PADDI Sleep Substudy: Statistical Analysis Plan

This is the second version of the SAP and was written after the data had been de-identified as regards to treatment and with further analysis added.

General principles

The analysis and reporting of the results will follow the CONSORT guidelines. [1] Baseline characteristics will be tabulated by Dexamethasone and placebo groups using appropriate summary statistics and will include PSQI score. [2] Data for the primary endpoint will be derived from those patients enrolled into the PADDI-SLEEP substudy (those who completed the extra sleep questionnaires). Data for all endpoints will be analysed using the modified intention-to-treat (mITT)and per protocol (PP) populations, with the mITT analysis regarded as the principal analysis. Full definitions of mITT and PP are provided below.
Further sensitivity analyses will make post-hoc adjustment for any variables exhibiting substantial imbalance across treatment arms at baseline (Table 1). Interpretation of all endpoints will be based on post estimates, confidence intervals and P-values. A nominal 5% significance level will be employed.

Null hypothesis

The intraoperative administration of intravenous dexamethasone 8 mg to patients undergoing elective non-cardiac and non-obstetric surgery, compared with placebo, is ***non-inferior*** to placebo in terms of postoperative sleep quality.

Primary outcome

Patient self-assessed sleep quality measured on postoperative night one.

Secondary outcome

Patient self-assessed sleep quality measured on postoperative night two.

Sample size analysis

There are no published data available to use for accurate sample size estimation. We have collected data on 30 patients at Westmead Hospital that suit the PADDI inclusion criteria but who have not received dexamethasone. The mean RCSQ score on night one postoperatively was 50.17 mm, with a standard deviation of 25.28. A decrease in a patient's RCSQ score by 7.5mm (15% relative decrease) would be considered a clinically meaningful difference and hence we have chosen this as our non-inferiority margin (delta). To detect a non-inferiority margin of 15% with 90% probability (power), where non-inferiority is concluded if the upper endpoint of the two-sided 95% confidence interval for the difference in sleep quality is less than 7.5mm, requires a sample size of 195 patients per group (total 390 patients). Target recruitment set at 410 patients in total to account for 5% losses to follow up.

Statistical Analyses

A. Modified ITT (mITT) population

The mITT population will consist of all randomised patients who undergo induction of anaesthesia and eligible surgery (surgery with a total surgical incision length >5 cms; this is an arbitrary incision length, chosen by using a Delphi approach among the members of the trial steering committee). The mITT patients will be analysed according to the group to which they were randomised, whether they receive study drug or not, or whether they receive additional (non-study) glucocorticoid or not. The only exclusions will be for:

a) patients who do not undergo surgery under general anaesthesia on the scheduled date
b) patients who withdrew consent prior to surgery
c) clinician refusal at the time of surgery
d) duplicate randomisation
e) study drug not available at the time of surgery
f) screening failures

Patients whose consent is withdrawn post-operatively will have their data used up until the time of withdrawal.

B. Per Protocol (PP) population

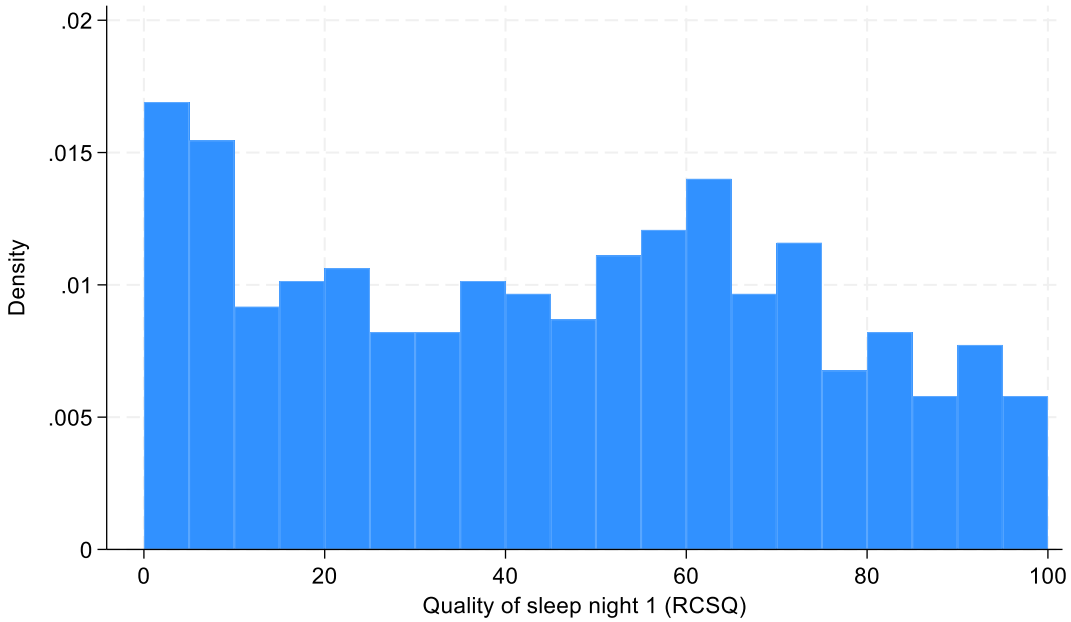
The PP population will comprise those patients who completed the treatment to which they were originally allocated, meaning ONLY those patients who receive a single dose of study drug or placebo according to their original randomised allocation. This analysis specifically excludes patients who were not given their randomised study drug at the commencement of surgery ***AND*** patients who received their study drug but also receive non-study glucocorticoid within the 24 hours following surgery. This also excludes patients randomised to dexamethasone whose randomisation was overridden and received open-label dexamethasone within the 24 hours following surgery. Patients who withdraw consent will have their data used up until the time of withdrawal.

