

## Casus Wetenschappelijke Integriteit

2022

### Manipulation and fabrication of data in scientific publications that are part of PhD-thesis – PhD thesis does not comply with standards of research integrity.

Universiteit Utrecht

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*The complaint was filed and handled in English.*

1. Report of findings and recommendation of the UU Research Integrity Committee (CWI)

#### **REPORT OF FINDINGS AND RECOMMENDATION by the Utrecht University Research Integrity Committee (CWI) concerning the complaint of [...] (complainant), [...], about a possible breach of research integrity by [...] (defendant), [...].**

The allegations made by complainant concern a possible breach of research integrity, specifically possible manipulation and fabrication of data in scientific publications that are part of the PhD-thesis [title] of defendant on the basis of which the College voor Promoties (Board for the Conferral of Doctoral Degrees) of Utrecht University awarded defendant a doctoral degree on [date], pursuant to Article 7.18 of the Wet op het Hoger onderwijs en Wetenschappelijk onderzoek (WHW).

The complaint was handled according to the Research Integrity Complaints Procedure Utrecht University 2019 (Complaints Procedure). A committee was established to investigate the complaint. The members of the committee were:

- [...]
- [...]
- [...]

The committee was supported by [...] LLM and [...] LLM from the Legal Department of Utrecht University.

The Netherlands Code of Conduct for Academic Practice of 2004 applies in this case.

#### **Procedure / Timeline**

In August 2020, the Executive Board of Utrecht University was made aware of possible data manipulation in several scientific publications of defendant. This claim was substantiated in a scientific publication [Publication X]. In this publication, several papers of defendant have been analysed. All nine papers in the PhD-thesis are part of this analysis.

Defendant replied publicly to the allegations ([title]) and discussed the statistical methods used by [authors of Publication X] in their analysis.

We refer to the Appendix of our report for a summary, made by this committee, of the methods and allegations in [Publication X], in relation to the publications of the defendant.

In [date], the journal [title] published retractions of [...] papers by defendant, [...] which are part of the PhD-thesis [...], and published expressions of concern for [...] further papers by defendant, [...] which are part of the PhD-thesis [title].

In September 2020, the Executive Board asked the CWI to do a preliminary investigation of the public allegations against defendant and to assess the evidence of alleged misconduct that had been presented as well as the strength of the argumentation by the journals involved. The Executive Board had not yet received a formal complaint by complainant, it based its assignment on Article 2.3 of the Complaints

Procedure. The CWI learned that the defendant's employer, [...], was also investigating allegations concerning the integrity of the work of defendant.

On [date], a description of the allegations in [Publication X] and subsequent retractions appeared on the public website [title].

On 25 November 2020, the CWI informed the Executive Board of the findings of the preliminary investigation and recommended to wait for the outcome of the investigation that [defendant's employer] had already started. Depending on the outcome of this investigation, the Executive Board could then assess whether the conclusions would be based on a thorough investigation in line with Utrecht University standards and decide how to proceed.

On 7 April 2021, the CWI received a formal complaint by complainant. The complainant was asked to complete his complaint with additional information before 28 April 2021.

On 18 May 2021, complainant was informed by the CWI that his complaint had been deemed admissible and would be dealt with in substance.

On 19 May 2021, defendant was informed about the formal complaint and was asked to reply before 9 June 2021.

On 7 June 2021, the CWI received a message from [...], secretary of defendant, stating that defendant had been infected with Covid 19 a month earlier and was still under extensive treatment and unable to respond to any request. [The secretary of defendant] would update the CWI regarding the condition of defendant.

On 14 June 2021, complainant was informed about the situation.

On 26 August 2021, the CWI sent defendant a reminder.

On 8 September 2021, the CWI received a reply to the complaint by [the secretary of defendant], on behalf of defendant. According to this message defendant was still under the care of the medical team and unable to communicate directly with the CWI. Defendant would not be able to attend a hearing.

On 11 October 2021, the CWI sent defendant additional questions for clarification.

On 13 October 2021, the CWI received a reply to the additional questions by [the secretary of defendant], on behalf of defendant. The complainant was informed by the CWI about the defendant's replies.

