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Hospital Foundation). He also received payment for being on a panel at the American Diabetes Association, for a talk at the Toronto Reference Library, for writing a brief in an action for side effects of a drug for Michael F. Smith, Lawyer and from the Canadian Institutes of Health Research for presenting at a workshop on conflict-of-interest in clinical practice guidelines. He is currently a member of research groups that are receiving money from the Canadian Institutes of Health Research and the Australian National Health and Medical Research Council. He is member of the Foundation Board of Health Action International and the Board of Canadian Doctors for Medicare. He receives royalties from University of Toronto Press and James Lorimer & Co. Ltd. for books he has written.

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We welcome the publication of the Bacloville study (1), as we have been questioning its delay in publication (2) and have called for data sharing (3) to facilitate an independent re-analysis as part of the RIAT initiative (4). Indeed, preliminary reports showed major modifications of the original protocol. Our concerns have not been adequately addressed in the past (2,3) and the publication revealed new modifications from the original protocol, raising serious ethical and scientific alarms. In this critique, we present a series of major concerns that we have with this trial.

First, the possibility that patients could be switched from their initially assigned group to open label treatment before the end of the trial is a major breach in equipoise, a mandatory principle for any randomized controlled trial (5). On the one hand, if one accepts the principle of equipoise, there is no justification for switching non-responders to a drug with no established efficacy. On the other hand, this choice, made during the study, had devasting consequences on the validity of the trial results as it implied a change in the primary outcome. The protocol (v.05, October 10, 2014) defined the primary outcome "as alcohol consumption at one year measured according to WHO standards (6) (units of alcohol (AU) of 10 g) with the presence of abstinence or a low risk level of consumption throughout the 12th month according to WHO criteria". The primary outcome presented in the publication is different as it specifies that a switch to open-label baclofen or alcohol- or study-related death is a failure, an outcome that was not initially included. The primary outcome to be assessed at 12 months was therefore changed, not only for the duration of follow up (switches could occur at any time) but also based on a criterion which was not defined but was totally subjective as reasons for switching were not pre-specified in the protocol (reasons could have been the occurrence of a serious adverse event, for instance).

The issue around switching patients is key, as the results of the study mainly depend on the fact that patients who were switched were considered as treatment failures. Twenty-five percent of patients were switched: 19 of 162 (12%) patients in the baclofen group and 60 of 158 (38%) in the placebo group received open-label baclofen before the end of the study ($p < 0.001$ for differences between groups).

Second, the date when the primary outcome was changed in the protocol is crucial for knowing whether the trial was adequately blinded. As we understand, the change in the primary outcome appears in the statistical analysis plan (SAP) and not in the protocol. The

SAP (Version 4.0, August 23rd, 2016) mentions that the statistician had no access to the data before completing the SAP, but was that the case for everyone else associated with the study? This information is crucial as the delay between the end of the study and the finalization of the SAP was unusually long with at least 3 previous versions of the SAP not released with the publication. The last follow up visit of the last patient was in August 2014, the database was locked in October 2015 (7) and the SAP (Version 4.0) was not completed until August 2016. Access to the data about side effects and/or details about switches during this period would likely have made it easy to guess which patients were allocated to baclofen and which to placebo. This knowledge might have precipitated the change to the protocol and subsequently the way that the SAP was planned. Accordingly, the authors should provide the date and details of the amendment concerning the new definition of the primary outcome which should have been submitted to the relevant Research Ethics Committee (Article L. 1123-7 of the Public Health Code), ideally before the last visit of the last patient.

The reality about whether there was adequate blinding is even more challenged by the baclofen titration process going from 15 up to 300 mg/day as it may have increased the likelihood of adverse effects occurring (8). Therefore, the authors must provide the results of the analysis of the effectiveness of the blinding procedure. This is a such a critical issue that this analysis was planned in the original protocol (v. 5.0, paragraph 8.1). Unblinding, deliberate or not, potentially invalidates any study.

Third, the authors found no difference (absolute risk reduction = 6 %, 95% CI [-7%; 20%]) on a "secondary outcome" that is nearly similar to the primary outcome, but one where patients switched to open-label baclofen were not considered as failures "unless they did fail". This latter method of analysis is the appropriate one as it is based on a conservative scenario (i.e., a scenario where possible bias leads to the conclusion that the treatment is ineffective). The distinction between the two outcomes appears to be post-hoc as this "secondary" outcome does not appear in the protocol (v.5.0, October 10, 2014). The way the results are presented may give readers the impression that the study is "positive" on its primary outcome while being negative on a less important secondary outcome. However, the correct interpretation is rather that the results presented for the primary outcome lack robustness and therefore, the conclusion that "baclofen was more effective than placebo in reducing alcohol consumption to low-risk levels" is not acceptable.

