How Conducting a Clinical Trial Affects Physicians' Guideline Adherence and Drug Preferences

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Context General practitioners are frequently involved in clinical trials sponsored by pharmaceutical companies but the effects of participation on their prescribing patterns have not been evaluated.

Objective To determine how conducting a company-sponsored clinical trial influenced physicians' adherence to international treatment recommendations and their prescribing of the pharmaceutical company's drugs.

Design, Setting, and Patients Observational cohort study in Funen County, Denmark, comparing 10 practices that were conducting a trial on asthma medicine with 165 control (non–trial-conducting) practices. The study population included 5439 patients treated with asthma drugs from the trial-conducting practices and 59 574 patients from the control practices. Practices conducted the trial between April 26, 2001, and October 7, 2002.

Main Outcome Measures Adherence to guidelines measured as use of inhaled corticosteroids among asthma patients. Prevalence of use of the company's drugs and the trial sponsor's share of the total volume of asthma drugs prescribed.

Results The baseline proportion of asthma patients using inhaled corticosteroids was 68.5% in trial-conducting and 69.1% in control practices. Conducting the trial did not influence guideline adherence (odds ratio [OR] after 2 years, 1.00; 95% confidence interval [CI], 0.84-1.19). In trial-conducting practices, the sponsoring company's share of the total prescribed volume of asthma drugs increased compared with control practices (6.7%; 95% CI, 3.0%-11.7%). This could be attributed to a significantly higher preference for the company's inhaled corticosteroids (OR, 1.26; 95% CI, 1.04-1.54) and trends toward increased prescribing of the company's other asthma drugs.

Conclusion Conducting a trial sponsored by a pharmaceutical company had no significant impact on physicians' adherence to international treatment recommendations but increased their use of the trial sponsor's drugs.

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PHARMACEUTICAL COMPANIES are frequently involved in clinical trials in general practice. Such projects imply intense monitoring of the enrolled patients and trial-conducting physicians are likely to become particularly familiar with the treatment principles and may therefore seek to optimize the treatment of patients with the targeted disease. Conducting a trial also may trigger an increase in the use of the sponsoring company's products due to the physicians' experience with these products. This effect may be further strengthened by close physician-company cooperation, which is likely to create physician loyalty toward the company. The effect of participation in company-sponsored studies on drug preferences has been evaluated in secondary care but not in primary care.[1,2]

The present study investigated the effects of physicians conducting a trial sponsored by a pharmaceutical company aimed at improving patients' use of asthma medicine. Our objective was to determine whether participation in the trial influenced physician adherence to international treatment recommendations for asthma and if it affected preferences for the sponsoring company's drugs.

For editorial comment see p 2787.

METHODS

We performed a retrospective cohort study in the Danish County of Funen (472 000 inhabitants) to measure the effects on prescribing for general practitioners involved in a trial managed and sponsored by AstraZeneca (SymbiAC; Symbicort Asthma Control Plan). The cohort included 10 trial-conducting practices (40 781 listed patients) and 165 control (non–trial-conducting) practices (410 363 listed patients) (TABLE 1).

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Table 1. Trial-Conducting and Non–Trial-Conducting Practices Included in the Study

	Trial-Conducting Practices	Non–Trial-Conducting Practices (Control)
No. of practices	10	165
Type of practice		
Solo	1	102
Group	9	63
No. of physicians	26	271
No. of listed patients	40 781	410 363
No. of patients prescribed any asthma drug	5439	59 574
No. of patients with regular use of inhaled β_2-agonist*†	2055	22 992
No. of patients prescribed asthma drug†		
Fixed combination inhaled long-acting β_2-agonist and corticosteroid	508	5820
Noncombination inhaled corticosteroid	2154	24 207
Noncombination inhaled β_2-agonist	3021	33 914

*Patients who had redeemed an inhaled β_2-agonist prescription (including fixed combinations with anticholinergics or corticosteroids) during the observation period and at least 1 other prescription during the preceding 365 days.
†Subpopulations are not mutually exclusive.

The study population comprised 5439 patients prescribed asthma drugs from trial-conducting practices and 59 574 patients from control practices. We used information from the SymbiAC trial and health care databases.