On [date], a public blog appeared written by [dr. Y] containing another statistical analysis of publications by the defendant, including all chapters of the PhD-thesis. The blog's web address is [...]. The committee felt it relevant to take this into account in its procedure. We refer to the Appendix of our report for a summary, made by this committee, of the method and main findings of [dr. Y], in relation to the publications of the defendant.

On 7 December 2021, the CWI asked an independent expert, [...], of the Department of [...] at [...] University, to assess the analyses by both [authors of Publication X] and [dr. Y] of the publications of the defendant and to answer specific questions from the CWI on the appropriateness and reliability of the methods that were used.

On 24 December 2021, the CWI received the assessment by [the independent expert].

On 27 January 2022, the CWI informed both complainant and defendant about the assessment by [the independent expert] and asked them for their comments.

On 29 January 2022, the CWI received the response of complainant.

On 11 February 2022, the CWI received the response of [the secretary of defendant], on behalf of defendant. The response consisted in its entirety of a report written by a third party, prof. [Professor Z]. Both parties were informed about each other's responses. No further reactions were requested as the committee felt sufficiently informed to formulate the advice.

## **Facts**

Defendant has never been an employee of the University Medical Centre Utrecht (UMCU) or Utrecht University (UU). He was an external PhD-candidate. All research for his PhD-thesis was carried out in his

home institution [...] and all co-authors are from that institution. The PhD-thesis is publicly available from the UU-website (Utrecht University Repository) and from DANS/Narcis. The promotor and co-promotor were not involved as co-author in any of the papers and none of the papers has an affiliation to UMCU or UU.

The PhD-thesis consists of the following nine papers. All were published at the time of the completion of the manuscript for the PhD-thesis and the public defence on [date] (either in definite form with volume and page numbers or online on the journal's websites). Below are the final references, with volume and page numbers, in the order in which they appear in the thesis:

- Chapter 2. [title]
- Chapter 3. [title]
- Chapter 4. [title]
- Chapter 5. [title]
- Chapter 6. [title]
- Chapter 7. [title]
- Chapter 8. [title]
- Chapter 9. [title]
- Chapter 10. [title]

Up until the date of finalizing this report, the journal [title] has published retractions of [...] papers, [...] and [...], and has published expressions of concern for [...] further papers, [...] and [...]. The journal [title] has published an Editor's Note of concern for a further paper, [...].

### **Arguments of the complainant**

The complainant is the last author of [Publication X] (2020). His complaint is based on the arguments in this publication [date], later augmented with the publicly available statistical analysis of [dr. Y] [date]. The complainant's specific concern on the PhD-thesis of defendant is based on allegations of copying of tables from one chapter to another chapter. According to complainant, the evidence in [Publication X] shows that defendant copied data from other chapters or from his earlier publications in seven of his nine thesis chapters.

Complainant provided the CWI with this overview:

[table]

The publications of the defendant were subjected to four different methods of analysis: i) last digit analysis (by [authors of Publication X].); ii) random sampling analysis of baseline characteristics using a method of Carlisle (by [authors of Publication X].); iii) comparison of tables with baseline characteristics ([authors of Publication X]); and iv) re-analysis of the statistical tests reported in the publications (by [dr. Y]).

The aforementioned concern of the complainant, possible copying of tables, concerns the third of these methods. A second part of the complaint is the allegation in [Publication X], using the 'Carlisle method' that randomisation in the Randomised Controlled Trials (RCTs) has not been properly carried out. The complainant argues that this suggests serious data integrity issues in the published RCTs, among them the chapters of the PhD-thesis of the defendant. See the Appendix for more details on Carlisle's method in relation to the RCTs published by the defendant.

The complainant states, in his response of 29 January 2022, that the statistical analysis of [dr. Y] shows that the thesis of defendant “is full of statistical errors and that the evidence of data-copying of the tables explains why these statistical errors are there; defendant never did any analysis, but just made up the data, hence the mistakes.” According to complainant, the fact that the last digit analysis of [authors of Publication X] is not considered persuasive by the independent expert, [...], does not play down any of the evidence that proves fabrication of the PhD-thesis.