The primary analyses will be in the mITT population, per protocol (PP) populations and a sensitivity analyses will make post-hoc adjustment for any variables exhibiting substantial imbalance across treatment arms at baseline. The mITT analysis will be undertaken as per the main Statistical Analysis Plan for the PADDI trial. The per protocol analysis will only exclude those who did not get the study drug or those who got non-study dexamethasone during surgery or in PACU, that is they received non-study dexamethasone prior to the primary outcome occurrence. Because the patients not meeting the PP population definition have been excluded, there may no longer be balance in patient characteristics between dexamethasone and placebo arms. The baseline and pre-operative characteristics in the dexamethasone and

placebo arms will be tabulated and compared for the 'compliant' (PP) patients. Any variables exhibiting imbalance will be adjusted for.

Outcomes

The primary outcome is sleep quality on night one (as assessed using the RCSQ). As the distribution of the sleep score is not normal, median regression will be undertaken to assess the difference in medians between the two treatment groups. For the sensitivity analysis, baseline characteristics will be examined and adjustment will be made for differences between the groups. The variable, preop sleep quality, is considered a major confounder and will be included in the adjusted models.



Histogram of sleep quality night one showing two peaks.

The secondary outcome is sleep quality on night two. The same analysis will be undertaken as per night one. Some people would have been discharged on day 1 but for consistency the same variables will be adjusted for as for night one in the sensitivity analysis.

Postoperative variables of interest

1. Any nausea or vomiting postoperatively to 24 hours following surgical incision.
2. Any antiemetic usage postoperatively to 24 hours following surgical incision.
3. Nausea –
   a. Worst nausea as measured on a numerical rating scale (numerical rating scale [NRS], 0–10) in PACU and post PACU up to the first 24 hours following surgical incision.

b. Antiemetic usage in each of these periods.

4. Vomiting- Any vomiting and number of vomiting events in PACU and post PACU up to the first 24 hours following surgical incision.
5. Highest pain score (NRS, 0–10) at rest and on movement in PACU and post PACU up to the first 24 hours following surgical incision.
6. Quality of recovery score Day
7. Sleep location night 1 and night 2
8. Noise level night 1 and night 2
9. Non-study dexamethasone intraoperative, PACU and day 1

These outcomes will be tabulated according to the treatment group but no formal comparison will be performed because we know that dexamethasone administration alters these outcome variables. It is also possible that these outcomes might interact with the sleep outcomes, but we do not plan to examine this. For non-normal continuous distributions, median regression via quantile regression will be undertaken. For binary outcomes, binomial regression to estimate risk ratios together with 95% CI will be undertaken. Should the regression model fail to converge, a linear model with identity link or Poisson model with logarithmic link (respectively) and robust standard errors will be employed.

**********TABLES**********

Table 1: Baseline characteristics of sleep subgroup population by treatment group

	Dexamethasone	Control
Age		
Sex		
Weight		
BMI		
ASA		
1/2		
3		
4		
Diabetes		
Chronic pain		
Opioid therapy for chronic pain		
Surgery type		
Length of surgery		
Planned use of opioids post-operatively		
PCA		
Neuraxial (intrathecal / epidural)		
Regular opioids (oral / intravenous / patch)		
PSQI score		

Sleep at home		
Sleep apnoea diagnosis		
CPAP regular use		

Table 2: Primary outcome analysis by mITT, per protocol and post-hoc adjustment for night one and secondary outcome night two.

Night	Method	Placebo	Dexamethasone	Difference (95% CI)	p-value	Missing
One (n)						
	mITT					
	Per protocol					
	Post-hoc adjustment					
Two (n)						
	mITT					

Results will be presented as a graph for night one and in table format. A graph of the estimates from the three methods will be presented (similar to a forest plot), with the non-inferiority margin (Δ) of -7.5 drawn in as a line.