In brief, the SymbiAC trial was an open-label, multicenter, randomized trial comparing 2 different dosage regimens (individually adjusted dosing and fixed dosing twice daily) of Symbicort Turbuhaler (fixed combination of budesonide and formoterol). The trial included patients treated with both inhaled glucocorticosteroids and β_2-agonists (long- or short-acting) in whom symptom levels indicated further therapy. The individualized dose regimen involved patients and physicians in implementing step-up and step-down therapy according to predetermined treatment principles based on current symptom levels and supported by an electronic system advising patients about dose adjustment. Trial-conducting general practitioners were responsible for recruiting patients and for seeing them at 3 follow-up visits and were paid a fee of 5000 Danish kroner (DKK) (US $800) for each patient enrolled. The trial was approved by the Scientific Ethics Committees and the Danish Medicines Agency. Results of the trial have not been published.

AstraZeneca provided information from the trial database on the identity of the trial-conducting general practitioners in Funen County, Denmark, and the inclusion dates of patients. Eleven general practitioners in 10 different practices were listed as investigators. The study enrolled 69 patients (median, 7; range, 1-11 patients per practice). Practices enrolled their first patient between April 26 and November 10, 2001. The last patient was enrolled February 18, 2002, and completed the study on October 7, 2002.

Health Care Databases

The Danish health care system is a tax-funded state system with universal, free, and equal access to health care services both from hospitals and physicians outside of hospitals. The local county health administration is responsible for the provision of health care services and for drug reimbursement. Approximately 97% of the population is listed with a general practice.

Data on practices and patient demographics were retrieved from the Danish health administration and linked to the trial data using the practice registration number (Table 1). Physicians in group practices share the same registration number. A total of 194 practices were registered during 1999-2003. The 10 trial-conducting practices (26 physicians) consisted of 1 solo practice (1458 listed patients) and 9 group practices (2 to 5 general practitioners) that had a median of 3838 patients (range, 2954-8061 patients). Among the 184 potential control practices, 19 were excluded due to incomplete follow-up. In the remaining 165 control practices (271 physicians), 102 were solo practices that had a median of 1540 patients (range, 471-2494 patients) and 63 were group practices (2 to 6 general practitioners) that had a median of 3415 patients (range, 1504-10 208 patients).

The Odense Pharmacoepidemiological Database maintained by the University of Southern Denmark contains information on all reimbursed drugs sold by pharmacies in the County of Funen.[3,4] For each prescription, the following information is recorded: patient identity including sex and date of birth, date of drug purchase, number of packages purchased, brand name, strength, form, Anatomical Therapeutic Chemical classification code,[5] volume in defined daily doses,[5] and the practice registration number of the prescriber. Indication for treatment and dosage instructions are not recorded. Asthma drugs were all reimbursed in a general scheme covering all patients. Patients aged 18 years or older paid a deductible of 500 DKK (US $80) per year for total prescription costs. Patients younger than 18 years had a deductible of 250 DKK (US $40). The deductible increased to a maximum of 3600 DKK (US $576) as more prescriptions were being filled and reimbursement increased from 50% to 100% of expenses. All drug purchases covered by this scheme were recorded. The practice in which the patient was listed was the main provider of prescriptions for the patient. The study was approved by the Danish Data Protection Agency.

Outcome Measures

To assess whether conducting the trial changed physicians' prescribing patterns, a 1-year baseline period before a defined index date was compared with the first and second year after this date.

For the 10 trial-conducting practices, the index date was the date the practice included the first patient in the trial. For each of the 165 control practices, 1 of these 10 index dates was randomly chosen to avoid seasonal confounding.

International recommendations for asthma treatment emphasize the relevance of preventive treatment with inhaled corticosteroids even for mild asthma.[6] Among users of inhaled β_2-agonists, the percentage of patients using inhaled steroids has been used as a measure of physicians' guideline adherence.[7] We calculated this percentage as a period prevalence. The denominator was the number of current regular users of inhaled β_2-agonists who had redeemed a prescription during the observed period and at least 1 other prescription during the preceding 365 days. Fixed combinations of inhaled β_2-agonists with anticholinergics or corticosteroids were included. The numerator was the number of persons fulfilling this criterion who had also purchased inhaled steroids at any time during the 365 days preceding the last date of this period.

Using the brand name and the Anatomical Therapeutic Chemical classification code, we identified all asthma drugs produced or imported by AstraZeneca at any time during 1999-2003. Danish pharmacies are required to make a generic substitution to provide the least expensive drug. Therefore, generic alternatives among AstraZeneca's asthma drugs were included. These were without exception parallel imported AstraZeneca drugs. Competing drugs from other firms that had similar indications but could not be substituted with an AstraZeneca drug were classified as alternative choices. Symbicort was introduced on the Danish market on April 2, 2001. AstraZeneca provided Symbicort for enrolled patients during the trial and this was not recorded in the Danish prescription database. Symbicort prescriptions outside the trial were included. Only prescriptions from the practice to which patients were listed were included.