Complainant wants Utrecht University to retract the doctoral degree awarded to defendant in [date], because of the manipulation and fabrication of data in his PhD-thesis. Complainant also asked to investigate the role of the co-promotor, [...], professor at [...] University.

### **Arguments of the defendant**

The defendant states that he started his career in [...] since 1990, became a full professor in [year] and that “he was not charged, before this situation, over the years with any fraud in his research” and “was deeply insulted after all these years of professional and academic careers to face accusation like this”. He writes that “the PhD bestowed on him in Utrecht university was an honorary degree for him” (underlining by defendant). Moreover, he wonders “why there should be any doubts about the research integrity in such a situation while there were no obligations to do it from the start.” In his final words, he remarks that he “can return back the honour bestowed on me by Utrecht University (...) if you see that this [is] appropriate for my reputation as well as the name of your university” (underlining by defendant).

According to the defendant, “all the studies included in the thesis are dating back to 13-16 years and the raw data are not, as expected, available due to absence of electronic recording, by that time, both in the governmental and private settings”. The defendant states in his reply of 8 September 2021: “By that time we had no electronic system of recording and our formal IRB was established in 2015 before which no obligations for keeping the raw data of published research for that long time. Also, the journals by that time did not have, in their agreement form, a similar obligation for publication.” According to the defendant the precise answers on specific queries would therefore be difficult. The defendant further states on 8 September 2021: “However, as shown in all the studies randomization was done using numbers in closed envelopes handed to the patients by the nurse in charge. This was done for the patients in the hospital and the private settings.”

The defendant points to the formal reply to the article of [authors of Publication X](2020) in his publication: [title] ([journal], 2020). According to the defendant, his public reply shows clearly that there was no unusual proximity in the data base of the studies. In addition, in his statement of 8 September 2021, the defendant points to “recent papers and correspondences about the inaccurate methods used by the complainant and his team trying to show the possibility of research integrity issues in the papers”.

According to the defendant, “the publication committee of [journal] took a hasty and rapid decision of retraction of some old papers based on false information and they did not wait until the formal investigation was completed”.

The defendant states that he has doubts about the motives of the complainant and speaks of a “flamed relationship between the complainant” and him.

The defendant also “formally requests the testimony of Professor [...], the supervisor of the thesis and [...], the co-supervisor in this case”.

On 11 February 2022, the defendant responded to the assessment by the independent expert, [...], by sending a report dated 10 February 2021, written at his request by a third party, [Professor Z], Department of [...], Faculty of Medicine, University of [...], [country].

[Professor Z] states that he “has prepared his report as an independent expert” and that in this report he has undertaken an overall academic appraisal of post-publication integrity tests including those in the

paper by [authors of Publication X]. [Professor Z] further states that he hasn't had access to the peer-review reports, editorial assessments or the raw data of the trials in question. [Professor Z] emphasizes that all clinical trials, however well planned, executed and analysed, are error-prone. [Professor Z] states: "The age of the trials in question is an important factor. The relevant standards are the standards to be applied at the time of trial approval, conduct and publication. It is important to recognise that current standards are not applicable retrospectively."

[Professor Z] assesses the methods used by [authors of Publication X]: (a) last digit distribution, (b) baseline comparisons within trials, and (c) comparisons across trials. According to [Professor Z], "the tools currently available for 'after-the-fact' integrity checking have generally not been robustly validated."

[Professor Z] further states that he has not analysed the additional analysis in [dr. Y's] blog and that he considers a blog to be a publication that is entirely within the author's own control, not subjected to peer-review.

## Legal framework

The Complaints Procedure contains rules regarding the scope of the investigation by the CWI and rules authorising the CWI to advise the Executive Board to refrain from taking up the substance of a complaint. In this case, the following rules are relevant:

### Paragraph 1 Definitions, Article 1.5:

(...)

1.5 Employee: The person who has or used to have an employment agreement with the institution or is or used to be otherwise employed under the responsibility of the institution.

This includes those persons who are not employed with the institution or are only employed with the institution on a part-time basis, insofar as they participate in the institution's research or publish their research under the name and responsibility of the institution. It excludes those persons who are only involved in the research in a supporting role.

(...)

