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# Ethics, consent and blinding: lessons from a placebo/sham controlled continuous positive airway pressure cross-over trial

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**Ethics, consent and blinding**: **lessons from a placebo/sham controlled continuous positive airway pressure cross-over trial**

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**Competing interests**

We received support from Philips Respironics, the CPAP manufacturer that provided the active and placebo/sham CPAP machines for use in this study. No other support from any organisation for the submitted work was received; we do not have financial relationships with any organisations that might have an interest in the submitted work in the previous three years, and we do not have other relationships or activities that could appear to have influenced the submitted work.

**Ethics approval:**

Granted by Sydney South West Area Health Service, NSW, Australia (Royal Prince Alfred Hospital Zone) with protocol number X05-0128

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**Conflicts of Interest statement for all authors:**

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and RG and CLP declare support from the Australian NHMRC organisation as described above, for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

The data from this study is available by request.

**Authors Contribution:**

RRG, NSM, CLP were responsible for the conception and design of the study. NSM, ALD, YD, CLP, MRC were responsible for the acquisition of data. NSM and CLP performed the

statistical analyses. All authors contributed to the interpretation of data, drafting and revising of the article and final approval of article. YD is the guarantor.

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**Clinical trials registration**:

This clinical trial is registered with the Australian and New Zealand Clinical Trials Registry at www.anzctr.org.au (ACTRN 12605000066684).

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**Key question**: Is it possible to blind patients and investigators to treatment allocation in randomised sham CPAP controlled cross-over trials?

**Bottom line**: Patient blinding may be possible with lack of full disclosure but investigator blinding is unlikely to be achieved.

**Why read on?** This is the first study to raise important practical, scientific and ethical issues for any non-implantable medical device-based crossover trials where the maintenance of blinding depends on deliberately withholding full disclosure of the sham device.

**Abstract**

Introduction:

Performing rigorously designed clinical trials in device-based treatments is challenging. Continuous positive airway pressure (CPAP) is the most effective device-based treatment for obstructive sleep apnoea (OSA). We performed a randomised cross-over trial of CPAP versus placebo therapy, and did not disclose the presence of placebo. We assessed rates of staff unblinding, the likelihood of patient unblinding and obtained patient perceptions on lack of full disclosure.

Methods

All patients (n=30) underwent a semi-structured exit interview. Prior to full disclosure patients were asked questions to ascertain whether they suspected one therapy was ineffective. The use of placebo was then disclosed and additional questions were administered to indicate the likelihood of unblinding had full disclosure occurred during consent. Staff unblinding was determined by means of a questionnaire that was completed after each patient encounter.

Results

Whilst the lack of full disclosure prevented patient unblinding during the trial, patients revealed a clear preference for active CPAP. After disclosing the presence of placebo, 73% (n=22) felt they would have been unblinded had they known at the start of the trial. Only one patient described unease about the lack of full disclosure. Staff thought they were unblinded in 6% (n=16/282) of encounters. They correctly identified the treatment device in 69% of cases (n=11/16, $p<0.001$).

Conclusion

Successful patient blinding was achieved, however, this was probably reliant on the lack of full disclosure. Staff unblinding occurred and highlights the difficulty with investigator blinding in device-based trials. Ethical challenges in this type of study are likely to compromise research feasibility.

## Introduction

In trials using pharmacotherapy, the use of an inert tablet is usually an appropriate control for placebo effects when used in conjunction with blinding of both patients and investigators. However, under the usual conditions of full disclosure, blinding of the patient is more challenging when using a non-pharmacological treatment such as a non-implantable medical device. The proportion of new treatments that are device based is increasing relative to drugs and other modalities. There is also concern about the differential standards for efficacy and safety applied to drugs and devices even when used to treat the same conditions. This has resulted in greater scrutiny of the evidence base for the effectiveness and safety of devices with the resultant need to design and encompass matching placebo devices in randomised controlled trials. However when devices have clear and immediate physical effects, it becomes challenging to successfully blind both participants and investigators under conditions where full disclosure is mandatory.

One example of a non-implantable medical device is continuous positive airway pressure (CPAP) which is the standard treatment for obstructive sleep apnoea syndrome (OSA). It acts as a pneumatic splint of the upper airway during sleep by delivering air pressure from a pump to a mask worn on the face.

A sham form of a CPAP device can be used as a placebo comparison for active CPAP. An active CPAP device ordinarily delivers pressures anywhere between 4 cm $H_20$ and 20 cm $H_20$. In a sham CPAP device, the exhalation port of the CPAP mask is increased in size, and a resistor is added between the pump and the tubing. In this way a pressure of less than 1 cm $H_20$ is delivered to the mask whilst maintaining the same appearance and noise of an active

CPAP machine [1]. However, because air pressure is the mechanism of action, sham devices feel different due to a markedly lower mask air pressure compared to the therapeutic device.

