# Applying for access to the clinical study reports and protocols for placebo-controlled trials of anti-obesity drugs submitted for marketing approval

Anders Jørgensen, MD, PhD student, a.w.j@dadlnet.dk
Peter C Gøtzsche, director, DrMedSci, MSc, pcg@cochrane.dk

Nordic Cochrane Centre, Rigshospitalet, Copenhagen
www.cochrane.dk

29 June 2007

We hereby apply for access to the clinical study reports of the placebo-controlled clinical trials and corresponding trial protocols of amfepramone, rimonabant, sibutramine and orlistat submitted to the Danish Medicines Agency and the European Medicines Agency (EMEA) for marketing approval.

We believe it is essential that the submitted clinical study reports and corresponding trial protocols of anti-obesity drugs become available for additional analyses by independent researchers, because of the likely widespread use in the future of these drugs, the serious safety concerns that have been raised, and the relatively small effects on overweight that have been published. As explained below, we believe that such additional analyses are needed before the patients and their doctors can obtain a balanced view of the benefits and harms of these drugs. We therefore also believe that the societal interests in having access to these data should overrule the exemptions in national Freedom of Information Acts. In Denmark, for example, "Retten til aktindsigt" describes that the request for getting access is not accepted if technical devices or procedures, or operational or business matters, or similar, are of substantial financial importance for the person or company the information relates to ("tekniske indretninger eller fremgangsmåder eller om drifts- eller forretningsforhold eller lignende, for så vidt det er af væsentlig økonomisk betydning for den person eller virksomhed, oplysningen angår, at begæringen ikke imødekommes").

Secrecy is clearly not in the best interest of the patients. In fact it has been shown repeatedly that biased reporting of drug trials is common (1,2), resulting in suboptimal treatment, as doctors do not know what the true effects are. We have previously reviewed a large number of trial protocols of industry-initiated trials, approved by the Scientific-Ethical Committees for Copenhagen and Frederiksberg (1). We had no problems with getting access to these protocols and we did not find anything that, with any reasonable justification, could be regarded as confidential to such a degree that it should preclude independent researchers from getting access to the protocols.

## Background information

Recently, FDA's Endocrinologic and Metabolic Drugs Advisory Committee recommended against sale of the anti-obesity drug, rimonabant, in the United States based on currently available safety data that showed an increased incidence of psychiatric adverse events such as suicidal events and ideation (3). FDA usually follows the recommendations of its

panels, and it is expected that a decision whether or not to approve rimonabant in the U.S. is to be taken by the end of July 2007.

More than 100,000 Europeans, including about 4,500 Danes, have purchased rimonabant over the last year (3). Apparently, EMEA has strengthened the demands for rimonabant, and in general, the standards will be tougher for anti-obesity drugs (4).

In addition to the adverse effects of anti-obesity drugs, the large numbers of dropouts in the placebo-controlled trials is an important issue. A Cochrane review of long-term pharmacotherapy (at least one year) found average dropout rates of 33% and 43% for orlistat and sibutramine, respectively (5). This makes interpretation of the results difficult. Handling missing data due to dropouts or patients lost to follow up must be done carefully as the risk of bias is considerable (6)(7), especially if the reasons for dropping out tend to be adverse effects in the actively treated group and lack of effect in the placebo group.

One way to handle dropouts is to perform intention-to-treat analyses (ITT). The principle of ITT has become widely accepted for the analysis of randomized clinical trials and is now part of several guidelines and recommendations (8)(9). ITT is a strategy aimed at reducing bias in trial reports. It implies that all allocated individuals are included in the analyses, regardless of whether or not they satisfied the entry criteria, received the treatment to which they were originally allocated, or were subsequently withdrawn or deviated from the protocol in other respects (10). Frequently, however, the ITT approach is inadequately described and inappropriately applied (7,10).

The Cochrane review on anti-obesity drugs only included trial reports that contained an ITT (5). However, in all the reports, the technique “last observation carried forward” (LOCF) was used for missing values. LOCF may be the most widely adopted strategy for dealing with incomplete, longitudinal data in pharmaceutical trials, but simple techniques such as LOCF commonly produce severely biased estimates of the drug effects (6)(11)(12)(13). Using LOCF in obesity trials might lead to biased estimates, as obese patients loose most of their weight during the first months and most of it is regained later (5)(14), and as differential drop-out might occur, as noted above.

Often, only one type of analysis or imputation is reported in published articles of anti-obesity drugs. This is problematic, as illustrated by a comparison of trial reports of selective serotonin reuptake inhibitors submitted for marketing approval in Sweden, and the published papers of the same trials (2). Results favouring the company’s drug were published more often than negative results (2), and selective within-trial reporting also occurred, as the authors of many publications had ignored the results of the available ITT analyses and had only reported the more favourable per-protocol analyses.

**Plans for our research**

For the placebo-controlled trials of anti-obesity drugs we aim to:

1. Explore the robustness of the results by using various imputations for the many missing values in these trials (e.g. first observation carried forward, last observation carried forward, completers analyses, per-protocol analyses and multiple imputation). We have

access to individual patient data from older anti-obesity trials that will facilitate such imputations.

2. Compare the unpublished results with the published ones, and compare the published reports with the trial protocols to check for possible outcome reporting bias (1).

3. Compare the unpublished trials with the published ones to check for possible publication bias, using standard methods (7).

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