### Paragraph 4 Research Integrity Committee, Article 4.5 d I.

(...)

d. The committee is authorised to recommend that the Board not deal with the substance of the complaint if

I. too much time has passed since the supposed breach, or the complainant has waited an unreasonably long time to submit the complaint. In this regard, in principle, a term of ten years applies;

(...)

The Netherlands Code of Conduct for Academic Practice of 2004 (Code of Conduct 2004), which applies in this case, contains the assessment framework for proper research practice. The Code of Conduct 2004 was adopted by the General Board of the Association of Universities (Algemeen Bestuur van de Vereniging van Universiteiten) on 17 December 2004 and came into force as from 1 January 2005.

The Code of Conduct 2004 contains principles that all members of the academic community should observe both individually and vis-à-vis each other and society. These principles can be read as general notions of good academic practice and as a self-regulatory instrument. The overarching principle is that every academic practitioner is bound by the frameworks established by Dutch and international legislation. A second overarching principle is transparency; every academic practitioner must (be able to) demonstrate how they put these principles into practice.

The Code of Conduct 2004 sets out five principles of proper academic practice:

- I. Scrupulousness
- II. Reliability
- III. Verifiability
- IV. Impartiality
- V. Independence

These principles are detailed further in the respective “Elaboration” sections of the Code of Conduct 2004. These elaborations, which provide a set of standards for the conduct of teachers, researchers, students, and administrators, reflect the national and international best practices of good academic teaching and research. Here, we give the principles, standards, and elaborations the committee considers most relevant to the complaint.

#### I. Scrupulousness:

Standard I.1: The first aspect of the elaboration of this principle states that “Academic practitioners know that the ultimate aim of science is to establish facts and they therefore must present the nature and scope of their results with the greatest possible precision”. Researchers must therefore work with the dedication and precision that “a proper exercise of the profession requires”. This scrupulousness extends, according to the Code, to not unnecessarily or disproportionately harming the interests of third parties.

#### II. Reliability:

Standard II.1: The first aspect of the elaboration of this principle states that “Research data have indeed been collected”. In the further elaboration of this principle, the Code states that reliability refers to both the behaviour of the scientist and the written work that is produced. It then specifies that an important aspect of the principle is to be found in the concept of statistical reliability.

#### III. Verifiability:

Standard III.1: The first aspect of the elaboration of this principle states that “Research must be replicable in order to verify its accuracy”. It moves on to state: “The choice of research question, the research set-up, the choice of method and the references to sources used are accurately documented in a form that allows for verification of all steps in the research process.”

Standard III.2: The second aspect of the elaboration of this principle states that “The quality of data collection, data input, data storage and data processing is closely guarded. All steps taken must be properly reported and their execution must be properly monitored”.

Non-compliance with standard II.1 includes fabrication and falsification of data.

Fabrication means the invention of data or research results and reporting them as if they are fact. Falsification means the manipulation of data or research material, equipment or processes to change, withhold or remove data or research results without justification

Fabrication and falsification are clear examples of serious misconduct. Non-compliance with this standard constitutes research misconduct on the part of the researcher involved.

#### **Deliberations of the committee**

The committee considered whether — in addition to the defendant — the co-promotor, [...], should be included in the investigation by the CWI, as stated by complainant. However, based on article 1.5 of the Complaints Procedure, the committee concluded that in this particular case the co-promotor doesn't fall within the scope of the Complaints Procedure. The co-promotor was not involved as co-author in any of the papers of defendant used in the PhD-thesis. The extent of his involvement in the education of

defendant as a researcher and the genesis of the research that is the foundation of the PhD-thesis was limited. Article 1.5 of the Complaints Procedure excludes those persons who don't publish their research under the name and responsibility of the institution and/or are only involved in the research in a supporting role. Moreover, insofar as aspects of the quality control of manuscripts for PhD-theses are concerned, the functioning of the (co-)promotor — as well as the functioning of the Assessment Committee and the Doctoral Examination Committee — are not part of the remit of the CWI but of the Board for the Conferral of Doctoral Degrees of Utrecht University.

The committee further concluded that despite the fact that the PhD-thesis was published over ten years ago, the complaints against [...] are admissible and should hence be dealt with in substance. The committee notes that complainant has put forward a very serious suspicion of violation of research integrity, with potentially grave consequences for the science in this field. Also, complainant submitted his complaint shortly after finishing the statistical analysis of the publications of defendant.