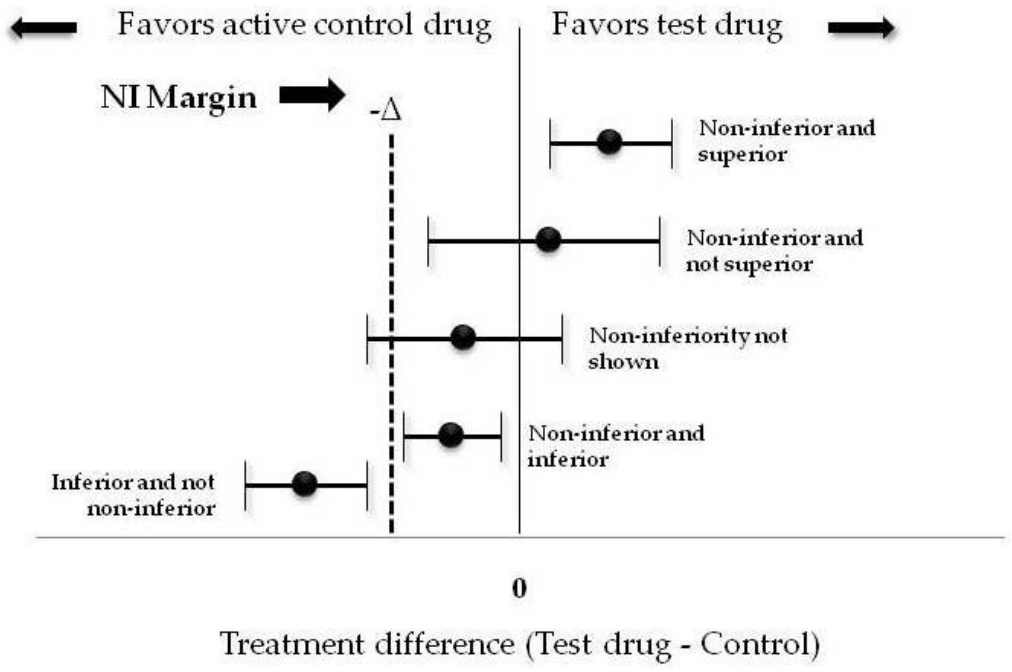


Image as per Schumi, J., Wittes, J.T. Through the looking glass: understanding non-inferiority. *Trials* **12**, 106 (2011). https://doi.org/10.1186/1745-6215-12-106

Table 3: Variables of interest post randomisation.

	Dexamethasone	Control	Estimate (95% CI)	p-value
Any nausea or vomiting up to 24 hours post-surgery				
Any antiemetic up to 24 hours post-surgery				
Worst nausea rating PACU				
Anti-emetic PACU				
Anti-emetic Day 1				
Worst nausea rating Day 1				
Any vomiting PACU				
Any vomiting Day 1				
Number of vomiting events PACU				
Number of vomiting events Day 1				
Worst pain (movement) PACU				
Worst pain (rest) PACU				
Worst pain (movement) Day 1				
Worst pain (rest) Day 1				
Sleep location night 1				
Noise level (VAS score) night 1				
Sleep location night 2				
Noise level (VAS score) night 2				
Non-study DXA during surgery				
Non-study dexamethasone PACU				
Non-study dexamethasone Day 1				

Table 4: Individual components of the Quality of Sleep Questionnaire (will not test)

	Placebo	Dexamethasone
Night one		
My sleep last night was: light (0) - deep (100)		
Last night, the first time I got to sleep I: just never could not fall		

asleep (0) - fell asleep almost immediately (100)		
Last night I was: awake all night long (0) - awake very little (100)		
Last night, when I woke up or was awakened I: couldn't get back to sleep (0) - got back to sleep immediately (100)		
I would describe my sleep last night as: a bad night's sleep (0) - a good night's sleep (100)		
I would describe the noise level last night as: very noisy (0) - very quiet (100)		
Night two		
My sleep last night was: light (0) -deep (100)		
Last night, the first time I got to sleep I: just never could not fall asleep (0) - fell asleep almost immediately (100)		
Last night I was: awake all night long (0) - awake very little (100)		
Last night, when I woke up or was awakened I: couldn't get back to sleep (0) - got back to sleep immediately (100)		
I would describe my sleep last night as: a bad night's sleep (0) - a good night's sleep (100)		
I would describe the noise level last night as: very noisy (0) - very quiet (100)		

Name_____ Date_____

Sleep Quality Assessment (PSQI)

What is PSQI, and what is it measuring?

