypothetical case examples. ORI has provided these case examples as representative scenarios that institutions may encounter and how the scope of research misconduct may be determined.

The information provided in this part does not prohibit or otherwise limit how institutions handle allegations of misconduct that do not fall within the PHS definition of research misconduct or that do not involve PHS support. The federal regulations do not replace the authority of institutions to establish their own professional norms on the responsible conduct of research.

ORI recognizes that these hypothetical case examples do not address all of the particular challenges or concerns that an institution may face when determining which leads or significant issues to pursue in their research misconduct proceedings. The Division of Investigative Oversight (DIO) can provide assistance concerning the scope of the research misconduct or the handling of cases. The DIO Director or DIO Scientist-Investigators can be contacted at (240) 453-8800 or by writing to AskORI@hhs.gov.

CASE 1: Allegation of reusing and relabeling Western blot panels in multiple figures in one (1) paper.

Background: The institution conducted an inquiry and identified additional issues with figures representative of RT-PCR and immunofluorescence experiments in the same paper. Fifteen (15) allegations were determined to merit proceeding to an investigation.

Institutional Actions: The institution conducted an investigation and determined that one of the two respondents committed research misconduct. The authors retracted the paper containing the questioned data. The investigation committee's review of the respondents' other papers and grant applications did not find any evidence of additional research misconduct. The investigation committee presented the findings as poll results of the committee members for each allegation but did not make a final determination for any of the allegations. The investigation committee did not recommend any administrative actions for the respondent who committed the research misconduct.

DIO Review: DIO's oversight review of the investigation report and evidence identified multiple concerns of image duplications in the form of relabeling and reusing images in several additional papers (including the ones reviewed by the investigation committee), grant applications, and grant progress reports. DIO requested that the institution:

1. Re-open the investigation.

2. Expand the scope to include the additional papers, grant applications, and grant progress reports (§ 93.310(h)).

3. Direct the investigation committee to make a final determination for each allegation, identify the responsible person for each allegation, and state the intent (§ 93.313(f)).

4. Direct the investigation committee to recommend specific administrative action(s) against the respondent.

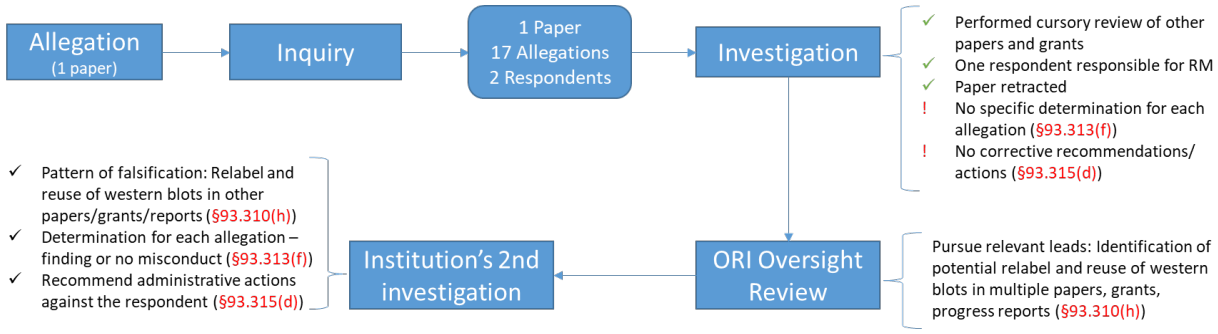
Scope Considerations: In accordance with § 93.310(h), the institution reviewed the respondents' other grant applications and papers but did not find any evidence of additional research misconduct. DIO's review included a comparison of Western blot images across the respondents' papers and grant applications, which identified additional instances of potential research misconduct in the form of relabeling and reuse of Western blot panels. Therefore, the following may assist the institutions in appropriately addressing the scope of research misconduct in this case:

1. Look for potential relabeling, resizing, and reuse of images (i.e., Western blot/PCR/microscopy lanes/panels) across different papers/grant applications/reports. This may extend to the review of individual data points or plots within one graph/image.

2. Look for a pattern of falsification, such as single or multiple instances of reuse and relabeling, horizontal/vertical rotation, reuse of the whole or a portion/section of a source image, and/or contrast or size manipulations to obscure/highlight bands/areas.

