INVITED PAPER:

Scientific misconduct in clinical hypertension research

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The COOPERATE Study, published in The Lancet 2003, found that combination therapy with losartan and trandolapril “safely retards progression of non-diabetic kidney disease” compared with single therapy with each drug, respectively. Five years later, three authors, while performing a meta-analysis, found a strange observation in the previous publication. In 263 patients, randomization succeeded to create three nearly identical groups of patients, even for genetic polymorphisms¹. The paper was retracted, and today it is common knowledge that the combination of ARB and ACE-inhibitors should not be used².

Retraction of original publications due to fabricated or falsified data is quite uncommon. In one study, scanning BioMed Central between years 2000-2015, 134 out of 190 514 articles were retracted (excluding supplements, corrections, retractions, and commissioned content)³. Fraud is often detected many years after the original publication. This was also the case with the Jikei Heart study, published in The Lancet in 2005⁴. Six years after the publication, someone read it and noticed that the statistician had an affiliation at a non-existing department at his university. Thereafter, it was found that the statistician was a Novartis employee, who had made changes in the data base, increasing the number of events in the control group, thereby making valsartan appear more beneficial. This was one of a series of five randomized controlled trials with valsartan (Kyoto Heart Study, Jikei Heart Study, SMART, VART and Nagoya Heart Study), published in high-impact journals between 2007 and 2012, that were found

to include falsifications and got retracted, later referred to as “the valsartan scandal”⁵⁻⁹.

Since January 2020, there have been an increasing number of retractions of original publications. Most of these retractions involve Covid-19 papers. According to Retraction Watch, at least 33 Covid-19 papers have been retracted so far¹⁰. High impact journals have not been protected, although a disproportionate amount of retractions have been from preprint services. The New England Journal of Medicine published the paper “Cardiovascular Disease, Drug Therapy and Mortality in Covid-19”, claiming to have analyzed data from an international registry, called the Surgical Outcomes Collaborative (Surgisphere), including 169 hospitals in 11 countries¹¹. Soon after publication, several authors requested the journal to retract the paper because they were not given access to raw data, and the primary data source could not be validated. The Lancet published the paper “Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis” from the same registry in May 2020¹². In June, it was retracted for similar reasons. Since then, Surgisphere’s social media accounts have been deleted and the website was taken offline. It is reasonable to assume that the intention to speed up our knowledge about Covid-19 have had some negative effects on the rigour among researchers, publishers, and reviewers alike.

Retraction of a published paper does not mean that there need to be a deliberate fraud. Sometimes, the authors find errors in their database, or the analytic method, after the paper has been

published, so called honest error. Plagiarism is a special case of research misconduct, that, although it should be quite easy to detect today, appear to be fairly common. One survey among 372 editors of scientific journals (half of them in medicine) estimated that they detected plagiarism in 2-5% of all submitted manuscripts¹³. In 2018, the European Journal of Pharmaceutical Sciences retracted an RCT comparing an olmesartan/amlodipine single pill combination with olmesartan or amlodipine single therapy because it was found that “The authors have published results from exactly the same clinical study and patient population in 6 separate articles, without referencing to the publications in any of the later articles”¹⁴.

All involved in scientific publishing (authors, publishers, peer reviewers, and readers) are responsible for the quality of published papers. To reduce the risk of scientific misconduct, all aspects of the scientific process needs to be transparent. Table 1 lists, with no intention of being comprehensive, efforts that could be considered at each stage to improve transparency, quality, and hopefully uncover fraud. It is easy to imagine, that many of the examples listed above could have been discovered earlier, had the listed items been complied with. For example, the Surgisphere papers would probably not have been published if preregistration would have been required for observational studies. Many journals have, or plan to introduce, routines aiming to decrease the risk for publishing papers with dubious data. In a recent statement, The Lancet, announced they will, among other things, require at least two authors have access to the data, and, for publications from large real-world datasets, peer reviewers will include someone with knowledge about the specific dataset, as well as a data scientist¹⁵.

In the March issue of HT News, we wrote a critical appraisal on the Hygia Chronotherapy Trial, published online in European Heart Journal in October 2019¹⁶. We raised several concerns regarding the randomization process, allocation concealment, outcome reporting, as well as the statistical analysis¹⁷. Our conclusion was that “It is difficult to draw conclusions from this interesting study as it is not transparently reported”; many of the concerns raised would have been clear had the paper been reported according to the CONSORT statement¹⁸. Many others have also published critical comments, including the present and several previous ESH presidents, advocating that the study should be disregarded¹⁹. It must be emphasized that this study has not been found to

include fraud, nor has it been retracted. However, in April 2020, the editors of the European Heart Journal published an Expression of Concern on behalf of the European Society of Cardiology²⁰.

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“The content and conduct of this RCT is currently under investigation” according to the Editors.

*Full reference list is available [here](#)

Table 1 – Efforts to improve transparency of published science

Stage in the scientific process	Item	Comment
Researcher	Preregistration	Registration of clinical trials has been required by most journals since more than a decade. However, for systematic reviews and observational studies, although encouraged, registration is seldom a requirement.
	Peer governance	Several recent investigations in Sweden have concluded that high-profile researchers are guilty of misconduct for being co-authors on papers where others have manipulated data. Data sharing and open dialogue within research groups should avoid such errands.
Publisher	Reporting guidelines	Most high-impact journals require checklists from reporting guidelines such as CONSORT, PRISMA, or STROBE, to supplement submitted manuscripts. Better reporting will not only improve readability, but also uncover irregularities in methods as well as results.
	Open data	Many journals, such as the BMJ, offer authors to share their data through open data repositories like Dryad. Open data will enable scrutiny and re-analysis by peers, post-publication; probably one of the most important steps towards transparency. One major obstacle that needs to be overcome is how to avoid invasion of privacy among study participants.
Reviewer	Use registers and checklists	Preregistration of scientific projects is only of value if someone goes back and compares the final manuscript with the registered protocol. Whether this is up to reviewers, or if it should be part of the editorial process, is debatable. Deviations from the original plan, like the massive increase in number of participants in the Hygia trial, should always be motivated thoroughly. Whereas many journals require reporting checklists with the submission, these needs to be critically assessed to improve the quality of published articles. It is our experience that a ticked box does not always mean that the item assessed is reported adequately.
	Count the numbers	Many fraudulent papers have been discovered because numbers do not add up, or add up a little bit too well, as in the example with the COOPERATE trial.
Reader	Speak up!	Whereas an article might meet two or three reviewers and a couple of editors before publication, the number of people reading it post-publication are often hundreds or thousands. It is reasonable that irregularities will sometimes be detected after print. Whereas a letter to the editor should be the first step if misconduct is suspected, critical comments published on twitter, as well as post-publication discussion forums, have had real scientific impact in recent years.

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