

Univ.-Prof. Dr. med. Michael Frass

Reply to an inquiry from the Spiegel editorial office regarding the following publication

Frass M, Lechleitner P, Gründling C, Pirker C, Grasmuk-Siegl E, Domayer J, Hochmair M, Gaertner K, Duscheck C, Muchitsch I, Marosi C, Schumacher M, Zöchbauer-Müller S, Manchanda RK, Schrott A, Burghuber O. Homeopathic Treatment as an Add-On Therapy May Improve Quality of Life and Prolong Survival in Patients with Non-Small Cell Lung Cancer: A Prospective, Randomized, Placebo-Controlled, Double-Blind, Three-Arm, Multicenter Study. *Oncologist* 2020;25:e1930-e1955. doi: 10.1002/onco.13548. Epub 2020 Nov 7.)

This is a brief summary followed by a more detailed comment of the most important points, which is why the work is so exceptionally robust and valid. Any falsification, fabrication or manipulation of the data can therefore be ruled out:

- 1) The study was accompanied and monitored by the planning statistician with the help of the computer-aided randomization program 'Randomizer' of the Medical University of Graz. This programme automatically writes a protocol (= audit trail), so that every inclusion or exclusion process was recorded. Subsequent exclusion ('post-hoc exclusion') is therefore not possible, as every step has been monitored.
- 2) The authors, most of whom were not interested in homeopathy, had control and access to the study data at all times.
- 3) The study was analyzed in a four-stage procedure, which is unusual for an academic study: The data were entered into the tamper-proof 'Research, Documentation and Analysis' (RDA) platform of the Medical University of Vienna, then forwarded by the planning statistician to the analyzing statistician by means of an elaborate clearing process at the Medical University of Vienna. This quadruple evaluation check proves the extraordinary quality of the results.

We therefore confirm the reliability, veracity and accuracy of the data presented in our article published in *The Oncologist*.

I would now like to reply in more detail to the concerns that have been expressed:

How valid are the accusations of the review commission from your point of view?

Michael Frass (MF): Firstly, it should be noted that this is a 'Final Statement' (FS) from the private organisation 'Austrian Agency for Research Integrity' (OeAWI) and not a scientific report. The difference lies, among other things, in the fact that the authors were not given the opportunity to comment after publication of the FS, although we clearly indicated our willingness to do so.

With such a reproachful report, one would expect a flawless FS. However, the OeAWI Commission has published a chronology of its own activities on page 2 of the FS. Surprisingly, there are 5 (in words five!) incorrect time specifications, e.g: 'Re-analysis of part of the data of the Study and preliminary report on the inquiry by F. R.

Rosendaal: 28 November 2022': this would mean that the re-analysis was carried out 2 months AFTER the deadline, namely 21 September 2022. For scientists, these 5 timing errors shed a significant light on the FS, which was obviously prepared in great haste.

The commission makes assertions that could have been clarified immediately and with minimal effort: The head of the commission, Prof Dr Rosendaal, has, by his own account, even been to Vienna in person without seeking an interview with the study authors, in particular with the statistician at the Medical University of Vienna (MUV) who planned the study. At the beginning of the FS, for example, the claim is made that the study was not performed double-blind from the outset. However, there are several control mechanisms that monitor and guarantee double-blinding, which are still easily verifiable today, e.g. in the randomization programme described in detail below or in the extensive documentation of the cooperating pharmacy. The committee obviously did not consider or incorrectly interpreted the submissions reported by the study authors to the MUV Ethics Committee and accepted by it.

All patients who participated in the study were treated double-blind. The blinding codes were stored by the independent statistician, who did not appear as a study author, in the randomization platform described in more detail below, to which the authors had no access. Therefore, no patients could have been removed (= 'post hoc exclusion') from the dataset unnoticed due to their outcome data: After all, all inclusion and exclusion events are automatically logged and traceably registered in the audit trail to this day.

Due to the maintenance of blinding until the actual statistical analysis by a second, previously uninvolved statistician, selective data manipulation within one or the other study arm would not have been possible. Speaking of blinding: The study medication was not handed over by the pharmacy, but by post. This unique study design, which excluded any influence by the pharmacy, is another exceptional quality feature.

Further concerns: The study authors are accused of having embellished the results by subsequently removing patients from the analysis who did not show the hoped-for course of the disease. Is that true? If so, in what way? If not, how can the Commission's findings be explained?