3. Look for differences in the figure legends, labels, and manuscript/grant application text descriptions.

Overview of Case 1



CASE 2: Allegations of falsification of Western blots in multiple figures in ten (10) papers published from 1995-2010.

Background: Allegations involving papers published more than 10 years ago were sent by an anonymous complainant to the institution in 2020. The institutional inquiry determined that there was a paucity of raw data and the evidence was sufficient only to proceed to an investigation for allegations involving one (1) published paper.

DIO Review: DIO's review of the inquiry report and evidence identified additional concerns with the figures not included in the original allegations. DIO requested that the institution: (1) proceed to an investigation; (2) determine PHS jurisdiction, in accordance with the subsequent use exception (§ 93.105(b)), for possible examination of the older papers; and (3) perform forensic image analysis of questionable figures included in the papers that are under ORI's jurisdiction per the subsequent use exception.

Institutional Actions: The institution determined that falsification occurred but was unable to determine the culpability for intentional, knowing, or reckless research misconduct. Institutional actions included retraction requests of four (4) published papers and imposition of a three-year supervision period for the respondent.

Scope Considerations: In this case, due to the time that had passed since publication of the papers, the institution determined that research misconduct either was out of ORI's jurisdiction (§ 93.105(a)) or did not warrant an investigation because of the lack of raw data. DIO's review determined that there were additional concerns of research misconduct in the figures that were not included in the original allegations. Therefore, the following may assist the institution in appropriately addressing the scope of research misconduct in this case:

1. A lack of raw data should not be the sole determinant in deciding not to proceed to an investigation. The regulation, specifically § 93.307, requires institutions to conduct an inquiry to determine whether an allegation warrants an investigation, not whether research misconduct occurred.

2. The lack of raw data should not automatically result in a no misconduct determination. Use other evidence, including testimony, emails, hard drives, and independent forensic image analysis to assist with the determination of intent and responsibility.

3. Investigate all Western blot panels in the figures in the papers included in the initial allegations and in those papers that fall within the subsequent use exception.

4. Perform forensic image analysis of the figures that have indicia of falsification.

5. Note the specific type of falsification/fabrication, pattern (i.e., reuse and relabeling, rotation and/or flipping of a section of the original image) and period of time during which the potential research misconduct occurred.

6. Use the type, pattern, and time frame to guide the determination of intent.

CASE 3: Allegations of falsified Western blot panels in multiple figures in seven (7) papers.

Background: ORI received and assessed the allegations and submitted them to the institution. Seven individuals were named as respondents in the inquiry. The institutional inquiry committee used the respondents' interviews and image analysis performed by the respondents to determine that although the data were altered, the research record was not misrepresented. The inquiry committee determined that there was no credible evidence of research misconduct and an investigation was not warranted. In accordance with § 93.309(c) and § 93.400(b), ORI requested a copy of the institution's inquiry report.[2]

DIO Review (Inquiry): DIO performed forensic image analysis of the images noted in the allegations and additional images included in the questioned papers. DIO analyzed additional papers of the respondents' that fell under ORI's jurisdiction as a result of the subsequent use exception. In total, figures in twelve (12) papers reviewed by DIO contained multiple indicia of cutting and pasting of Western blot and/or RT-PCR bands from different sources to potentially fabricate "composite panels." DIO's oversight review also identified following procedural concerns:

1. The institution's determined at the inquiry stage that research misconduct had not occurred, which resulted in its decision to not proceed to an investigation. The regulation, specifically § 93.307, requires institutions to conduct an inquiry to determine whether an allegation warrants an investigation, not to determine whether research misconduct occurred.

[2]An institution is not required to inform ORI of its decision to not proceed to an investigation, in accordance with § 93.309(c). However when ORI requests that an institution perform an inquiry under § 93.402, ORI recommends that the institution inform ORI of the outcome of its inquiry, per § 93.400(b) and § 93.300(g).

2. The institution relied on the respondents' image analysis.

3. The institution conducted a group interview of the respondents, with one respondent providing answers for the group.

DIO requested that the institution proceed to an investigation for the expanded scope of the twelve (12) papers containing images of concern.