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Fourth, differences identified in the primary outcome are mostly due to imputed data. Only 37/162 patients in the baclofen group and 18/158 in the placebo group had data that documented success (or failure) of the treatment. Imputation of data was not part of the initial protocol (v.5.0, October 10, 2014). This change, acknowledge in Table S3, provides no date for when the amendment was made. Failure to report consumption cannot be imputed as a treatment success/failure as trajectories of alcohol consumption are not accurately predictable. The statement that "the two analyses, assessing the effect of missing data on the primary outcome measure, confirmed [the] primary outcome results" is not correct. Between the two analyses success rates were changed in both the baclofen and placebo groups: rates of 57 % [baclofen] vs 36 % [placebo] in the main analysis, 25 % [baclofen] vs 10 % [placebo] and 28 % [baclofen] vs 12 % [placebo] in the two sensitivity analyses.

To illustrate the extent of the uncertainty surrounding analyses of the primary outcome, consider the most conservative sensitivity analysis possible. In this case, patients who were switched or had missing data in the baclofen group are considered as failures and patients who were switched or had missing data in the placebo group are considered as successes. Numbers for this analysis can be calculated using data from Table 5. According to this scenario, 7/158 (4 %) patients in the placebo group are considered as failures versus 138/162 (85 %) in the baclofen group ($p < 0.001$ in favor of placebo).

Fifth, there are conflicting discrepancies about baclofen toxicity between the publication and data submitted to French authorities. The public report of the French Medicines Agency (Agence Nationale de Sécurité du Médicament et des Produits de Santé [ANSM]) Temporary Special Scientific Committee of independent experts (9) notes that the "sponsor" declared to the ANSM that five of six deaths observed in the baclofen group were related to treatment. Why did the authors claim in the publication that none were attributed to the treatment? Causes of death and the methods used to assert that death was not related to treatment must be detailed. As well, the reasons for the difference compared to the data submitted to the French Medicines Agency needs to be explained. The report of adverse events in Table 6 is also confusing. The 223 patients appearing in the baclofen group might correspond to the 162 randomised patients in this group plus the 60 patients switched from placebo to baclofen plus one additional unaccounted for patient, but this is not made clear. In contrast, the placebo group presents only the 158 patients randomized to this group. Switched patients therefore appear in both the placebo and baclofen groups and have different durations of exposure (i.e.

the pre switch duration in the placebo arm and the post switch duration in the baclofen arm for patients who were switched). In addition, restricting the information in the table to specific events occurring in at least 5% of patients is in breach of the CONSORT guidelines for reporting harm (10). A more detailed and comprehensive description must be provided to allow for meaningful syntheses in any future meta-analyses.

Coincidentally, the authors also overlooked red flags about toxicity from a large pharmaco-epidemiological study (8). A comparison between 47,614 baclofen users versus 117,720 users of the approved treatments for alcohol disorders (acamprosate, naltrexone or nalmefene), all under 70 and without major comorbidity, showed a dose related increased in mortality with baclofen.

Sixth, transparency in describing the circumstances surrounding the trial, is an absolute prerequisite for confidence in the results. The disclosure of a grant from a private donor who has no conflict of interest (in particular no link with the pharmaceutical industry) is a non-verifiable statement. Moreover, there is no mention in the publication that on April 2015 the study data were provided by the sponsor (Paris Public Hospitals Authority) to Ethypharm, the corporation marketing baclofen in France (3) under a business agreement whose terms are protected by a commercial confidentiality ruling (see: French Transparency in Healthcare database:
https://www.transparence.sante.gouv.fr/flow/rechercheEntreprises?execution=e3s5). This undisclosed financial relationship warrants the publication of a correction according to Committee on Publication Ethics. (COPE) guidelines (https://publicationethics.org/). There are also concerns that need to be addressed about whether patients who agreed to participate in a trial sponsored by a public hospital with funding from the Department of Health also agreed to having their data sold to a drug company.

Finally, the plan of analysis was changed after the commercial transaction described above between the public sponsor and Ethypharm. The protocol provided with the publication (v.05, October 10, 2014) mentions the composition of the new statistical team which seems to have changed after the commercial transaction in 2015. Is there an error in the date in Version 05 of the protocol that was provided? Such an error in a time stamped document would be very problematic. Indeed, the validity of the peer review process relies on the fact that all documents used to appraise the quality of a given study are accurate and complete at the time

of peer review. This error, if real, would reinforce the need for full transparency and the detailed and time stamped history of all amendments to the protocol.

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