In chronic conditions such as OSA, randomised cross-over trials offer an efficient way to test interventions because of their relative statistical efficiency. Patients are exposed to both sham and active CPAP interventions to compare device effectiveness within patients. However, this approach has raised concerns due to the difficulty of preserving blinding. If patients were told in advance (full disclosure) that one treatment was inert it would unblind the trial because patients could immediately tell which treatment had the lower pressure. One authors' (NM) experience from a previous sham CPAP cross-over trial was that patients immediately noticed the pressure differences after cross-over. Though they were asked not to discuss this with study personnel, they would often mention their experience of pressure change thereby inadvertently unblinding study personnel [2]. Several research groups that have recently conducted cross-over trials have made it clear in their manuscripts that they did not fully disclose to patients that they would receive ineffective (placebo) treatment [2-7]. This is due to concern that the resultant unblinding would render the trial scientifically uninterpretable, a concern first raised by Karlawish and Pack more than a decade ago [8]. However, withholding information conflicts with the concept of true informed consent [9]. A summary of disclosure patterns of published cross-over trials using sham CPAP is presented in Table 1.

Despite these concerns, no studies to date have attempted to evaluate the success of blinding in randomised cross-over trials with sham CPAP. We conducted a placebo controlled cross-over trial of CPAP where the existence of a placebo was not disclosed [6]. Using data from patient interview questions and from staff questionnaires during the trial, we sought to

determine (1) whether staff unblinding occurred, (2) whether patients thought they would have been unblinded had they known there would have been a placebo used in the trial and (3) patient perceptions on lack of full disclosure.

**Methods**

This is an auxiliary study of a published randomised cross-over trial comparing the effects of two months of CPAP to sham-CPAP on lipid metabolism in patients with moderate to severe OSA (apnoea-hypopnoea index ≥ 25/h sleep) [6]. The active and placebo CPAP devices (Remstar Auto; Philips Respironics, Murrysville, PA) were identical. All other details regarding the study protocol may be found in the original report [6].

The patient information sheet disclosed that patients would be using two CPAP machines that "will deliver pressure in a different way." They were also told that one of the aims of the study was to determine "whether the way in which a CPAP machine delivers pressure is important in determining which machine you prefer to use."

Our local ethics committee was concerned about the lack of full disclosure and its effects on informed consent. However they also recognised the additional scientific problem that would be introduced by the trial becoming unblinded. They agreed to approve the study, inclusive of withholding knowledge of the placebo device from patients, provided further investigation was performed to assess the impact of this withheld knowledge. Full disclosure was made at an exit interview with each patient before study discharge. In this interview, the reasoning for not fully disclosing the nature of the placebo device during the consenting process was explained.

Final approval was sought from the Ethics committee (RPAH Zone) of the Sydney South West Area Health Service with study protocol number X05-0128.

*Patient Exit interview*

Patients underwent a semi-structured exit interview at the time of completion or withdrawal from the study. All interviews were undertaken by the same investigator (NM) who remained nominally blinded to treatment allocation. Appendix A lists the scripted prompts and questions that were used by the interviewer with patients. Patients were initially asked numerous questions about their treatment experience/preferences. This was designed to elicit from the patient whether they suspected the existence of a placebo or non-efficacious treatment. Subsequently, an unblinded investigator (AD) took over the interview and debriefed the patients on the true nature of the study. They asked the patients 1) whether they felt they would have been unblinded if there had been full disclosure at the start of the study and 2) how they felt about not having been told that there was a placebo treatment used in the trial. Patients were asked what their bed-partners thought about the relative performance of each machine.

*Staff questionnaires*

Staff members were asked to complete the questionnaires after any type of encounter with the patient to determine whether they had been unblinded. Encounters included events such as venepuncture. The questionnaires were not completed after every single patient encounter as we had intended, as study personnel were often busy. The exact denominator, or number of staff-patient encounters, is unknown. If staff thought they were *definitely unblinded*, they were re-assigned so as to no longer have contact with the patient.

*Statistical analysis*

We used descriptive statistics, frequencies and percentages to describe our data. Chi Squared tests were used to test whether staff treatment allocation guesses were statistically correct

more often than 50% of the time. Mixed model analysis of variance was used (SAS v9.3) to test whether adherence rates differed between treatments and whether the order in which treatment was received affected adherence. Patient numbers were used as random effects and treatment, order and order by treatment interaction were fixed effects.

