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Reply to comment on: Martin S, Schneider B, Heinemann L et al (2006) Self-monitoring of blood glucose in type 2 diabetes and long-term outcome: an epidemiological cohort study. Diabetologia 49:271–278

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The battle between those who believe that medical progress can only be reached through randomised controlled trials (RCTs) and those who argue that information from observational trials or animal experiments should not be ignored has filled many pages of leading medical journals in recent years [1–7]. In their letter [8], Meyer and Mühlhauser hold on to the traditional view and do not mention the shortcomings and limitations of RCTs, such as the selection of compliant non-multimorbid patients, specialised doctors, and the use of diagnostic, therapeutic and educational standards that are not representative of the ‘real world.’ Therefore, physicians are often at a loss when trying to translate RCT results into treatment for patients encountered in routine daily practice [3]. By contrast, Meyer and Mühlhauser criticise that physicians in the Retrolective Study ‘Self-monitoring of Blood Glucose and Outcome in Patients with Type 2 Diabetes’ (ROSSO) were of the real-world type and not the specially trained physicians who participate in RCTs [8].

Meyer and Mühlhauser did not mention that non-blinded RCTs are subject to confounding, since both physicians and patients are affected by the knowledge of the nature of treatment. Therefore, non-blinded RCTs cannot prove a causal relationship between medical intervention and outcome. Interestingly, Meyer and Mühlhauser complain about the heterogeneous quality of past non-blinded RCTs on self-monitoring of blood glucose (SMBG) in type 2 diabetes and their ambiguous outcome. However, the critical question is: why have the RCTs performed to date not provided clear conclusions, particularly in terms of

hard endpoints? The most likely answer is that it is virtually impossible to perform such studies in a scientifically acceptable format.

Regarding the criticisms of the design of ROSSO, we regret the apparently insufficient description and discussion. We wish to clarify that for this controlled study (a cohort of patients performing SMBG vs a cohort of patients without SMBG was analysed) we collected the data from all patient files in the randomly contacted primary care practices willing to participate. Our assumption was that the physicians in these practices treat their patients to the best of their ability, with the individual needs of each patient in mind. An enormous amount of data was collected, with 79 baseline parameters and >250 values for each follow-up year. A 100% source data verification was performed, and all data were entered in the database by double data entry and adequate query handling [9].

In the discussion section of our paper we highlighted the numerous possible pitfalls of a retrospective observational study and how we tried to avoid these by performing a high-quality study. Of major concern with observational studies are confounders not documented in patient files, in particular, data on educational/socioeconomic status. The results of the ROSSO study largely rule out this concern. First, in the statistical analysis the aim was to control for all confounding factors. Therefore, all available factors were included in the different models used in the statistical analysis. Using a different statistical analysis approach (propensity scores) that took confounding factors into account resulted in the same outcome. Second, we performed analyses of numerous subgroups that were not expected to show an equal distribution of all non-documented confounders. Such subgroups were defined by age, sex, region of habitation (city vs rural), treating physician (practitioner vs internist), baseline clinical data, metabolic control throughout the study, and public vs private medical insurance. For all subgroups we found fewer endpoints in the cohort performing SMBG. Finally, higher socioeconomic status has been found to be associated with better metabolic control, as reported

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previously by Mühlhauser et al. [10]. The SMBG cohort did not exhibit better metabolic control, which further invalidates the socioeconomic argument. We therefore conclude that the known confounding factors were included in the analysis. However, we agree, in principle, that there is a risk that (potential) confounding factors are not documented in the patient files. It is also true that this type of study is limited by the quality of the documentation by physicians in daily practice; however, this is the consequence of studying the real world, which is obviously of considerable value.

In summary, we wholly disagree with the statements of Meyer and Mühlhauser that the ROSSO study lacks internal validity and that a non-blinded RCT would be appropriate and feasible. The impressive results of our study are well in line with many other studies showing that empowerment of patients, or lifestyle changes, are an effective tool that has a clear impact on long-term outcome/hard endpoints. Pricking fingers and the associated altered lifestyle (including more attention from the physician when the patient shows the diary with SMBG results) could indeed be a most powerful way of improving long-term outcome. Just think of the finding (in non-blinded RCTs) that simply reminding people several times per year how to live more healthily decreased the rate of progression from metabolic syndrome to overt diabetes by more than half [11, 12], which is of similar magnitude as in ROSSO. Do Meyer and Mühlhauser really think that the only way of improving long-term outcome in type 2 diabetes is more intense medication?

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