The committee notes that much time has passed since the publications and the PhD-thesis based on these publications were produced by the defendant. Also, all research was performed at the home institution of the defendant in [country]. The defendant did not provide the committee with research data and indicated that the research data for these publications was no longer preserved. According to standard III.3 of the Code of Conduct 2004 it was common academic practice at that time to store raw research data for at least 5 years. The committee notes that defendant did not act in violation of the Code of Conduct 2004 by removing the research data and by not being able to make them available after 13- 16 years.

The absence of the raw data, lab journals and other relevant documentation makes that the committee cannot, from the information currently available, ascertain exactly how the research of defendant that was the basis of his PhD-thesis has been carried out.

However, the four statistical analyses (see the Appendix for an overview) of defendant's publications by [authors of Publication X] (2020) and by [dr. Y] (2021) that have since appeared in public media gave the committee strong indications that the data presented by defendant cannot be taken as reliable.

The committee approached [...], an independent expert in the four methods and someone who has experience in assessing their appropriateness and reliability in investigations of possible data manipulation and who can provide an informed opinion about the conclusions from these methods in this particular set of publications. For the sake of completeness, it is noted that [Professor Z] cannot be considered an independent expert in these proceedings because he was approached by a directly affected party.

Based on the response by [the independent expert], the committee decided to ignore the 'last digit analysis' in its assessment of the complaints.

The other three methods, however, are deemed relevant and valid. The 'Carlisle analysis' is aimed at assessing whether allocation of participants in RCTs has been suitably randomized. The method focusses on the reported baseline characteristics of the participants in such trials and can therefore be performed without access to the data underlying the publication. According to the expert:

"The Carlisle method must be seen as a good first step, and if irregularities are found, these studies deserve a closer look. Therefore, this method can be applied as a first step to this set of RCTs and also to the set of 9 RCTs from the dissertation. The results of [Publication X] indicate that this closer look is definitely warranted. The number of p values very close to 1 is especially striking. This means that the experimental and control groups are extremely similar on many measures, which is unlikely. This cannot happen by chance if the randomization procedure is applied, as stated by [defendant]. The reason why there are so many p values close to 1 is

unclear. It is sometimes unclear whether the SE or SD is reported in the papers by [defendant], and this might have influenced the p values as calculated in this Carlisle method. However, I doubt that this can explain all the irregularities. Thus, the results of the Carlisle method are a good reason to have a closer look at the specific results of the [defendant's] studies (...)."

Such a closer look is provided by the third and fourth method of analysis. The third method is illustrated in [Publication X] using publications that included chapters of the PhD-thesis of the defendant. Two examples of this comparison can be found in [Publication X]. These are given in figures 2 and 3 in the paper. Figure 2: [defendant] 2008c = Chapter 3; [defendant] 2009f = Chapter 7. Figure 3: [defendant] 2008b = Chapter 8; [defendant] 2009e = Chapter 6. In the figures, average values and their confidence intervals for various traits of participants are compared between the publications. Values that are exactly the same are marked with a green dot. According to the expert:

"In my study into reporting inconsistencies, we saw quite a few "copy-paste errors." This means that authors copy certain parts of their results to other parts to make sure that they, for example, follow the APA reporting standard and then forget to adapt these results. (...) Thus it might be hard to distinguish these types of errors from data manipulation. On the other hand, if the results cannot be trusted anymore because of the large number of errors, this is still enough reason to retract a paper in my opinion. More specific on the analysis of [authors of Publication X]: I would focus on the exact copies (green dots) and not on the ones with max 1 unit difference. This will give the original authors the benefit of the doubt, and there seem to be already many green dots."