MF: The study was accompanied and monitored by the planning statistician with the help of the computer-aided randomization programme 'Randomizer' from the Medical University of Graz, Austria. This internationally recognized, top-class programme automatically writes a protocol (= 'audit trail'), so that every process involving the study patients was recorded in an unswayable and sustainable manner. Therefore, 'post-hoc exclusion', as assumed by the Commission, is technically not possible, as every step was permanently monitored. Only the planning statistician had access to this randomization programme, so both theoretically and practically it is simply not possible for the study authors to intervene in this programme, which proves the high quality of the study. The commission of the OeAWI was obviously not aware of this innovative unique feature of the randomization programme.

Further proof of the top quality: the study was analyzed using a four-stage procedure, which is unusual for an academic study: The data were entered into the MUV's tamper-proof 'Research, Documentation and Analysis' (RDA) platform, then forwarded by the planning statistician to the analyzing statistician by means of an elaborate clearing process. This exceptional quadruple evaluation check proves the reliability of the results. This security check ensures that the integrity of the recorded data is maintained. We categorically state that there has been no 'selective deletion of records' and our assertions are fully confirmed by the objective audit trail.

Manipulation would also have been difficult to achieve: Here, 16 deserving study authors, who monitored the study at all times, would have had to take part in a falsification. Among them were two top scientists from the MU Manipulation would also have been difficult to achieve: Here, 16 deserving study authors, who monitored the study at all times, would have had to take part in a falsification. Among them were two top scientists from the MUW with no connection to homeopathy and the first author, who is internationally recognized as a figurehead for alternative airway devices thanks to the life-saving invention of the Combitube® for securing the airway and for ventilation in emergencies in all current textbooks and in the guidelines of the American Heart Association (AHA) and the Society of Anaesthesiologists (ASA). The cooperation between conventional and complementary study authors, the majority of whom have no affinity to homeopathy, guarantees constant mutual control and is a further seal of quality for the study.

The description of the survival curves as implausible in their progression is an arbitrary expression of opinion of the OeAWI without scientific support. Compared to other published Kaplan-Meier survival curves in lung cancer studies, our published data are well within the expected range. In particular, the prompt separation of the survival curves immediately after the start of the study is a frequently observed pattern. One can easily find examples of survival curves similar to those shown in our study. Entry dates into the study as well as deaths are known to be distinctive data that are tamper-proof.

The accusation of whitewashing or falsification of questionnaires on quality of life can be directly refuted by the facts and by statistical understanding: patients have, as is often the case with written questionnaires, re-evaluated one point or another and corrected the previous evaluation by hand. With over 26,000 (!) available data, this happened in 90 cases. Every biometrician will confirm that these changes, which are spread over various parameters and are approximately 3.5 ‰ of all collected data, cannot have any influence on the results. Any date changes on the questionnaires are due to the shifting of the examination dates, which may have been due to a shift in chemotherapy, an acute illness of the study patients, etc. These questionnaires were made available to the Commission by the first author immediately and in full upon request, which in turn proves that they were unaltered original questionnaires that were accepted 1:1 by the study patients without inspection or correction by the study authors.

The Commission criticizes the fact that several patients who reported maximum health status died within a few months, which is highly implausible. However, the

patients' perception of quality of life is explained by the process of coping: one of the study authors observed on the palliative care ward (outside the study) that even in the advanced stages of the disease, patients experience and describe their situation as very satisfactory, apparently because they can spend their last days of life well protected and pain-free.

The exclusion criteria described in the paper are standard in oncological treatment and were therefore naturally followed from the outset. The exclusion of the initially planned patients with glioblastoma and metastatic sarcoma was reported to and accepted by the MUW Ethics Committee due to inadequate recruitment. The change is also transparently recorded in the 'History of Changes' on clinicaltrials.gov. These points are not described in the 26-page paper, as they would not have meant any additional information for the readership.

It must be recognized that this study, which was conducted at the highest level, was very complex and therefore underwent adaptations due to new medical findings. These adaptations necessitated by the constant advances in conventional medicine and accepted by the MUV Ethics Committee and thus recognized by the highest ethical standards, are further proof of the quality of the study.

Conclusion: The OeAWI commission made every effort to scrutinize the study, but was unable to grasp the complexity of the study due to a lack of communication with the study authors and therefore came to incomprehensible conclusions. The FS is therefore a collection of unreliable assumptions and suspicions that can easily be refuted by the facts. The study is therefore valid and confirms earlier studies with regard to quality of life and survival.

Link to the study: <https://doi.org/10.1002/onco.13548>

Contact: Michael Frass, MD, retired Professor of Medicine, on behalf of the study authors

Comprehensive literature is available from the author.

Vienna, 17 May 2024