The impact on physicians' company-specific drug preferences was evaluated using the following outcomes measured as prevalences: (1) use of the trial drug (Symbicort) among all patients prescribed a fixed combination of inhaled corticosteroid and long-acting β_2-agonist, (2) use of the trial sponsor's inhaled corticosteroids among all patients prescribed a noncombination inhaled corticosteroid, and (3) use of the trial sponsor's inhaled β_2-agonist among all patients prescribed a noncombination inhaled β_2-agonist.

The overall company preference was measured as the trial sponsor company's share of the total prescribed volume of asthma drugs in defined daily doses. In addition to 1-year periods, all outcome measures for 3-month periods relative to the index date were calculated. The number of patients in subpopulations analyzed appear in Table 1.

Data Analysis

The use of a particular drug or drug category was analyzed as a binary outcome

Table 2. Asthma Drug Prescribing in Trial-Conducting and Non–Trial-Conducting Practices

	No./Total (%)		Odds Ratio (95% Confidence Interval)*		
	Trial-Conducting Practices	Non–Trial-Conducting Practices	Time Effect†	Group Effect‡	Trial Effect§
Inhaled Corticosteroid Use/Regular Inhaled β_2-Agonist Use‖					
Baseline¶	858/1252 (68.5)	10 006/14 475 (69.1)	1.00	0.91 (0.76-1.08)	
1 y#	957/1381 (69.3)	11 279/15 729 (71.7)	1.14 (1.08-1.20)		0.91 (0.76-1.08)
2 y#	1043/1430 (72.9)	11 846/16 157 (73.3)	1.23 (1.17-1.29)		1.00 (0.84-1.19)
Use of Trial Drug/Use of Fixed Combination Inhaled Long-Acting β_2-Agonist and Inhaled Corticosteroid					
Baseline¶	15/86 (17.4)	135/915 (14.8)	1.00	1.61 (0.62-4.19)	
1 y#	148/266 (55.6)	1043/3065 (34.0)	3.17 (2.56-3.94)		1.71 (0.86-3.36)
2 y#	236/426 (55.4)	1814/4484 (40.5)	4.24 (3.43-5.24)		1.46 (0.76-2.84)
Use of Trial Sponsor's Drug/Use of Noncombination Inhaled Corticosteroid					
Baseline¶	980/1310 (74.8)	10 966/14 908 (73.6)	1.00	1.05 (0.91-1.22)	
1 y#	1056/1344 (78.6)	11 254/14 998 (75.0)	1.08 (1.02-1.14)		1.14 (0.94-1.38)
2 y#	1045/1282 (81.5)	10 908/14 242 (76.6)	1.17 (1.11-1.24)		1.26 (1.04-1.54)
Use of Trial Sponsor's Drug/Use of Noncombination Inhaled β_2-Agonist					
Baseline¶	1219/1676 (72.7)	12 483/18 520 (67.4)	1.00	1.70 (1.51-1.91)	
1 y#	1274/1721 (74.0)	13 398/19 567 (68.5)	1.05 (0.87-1.20)		1.02 (0.87-1.20)
2 y#	1317/1716 (76.7)	13 039/18 874 (69.1)	1.07 (1.02-1.12)		1.18 (1.00-1.39)

*Based on random-effects logistic regression.
†Independent for first and second year vs baseline.
‡Trial-conducting practices vs non–trial-conducting practices at baseline.
§Interaction between time and group effects.
‖Patients who had redeemed an inhaled β_2-agonist prescription (including fixed combinations with anticholinergics or corticosteroids) during the observation period and at least 1 other prescription during the preceding 365 days.
¶One year before trial.
#First and second year after index date (date of including first patient in trial-conducting practices and randomly selected date in non–trial-conducting practices).

at the patient level using logistic regression. Patients in control practices at baseline were used as the reference category. A group effect and separate time effects were included for the first and second year after the index date. The effect of conducting the trial was estimated as a time × group interaction and thus adjusted both for differences between trial-conducting and control practices at baseline and for time effects, which were assumed to be identical in both groups. We fitted random-effects models[8] for patients nested within practices, allowing for within-practice correlation and for the same patients occurring more than once in the analysis. Results are presented as odds ratios (ORs) with 95% confidence intervals (CIs).