**Results**

In the original study, 38 patients were randomised and 29 completed the trial. Thirty-four patients started treatment but 3 withdrew almost immediately after initiating treatment. Staff questionnaires were obtained for the remaining 31 patients. Of these, 30 patients experienced both treatment arms and subsequently underwent the exit interview. One patient withdrew prior to completion of the second arm. No patients suspected the presence of a placebo during the trial.

*Patient Exit interview*

The patient perceptions of the two treatment arms are described in Table 2. Before being told that there was a placebo, the majority of patients identified the treatment arm with active CPAP as the preferred treatment, felt that it was better for their sleep, and preferred to use it in the long-term. More patients thought their bed-partner would report that CPAP was more effective than placebo.

After telling patients that there was a placebo, 73% (n=22, p=0.02) stated they felt they would have been able to determine which device was the placebo during the trial if full disclosure had occurred during the consenting process.

Only one patient stated that he felt slightly uncomfortable that full disclosure did not occur. All other patients reported that they understood why full disclosure had not occurred and that withholding this information was warranted. The interviewer also noted that very few patients remembered the contents of the informed consent documents they had signed and many had not retained these even though the trial was less than 6 months in duration. Some patients could not recall that there had been such a document.

*Staff questionnaires*

Staff questionnaires were completed for 31 patients. There were 282 staff-patient encounters documented. The number of staff encounters recorded per patient averaged 9 (SD 3, range 3-15 per patient). Figure 1 illustrates the results of the staff questionnaires.

Staff thought they were *definitely unblinded* in 6% (n=16/282) of recorded encounters and then mostly correctly identified the treatment (n=11/16, 69%, p<0.01). Staff thought they *might have been unblinded* in 22% (n= 61/282) of recorded encounters and they typically guessed correctly (n = 44/61, 72%, p<0.01). Of the 55 correct guesses/unblinding episodes, 21 occurred in the first arm and 34 occurred in the second arm (p=0.11).

*Adherence*

Adherence was compared in those that started with active CPAP then crossed-over to sham CPAP, and vice versa (Table 3). CPAP adherence was highest in those that started with active CPAP and reduced significantly on commencing sham CPAP (5.6 vs. 3.5 hrs). In those that started with sham CPAP, adherence was low and remained low after commencing active CPAP (3.3 hrs vs. 3.2 hrs).

## Discussion

In this study, we sought to determine whether staff unblinding occurred in our sham CPAP cross-over trial. We also assessed the likelihood of patient unblinding had full disclosure occurred during the consenting process. We purposefully did not disclose the presence of a placebo in an effort to preserve blinding. Informing patients that the study aimed at testing "two different deliveries of pressure" rather than telling them that one treatment would be ineffective meant that patients should not have been able to have pre-determined perceptions of reduced benefit in either arm. Our results demonstrate that the vast majority (72%) of patients felt that they would have been able to identify the placebo treatment had they been informed at the start of the trial. Prior to unblinding the patient, although no patient suspected that sham CPAP was used when directly prompted, the majority of patients were able to identify active CPAP as the more effective treatment. Examination of the staff-patient encounters reveals that unblinding occurs amongst staff. When staff members thought that they had been unblinded they were usually correct. Any degree of unblinding is undesirable and this study highlights the practical difficulties in preserving double blinding in a sham CPAP cross-over trial. We believe that staff blinding would be equally as problematic in parallel studies of sham CPAP.

We found that adherence was influenced by type of treatment and by order of treatment. Firstly, adherence was lower on sham CPAP regardless of order of administration. In our trial, this was to be expected given the clear differences in patient preferences. However, those that commenced on sham CPAP first followed by active CPAP continued to have lower adherence, potentially due to their discouraging initial experience. This may imply that adherence is predictably affected by order of treatment interaction, also noted by other investigators [4, 10]. This highlights a shortcoming of cross-over trials.

Amongst the cross-over studies that did not disclose the presence of placebo, all but one study demonstrated a clear discrepancy between adherence rates in each arm, with lower rates in the sham CPAP arm [2-7]. The only study that showed equivalent rates of adherence between arms was a study performed in patients with mild OSA[2]. These patients had no clear preference for active CPAP presumably due to milder symptoms and reduced symptomatic benefit. Overall, in these studies where there was lack of full disclosure there was lower use of sham CPAP devices.