Institutional Actions: The institutional investigation resulted in a determination of no misconduct due to: (1) the lack of raw data precluding the investigation committee's ability to determine if the composite panels were indicative of the actual data (respondents discarded the raw data on separate occasions); and (2) the inability to assign responsibility for each allegation to one respondent.

DIO Review (Investigation): DIO's review of the investigation report determined that twelve (12) papers contained figures with falsified/fabricated data. The research misconduct included composite panels assembled by cutting and pasting Western blot or RT-PCR bands from different source panels to fabricate a "composite panel" and placement of a black box over a set of bands to obliterate the presence of protein expression. One respondent admitted to making the figures reported in the papers and discarding the raw data. The Principal Investigator (PI) outlined each respondents' responsibility in the laboratory, and the image manipulations began to appear after the PI hired the specific laboratory member who admitted to making the figures. The evidence supported a finding of knowing and intentional research misconduct against one respondent and reckless research misconduct for another.

Scope Considerations: In this case, several procedural errors limited the institution's ability to identify leads and determine the scope of research misconduct. The institution relied on the respondents' image analysis to evaluate if the research misconduct occurred. Further, during group interviews one respondent answered for all of the respondents, which could have resulted in a missed opportunity for any one of the respondents to raise concerns or provide specific input regarding the questioned data or research practices in the laboratory. Therefore, the following may assist in identifying potential leads and determining the true scope of the research misconduct:

1. To help identify potential leads:

    a. Perform independent forensic image analysis (or hire a professional firm).

    b. Interview respondents individually, preferably at times not known to each other.

    c. Listen for different responses to the same question (by one or multiple respondents and other research staff) and the assignment of specific actions to one's self or to others. This assists in the assignment of culpability and intent.

    d. Review the papers for common authors (first, second, last) and briefly assess other grant applications/papers at the inquiry stage. This assists in determining scope and the assignment of responsibility.

2. During the inquiry stage, determine whether an allegation warrants an investigation (§ 93.307(d)), specifically that there is a reasonable basis for concluding that the allegation falls within the definition of research misconduct and involves PHS support, and determine whether preliminary information-gathering and preliminary fact-finding from the inquiry indicates the allegation may have substance.

3. Prior to determining that an investigation is not needed, briefly assess earlier papers/grant applications to elicit if there is a pattern/history of falsification/fabrication/plagiarism. This will also assist in determining which individual(s) may or may not be involved (i.e., additional respondents may be named and have their data sequestered after notification).

CASE 4: NIH referred an allegation involving possible reuse and relabeling of Western blot data in two different grant applications.

Background: The respondent submitted a grant application in 2018 to NIH reporting pilot data using a human cell line. The respondent then included portions of the same data in a NIH grant application submitted in 2019 representing results from a mouse study. DIO assessed the allegation and requested that the institution perform an inquiry.

Institutional Actions (Inquiry): The Research Integrity Officer (RIO) assessed the allegation and confirmed that the questioned images in the two grant applications shared a source image. Prior to performing the sequestration, the RIO informed the respondent of the allegation. The respondent stated that an honest error was made in figure preparation for the 2019 grant application, as a postdoctoral fellow provided the image from the 2018 grant as a "place holder" for the figure included in the 2019 grant. He apologized for the error and provided another Western blot image, which he reported represented the correct experiment.

The inquiry committee acknowledged that mistakes could occur when assembling figures and accepted the respondent's provision of the "correct" data. The committee determined that the reuse and relabeling of the image was an isolated incident due to honest error, research misconduct had not occurred, and proceeding to an investigation was not warranted.

DIO Review (Inquiry): DIO identified additional instances of reuse and relabeling images in the respondent's other NIH grant applications. DIO's oversight review of the inquiry report revealed the following concerns that could have affected determining the credibility of the allegations during the inquiry:

1. Failure to perform sequestration in a timely manner.

2. Notifying the respondent of the allegations prior to the sequestration of evidence.

3. Only interviewing the respondent and not considering an interview with the postdoctoral fellow.

4. The inquiry committee's determination that the research misconduct had not occurred even though § 93.307 requires institutions to conduct an inquiry to determine whether an allegation warrants an investigation, not whether research misconduct occurred.