The trial sponsor company's share of the total prescribed volume of asthma drugs was analyzed at the practice level. We used linear regression adjusting for baseline differences by including the baseline value as the covariable.[9] Results are presented as mean differences between trial-conducting and control practices with bootstrapped 95% CIs based on the bias-corrected and accelerated method.[10]

Logistic regression models were assessed for colinearity. Signs of colinearity were found only in the analysis of the trial drug preference and separate analyses for the first and second year indicated that it did not affect our results. Overfitting was avoided in the primary analysis because we had a model specified a priori with only time and group effects and a sufficient number of outcome events. Practice level analyses were supplemented and included "leave-1-out" validation to ensure that results could not be explained by only a few influential practices. In secondary analyses, we adjusted for patient age and sex. In the analysis of inhaled steroid use, average β_2-agonist dose was also adjusted for but no important confounding was found. Analyses were repeated including practices with incomplete follow-up and excluding solo practices, which did not change our findings. Data were analyzed using Stata software, release 9.1 (StataCorp, College Station, Tex).

RESULTS

The prevalence of inhaled steroid use among asthma patients increased from 68.5% at baseline to 72.9% during the second observation year in trial-conducting practices and from 69.1% to 73.3% in control (non–trial-conducting) practices (TABLE 2). The time effect was statistically significant but there was no impact of trial conduction on guideline adherence (OR for the second year after the index date, 1.00; 95% CI, 0.84-1.19).

Prevalence of physician prescribing of the trial sponsor's inhaled long-acting β_2-agonist and corticosteroid combination (trial drug) rose from 17.4% to 55.4% in trial-conducting practices and from 14.8% to 40.5% in control practices during the observation period. Thus, a marked time effect was observed but the trial conduction effect was not statistically significant.

Both trial-conducting and control practices had a gradually increased prevalence of use of the trial sponsor's inhaled corticosteroids. Prevalence increased from 74.8% to 81.5% in trial-conducting practices and from 73.6% to 76.6% in control practices. There was an increasing effect of trial conduction with an OR of 1.26 (95% CI, 1.04-1.54) for the second year.

The prevalence of use of the trial sponsor's inhaled β_2-agonists increased from 72.7% to 76.7% in trial-conducting practices and from 67.4% to 69.1% in control practices. The trial conduction effect OR for the second year was 1.18 (95% CI, 1.00-1.39).

The trial sponsor's share of the total prescribed volume of asthma drugs increased in trial-conducting practices compared with control practices by 6.7% (95% CI, 3.0%-11.7%) (TABLE 3).

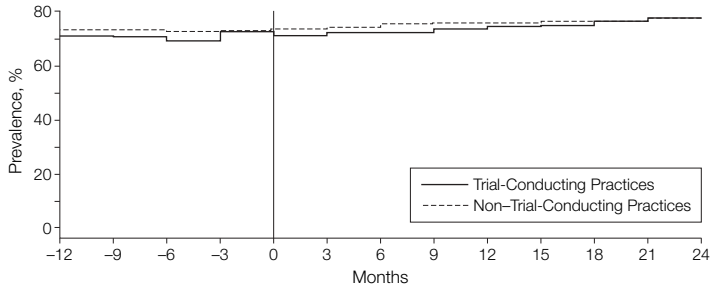
The 3-month data (FIGURE 1, FIGURE 2, and FIGURE 3) support that there was no difference in guideline adherence but there was an increasing difference in prescribing

Table 3. Sponsor's Share of Total Prescribed Asthma Drug Volume in Defined Daily Doses for Trial-Conducting and Non–Trial-Conducting Practices

	Trial-Conducting Practices, %*	Non–Trial-Conducting Practices, %*	Difference, % (95% CI)†
Baseline	52.9	52.8	
1 y	56.3	53.1	3.1 (0.2-5.0)
2 y	58.7	51.9	6.7 (3.0-11.7)

Abbreviation: CI, confidence interval.
*Average calculated or estimated at practice level.
†Linear regression with baseline value as the covariable, bootstrapped 95% CI.

Figure 1. Use of Inhaled Coricosteroid Among Inhaled β_2-Agonist Users



No. of Patients												
Trial-Conducting Practices	771	794	836	829	834	849	884	906	903	946	900	901
Non–Trial-Conducting Practices	9072	9473	9822	9941	9886	10318	10511	10614	10390	10482	10664	10574

Curves indicate prevalence for 3-month periods; 0 indicates index date.

of the trial sponsor's drugs between the trial-conducting practices and the control practices during the first and second year after the index date.