The fourth method of analysis has been carried out by [dr. Y]. This analysis is not based on the baseline characteristics of the RCTs, but at the reported outcomes of the trials. Specifically, the analysis checks the reported values of the test statistics and the p-values in the publications. These can be calculated by standard methods from the means, proportions, standard deviations, and group sizes reported in the outcome tables of the publications. According to the expert:

"In my view, [dr. Y] has carried out the analyses correctly. He takes differences due to rounding into account, and in his blog post, he also mentions the issue with the reporting of SE/SD. With these inconsistencies in the reported results, it is often unclear whether the descriptives, the test statistic, or the p-value is misreported. Therefore, we don't know what the correct values are and also don't know what the correct conclusions are. But the high number of errors in all these papers shows that the conclusions reported in the papers are not supported by the reported results. And according to me, that is enough to retract a paper. As stated above, you can do the same analyses for the basic characteristics to shed light on the high similarity between the experimental and control groups, as shown with the Carlisle method."

From their own reading of the documentation and the assessment by the expert, the committee concludes that standards I.1, II.1, III.1 and III.2 have been violated. The reliability of the reported data, the randomisation in the RCTs, the outcome of the trials, the statistical analysis of the outcome, and the conclusions in the PhD-thesis is seriously questionable. The defendant has not convinced the committee that these allegations are false. In fact, the defendant has not provided the committee with any explanation for anomalies, coincidences, and possible errors. Instead, the defendant has questioned the statistical methods that have been used and has sought to discredit the complainant and [dr. Y]. The independent expert consulted by the committee has verified the appropriateness of three of the four methods and reports that the anomalies are such that the conclusions of the publications in the PhD-thesis are not supported by the reported results and are therefore not credible. The committee, in addition, weighs heavily that the three methods of analysis all regard different aspects of the publications (baseline statistics, randomization, statistical analysis of the outcome). In all three aspects, the publications have been cast into serious doubt.

Based on the statistical analyses by [authors of Publication X] and [dr. Y], and on the assessment of [the independent expert], the committee concludes that there are too many serious, unexplained problems in the PhD-thesis of defendant, undermining the reliability of the research data and the credibility of the results and conclusions that are presented.

The committee takes into consideration that RCTs are seen as the ultimate test/'evidence' in medical research to show, for example, that a new treatment for a disease outperforms an existing treatment in some relevant measure of outcome. Important treatment decisions for patients are made on the basis of RCT-evidence, hence the absolute necessity to carry them out according to set protocols and guidelines. This is an important aspect of violations of standard I.1.

Given the seriousness of the allegations, defendant must be expected to provide a plausible explanation for the anomalies found in his PhD-thesis. However, defendant did not provide the committee with any explanations for these anomalies.

#### **Conclusion of the committee**

**Considering all the evidence, the committee concludes that defendant acted in violation of standard I.1, II.1, III.1 and III.2 of the Code of Conduct 2004 and is at least guilty of recurrent gross negligence in these standards of scientific practice; the integrity of the publications that form the basis of the PhD-thesis and the data on which they are based are not guaranteed.**

Utrecht, 18 May 2022

#### [Technical appendix:

Summary, made by this committee, of the methods used by [authors of Publication X] and [dr. Y], in relation to the publications of the defendant. ]

#### 2. Initial opinion of the Executive Board

The Executive Board announced the following initial opinion to the parties on 2 June 2022:

“We note that the complaint was handled in accordance with the applicable procedures. We agree with the report of findings and the recommendation of the CWI and adopt them as our initial findings. We therefore determine that the complaint is FOUNDED.

If you do not agree with these initial findings, you may - pursuant to Paragraph 5 of the Research Integrity Complaints Procedure Utrecht University 2019 - request an opinion from the National Board for Research Integrity (Landelijk Orgaan voor Wetenschappelijke Integriteit – LOWI), within six weeks of the date of this letter. After the lapse of that six-week period, or after receipt of the LOWI's opinion, we will determine our definitive opinion on the complaint.”

#### 3. National Board for Research Integrity (LOWI)

No request was received by the LOWI.

#### 4. Definitive opinion Executive Board

The Executive Board announced the following definitive opinion to the parties on 13 October 2022:

“The National Board for Research Integrity informed us that they didn’t receive a request concerning our initial findings. We have subsequently determined our definitive opinion about the complaint. Our definitive opinion is that the complaint is **FOUNDED**, based on the advice of the Research Integrity Committee of 18 May 2022.

We have submitted this matter to the Board for the Conferral of Doctoral Degrees to decide about the consequences regarding the PhD-thesis.”