DIO requested that the institution: (1) immediately sequester all data related to the allegations; (2) proceed to an investigation; (3) expand the scope of the investigation to include published papers and grant applications; and (4) inform the postdoctoral fellow that she/he was being named as a respondent.

Institution Actions (Investigation): The investigation committee identified multiple instances of image reuse and relabeling in several of the respondent's grant applications and PHS supported papers. As the respondent was unable to produce the original source data, the investigation committee was unable to determine the intent. The investigation committee made a determination of reckless research misconduct.

Scope Considerations: In this case, the following may assist the institution with identifying leads and determining the scope of the research misconduct and culpability for intentional, reckless misconduct:

1. Perform sequestration prior to or at the time the respondent(s) are notified of the allegations. This maintains the provenance of data and helps identify relevant leads, which can help to determine the scope of the research misconduct.

2. During the investigation stage, interview the respondent as well as other individuals involved in the research. Conduct separate interviews. Interviewing the research staff can aid in the determination of: (a) the scope (i.e., Is the potential misconduct limited to the two grant applications, or does it extend to the papers reporting the research?); (b) identifying the individual(s) responsible for the potential misconduct (i.e., Should the postdoctoral fellow also be named as a respondent?); and (c) the intent (i.e., Did the postdoctoral fellow provide the correct images to the PI? Did the PI change the images? Did the postdoctoral fellow change the images?).

3. During the inquiry stage, determine whether an allegation warrants an investigation (i.e., there is a reasonable basis for concluding that the allegation falls within the definition of research misconduct and involves PHS support) and whether preliminary information-gathering and preliminary fact-finding from the inquiry indicates the allegation may have substance. Please note, interviewing individuals other than the named respondent at the inquiry stage can help guide the inquiry and, if necessary, the subsequent investigation.

CASE 5: Allegations of possible reuse and relabeling of a microscopy image and the falsification of the reported sample size and *p*-values in a published paper.

Background: The named respondent was a graduate student and the first author of the published paper. DIO assessed the allegations and requested that the institution perform an inquiry.

Institutional Actions: The RIO and inquiry committee worked with the IT staff to identify, locate, and remotely access and acquire forensic copies of the research files located on the laboratory's shared network drive as well as the laboratory members' email contents. The RIO and IT staff subsequently notified the graduate student and the mentor of the allegations. At that time, the RIO and IT staff made forensic copies of all laboratory work computers, shared equipment computers, and external flash drives and made physical copies of all laboratory staff's physical notebooks.

The inquiry committee noted that the data recorded on the spreadsheets used in performing the statistical analyses did not accurately reflect the data used to generate the bar graphs for the paper. The reuse and relabeling of the source image, combined with the inaccurate data recorded for generation of the statistical analyses and graphs, resulted in the inquiry committee's determination that proceeding to an investigation was warranted.

The investigation committee evaluated recent NIH grant submissions, published papers, manuscripts in preparation, laboratory meeting presentations, and poster presentations and interviewed all laboratory staff. The key evidence identified during the investigation included:

1. Laboratory trainees generated all of the raw data.

2. The PI was solely responsible for generating the figures and conducting the statistical analyses included in grant applications and manuscripts submitted for publication.

3. The students generated the figures for posters and local research conference presentations.

4. Examination of the PI's computer revealed evidence of fabrication of data for generation of the false *p*-values.

5. No evidence of image duplication was located on the student's computer.

The investigation committee determined that the PI knowingly and intentionally falsified 20 figures and fabricated the statistical data and significance reported in four (4) NIH grant applications and six (6) published papers.

DIO Review: DIO conducted an oversight review and did not identify any additional concerns about possible falsified and/or fabricated data in other research records.

Scope Considerations: In this case, the following actions taken by the institution assisted in identifying leads and determining the scope of research misconduct as well as culpability for intentional falsification and fabrication of research data:

1. Early and adequate sequestration performed prior to or at the same time the respondents were notified of the initiation of the inquiry.

2. Consideration of more than one respondent.

3. Extension of the interviews beyond the respondent and complainant.

4. Evaluation of laboratory equipment and computer access and how the data was stored.

5. Evaluation of the research processes in the laboratory to assign responsibility.