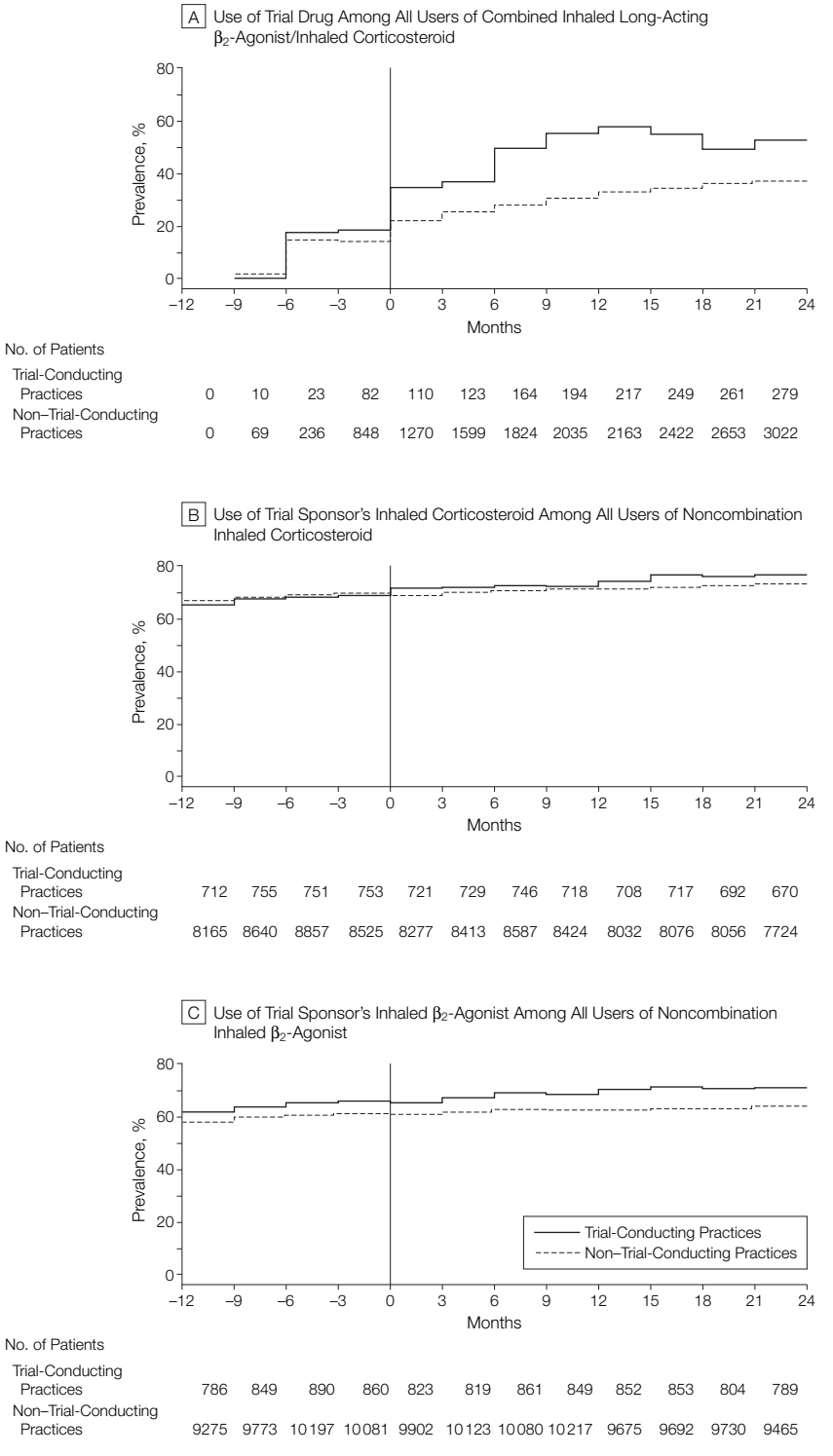
COMMENT

The observed lack of impact on guideline adherence (ie, treating asthma patients with inhaled steroids) should be interpreted with caution. First, taking into account the statistical precision, our study results for the second year are also compatible with a small increase or a small decrease in guideline adherence, corresponding to less than 4 percentage points in the prevalence of inhaled steroid use. Second, a "ceiling effect" should be considered. If there is no place for improvement, even the best intervention appears to be ineffective, and in our study the majority of β_2-agonist users (approximately 70%) were treated with inhaled steroids.