In contrast to the majority of cross-over trials, Weinstock et al [10] was the only group that we are aware of that clearly disclosed the existence of a placebo device at the time of consent (Susan Redline, personal communication). This study does not appear to have had significant issues with drop-outs, or dismal compliance on the sham arm as we may have predicted. However, they did find significantly lower adherence in the sham arm, particularly if it was provided on the second arm. One interpretation of this apparent success may be that patients did not remember the contents of the informed consent documents. Additionally, it is difficult to make conclusions about the effect of full disclosure based on only one study.

Interestingly, patients did not object to the lack of full disclosure when it was revealed to them. It may be because such a high proportion felt that their behaviour would have been influenced by this knowledge. From our interviews it appears that informed consent documents were not valued by patients. They often did not remember what was in them, or that they existed. They often did not retain their provided copies. This suggests that these documents may not be serving their intended function. Even though our study had not intended to investigate patient perceptions of informed consent documents in clinical trials, it

was apparent through the interviews that patients in our trial derived very little if any value from them.

Limitations include that we were unable to capture every single staff-patient encounter as they were numerous and the task relied on staff completion on every encounter. This might have led to preferential completion of the questionnaire after unblinding events. As such, the data might reflect spontaneous adverse event reporting data where unblinding events are more likely to be reported. In addition, after the exit interview and after full disclosure, we did not repeat the interview questions in Table 2 to verify that the -73% of patients who thought they could identify the active treatment actually could. A further limitation was that we never ascertained from the patients exposed to sham CPAP last, whether full disclosure would have resulted in them being less inclined to use it. This information would be important for ethics committees when considering future trials.

The proportion of device-based treatment is on the rise. Rigorous research in this area differs to pharmacologic agents and is challenging with practical difficulties. Investigator blinding is difficult if not impossible to achieve both in parallel and cross-over design trials. We have found that with the use of sham CPAP in a cross-over trial, the only solution to maintaining patient blinding and scientific integrity is to abstain from disclosing to patients the existence of a placebo. This in turn creates an ethical dilemma and is a challenge that warrants further attention and discussion.

*Table 1. Summary of level of disclosure in published randomised cross-over trials using sham CPAP*

| Author | | Full placebo disclosure | Available information on level of disclosure |
|---|---|---|---|
| Marshall 2005[2] | | No | Manuscript states: "patients were informed that the study was 'testing two different pressures of humidified CPAP'" |
| Robinson 2006 [3] | | No | Personal communication: patients were not told that one pressure was completely ineffective* |
| Coughlin 2007[4] | | No | Manuscript states: "Low pressure alternative that might provide some symptomatic benefit" |
| Cross 2008[5] | | No | Personal communication: similar protocol as per Jones paper below^ |
| Phillips 2011,[6] Phillips 2012, [11] McEwen 2012[12] | Same trial | No | Patients were informed that they would be receiving two different pressures |
| Jones 2013[7] | | No | Patient information sheet: "You will receive two different types of CPAP. CPAP machines can be set to provide air at different pressures. You will receive one such pressure for three months, and a different pressure for the second three month period." |
| Arias 2006[13] | | Unclear | Manuscript states: "patients were not informed of the type of therapy they were receiving." Personal communication confirmed patients were blinded. |
| Alonso-Fernandez 2006[14] | | Unclear | Manuscript states:"…they were not informed of the type of therapy there were receiving" |
| Arias 2008[15] | | Unclear | Manuscript states: "they were not informed of the type of therapy there were receiving." Personal communication confirmed patients were blinded. |
| Alonso-Fernandez 2009[16] | | Unclear | Manuscript states: "No information about the type of therapy they were receiving was given" |
| Weinstock 2012 [10] | | Yes | Full disclosure was made to patients regarding the use and implications of sham CPAP [$] |

**personal communications with Grace Robinson and John Stradling*
*[#]personal communications with Miguel Arias*
*[$]personal communications with Susan Redline*
*^personal communications with Anne Jones and Renata Riha*

***Table 2. Patient perceptions of the two treatment arms, active CPAP and sham CPAP, at the exit interview (n=30).*** *Active CPAP was consistently identified as the preferred treatment before disclosure of the presence of a placebo had occurred.*

| | **True CPAP (%)** | **Sham CPAP (%)** | **Unsure/ Equal (%)** | **Don't know/ no bed partner (%)** |
|---|---|---|---|---|
| Overall preference | 19 (63) | 8 (27) | 3 (10) | - |
| Led to better sleep | 19 (64) | 7 (23) | 4 (13) | - |
| Preferred for long term use | 20 (67) | 8 (27) | 2 (6) | - |
| Presumed bed partner preference | 12 (40) | 5 (17) | 8 (27) | 5 (17) |