The Pittsburgh Sleep Quality Index (PSQI) is an effective instrument used to measure the quality and patterns of sleep in adults. It differentiates "poor" from "good" sleep quality by measuring seven areas (components): subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, and daytime dysfunction over the last month.

INSTRUCTIONS:

The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month. Please answer all questions.

During the past month,

1. When have you usually gone to bed? _____
2. How long (in minutes) has it taken you to fall asleep each night? _____
3. What time have you usually gotten up in the morning? _____
4. A. How many hours of actual sleep did you get at night? _____
   B. How many hours were you in bed? _____

5. During the past month, how often have you had trouble sleeping because you	Not during the past month (0)	Less than once a week (1)	Once or twice a week (2)	Three or more times a week (3)
A. Cannot get to sleep within 30 minutes				
B. Wake up in the middle of the night or early morning				
C. Have to get up to use the bathroom				
D. Cannot breathe comfortably				
E. Cough or snore loudly				
F. Feel too cold				
G. Feel too hot				
H. Have bad dreams				
I. Have pain				
J. Other reason (s), please describe, including how often you have had trouble sleeping because of this reason (s):				
6. During the past month, how often have you taken medicine (prescribed or "over the counter") to help you sleep?				
7. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?				
8. During the past month, how much of a problem has it been for you to keep up enthusiasm to get things done?				
9. During the past month, how would you rate your sleep quality overall?	Very good (0)	Fairly good (1)	Fairly bad (2)	Very bad (3)

Scoring

Component 1	#9 Score	C1 _____
Component 2	#2 Score (<15min (0), 16-30min (1), 31-60 min (2), >60min (3)) + #5a Score (if sum is equal 0=0; 1-2=1; 3-4=2; 5-6=3)	C2 _____
Component 3	#4 Score (>7(0), 6-7 (1), 5-6 (2), <5 (3)	C3 _____
Component 4	(total # of hours asleep) / (total # of hours in bed) x 100 >85%=0, 75%-84%=!, 65%-74%=2, <65%=3	C4 _____
Component 5	# sum of scores 5b to 5j (0=0; 1-9=1; 10-18=2; 19-27=3)	C5 _____
Component 6	#6 Score	C6 _____
Component 7	#7 Score + #8 score (0=0; 1-2=1; 3-4=2; 5-6=3)	C7 _____

Add the seven component scores together _____ ***Global PSQI*** _____

A total score of "5" or greater is indicative of poor sleep quality.
If you scored "5" or more it is suggested that you discuss your sleep habits with a healthcare provider

Quality of Sleep Questionnaire

We would like to review the quality of your sleep last night.

Please answer the questions in relation to your SLEEP LAST NIGHT by putting a vertical mark on the line that best describes your response.

Example:

1. Cats are better than dogs:

disagree ——————————I—————————— agree

0 100

****

****

1. My sleep last night was;

light sleep ———————————————————— deep sleep

0 100

2. Last night, the first time I got to sleep I:

just never could fall asleep ———————————————————— feel asleep almost immediately

0 100

3. Last night I was:

awake all night long ———————————————————— awake very little

0 100

4. Last night, when I woke up or was awakened, I;

couldn't get back to sleep ———————————————————— got back to sleep immediately

0 100

5. I would describe my sleep last night as:

a bad night's sleep ———————————————————— a good night's sleep

0 100

6. I would describe the noise level last night as:

very noisy ——————————————————————— very quiet

0 100

7. I would describe my sleep at home as:

extremely poor; the worst I could imagine ——————————————————————— excellent sleep; solid and completely restful

0 100

Modified Richards-Campbell Sleep Questionnaire (RCSQ) for PADDI Substudy Version 1.2

Appendix 4
Quality of Sleep Questionnaire Substudy eCRF Page

Day 1.

Patient has diagnosed OSA? □ **Yes** □ **No**

Uses CPAP machine regularly? □ **Yes** □ **No**

Where did the patient sleep last night? □ **Ward** □ **High dependency/ICU**

1. My sleep last night was; ☐ **mm**

2. Last night, the first time I got to sleep I: ☐ **mm**

3. Last night I was: ☐ **mm**

4. Last night, when I woke up or was awakened, I; ☐ **mm**

5. I would describe my sleep last night as: ☐ **mm**

6. I would describe the noise level last night as: ☐ **mm**

7. I would describe my sleep at home as: ☐ **mm**

REFERENCES

1. Schulz KF, Altman DG, Moher D, Group C: **CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials**. *BMJ* 2010, **340**:c332.
2. Buysse DJ, Reynolds CF, 3rd, Monk TH, Berman SR, Kupfer DJ: **The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research**. *Psychiatry Res* 1989, **28**(2):193-213.