The effect on drug preferences seems more reliable. Because data were based on a highly valid and complete register[3] covering all prescribed asthma drugs, bias caused by self-reporting of behavior was avoided. Furthermore, the physicians were not informed in advance about our study, and awareness of being monitored therefore did not influence their prescribing patterns. Increased prescribing of the trial sponsor's drugs among trial-conducting practices was observed in different categories of asthma drugs and supported by the trends seen in the 3-month prevalence data.

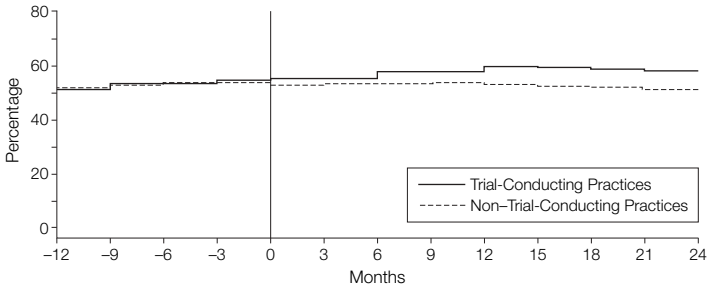
A major limitation of our study is that we could not distinguish between individual physicians in group practices. Not all physicians in the trial-conducting practices were investigators in the trial and the practice colleagues of investigators could not have been directly influenced by the trial. Our results reflect a mixture of the investigators' and their colleagues' prescribing patterns leading to underestimation of effects on both guideline adherence and drug preferences. If there was no change in prescribing patterns among the practice colleagues of the investigators, we

Figure 2. Use of Combined Inhaled Long-Acting β_2-Agonist/Inhaled Corticosteroid Compared With Use of Noncombination Inhaled Corticosteroid or Noncombination β_2-Agonist



Curves indicate prevalence for 3-month periods; 0 indicates index date.

Figure 3. Sponsor's Share of Total Prescribed Asthma Drug Volume



No. of Patients												
Trial-Conducting Practices	1566	1675	1748	1681	1583	1665	1737	1715	1667	1767	1688	1634
Non–Trial-Conducting Practices	16732	18442	19290	18739	17775	19174	19452	19176	18205	19056	19219	18542

Curves indicate percentage for 3-month periods; 0 indicates index date.

have measured only approximately 40% of the true effect. Furthermore, interactions between trial-conducting physicians and other general practitioners in educational groups could have given rise to a spillover effect among control practices. We assume, however, that the possible underestimation caused by such spillover is small. We did not have access to practice patient lists, and misclassification of the patient-practice relationship could have led to a small bias toward no effect.

Interactions between the pharmaceutical industry and physicians have been discussed[11] and few other medical issues can provoke more discussion among general practitioners. Most articles focus on whether pharmaceutical industry marketing entails suboptimal or even harmful or unnecessarily expensive prescription patterns,[1,2,11-15] whereas the industry's role in improving drug use has received much less attention. Our study confirms the hypothesis that physician involvement in clinical trials is a powerful tool for influencing company-specific drug preferences. Several mechanisms may be responsible, including setting up a gift relationship by payment to the trial-conducting physicians. If we had access to information on the costs of the trial, it would have been possible to evaluate if these trial costs were counterbalanced by the revenue from the trial sponsor's increased market share. Whether conducting a clinical trial can lead to minor improvements in guideline adherence can only be addressed in large-scale studies.

In conclusion, conducting a pharmaceutical company–sponsored trial did not influence physicians' adherence to international treatment recommendations but significantly increased prescribing preference for the trial sponsor's drugs.

Author Contributions: Dr Andersen had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Andersen, Kragstrup, Søndergaard.
Acquisition of data: Andersen.
Analysis and interpretation of data: Andersen, Søndergaard.
Drafting of the manuscript: Andersen, Søndergaard.
Critical revision of the manuscript for important intellectual content: Andersen, Kragstrup, Søndergaard.
Statistical analysis: Andersen.
Obtained funding: Andersen, Kragstrup, Søndergaard.
Administrative, technical, or material support: Kragstrup.
Study supervision: Kragstrup, Søndergaard.
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Role of the Sponsor: The sponsor contributed with data on the SymbiAC trial. The sponsor did not get insight into prescription data at the level of the individual physicians or patients and was not involved in the design of the study, the management, analysis, and interpretation of the data, the preparation, review, or approval of the manuscript, or the decision to submit it for publication.
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