*Table 3. CPAP adherence rates in each arm before and after cross-over.*

| **Order of cross-over** | **Adherence (Hours per night) 1st arm (95% CI)** | **Adherence (Hours per night) 2nd arm (95% CI)** |
|---|---|---|
| Active CPAP then sham CPAP | 5.6 (4.4 - 6.8)** | 3.5 (2.4 - 4.7) |
| Sham CPAP then active CPAP | 3.3 (2.1 - 4.4) | 3.2 (2.0 - 4.3) |

**p<0.01 for comparisons with every other cell. CPAP adherence is higher in the first arm than all other combinations. None of the other 3 cells are different from one another. This effect drove the difference in adherence seen in the trial overall between active and sham CPAP (1 hour 95% CI 0.2, 1.7, p=0.01) and the overall p-value for the interaction between treatment and the order in which it was received was <0.01.

*Figure 1. Staff perceptions on patient treatment assignment after each staff-patient encounter.*

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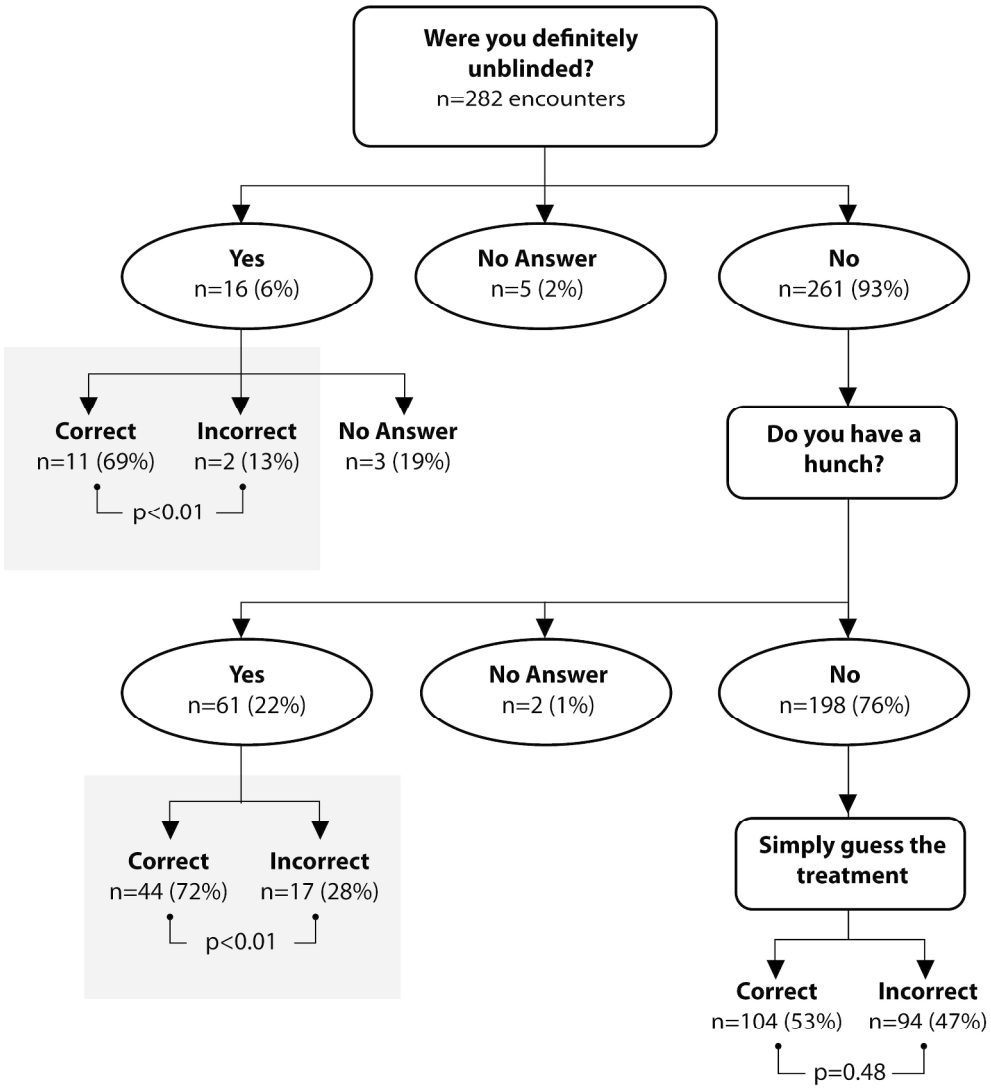


Figure 1. Staff perceptions on patient treatment assignment after each staff-patient encounter.
249x283mm (300 x 300 DPI)