

# Efficacy and outcome of sacral nerve stimulation in slow transit constipation: A randomised, double-blind, placebo-controlled, two phase crossover study.

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Australian and New Zealand Clinical Trial Registry: 12611001192976

# Background

## Sacral nerve stimulation for constipation

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**Background:** For over 10 years sacral nerve stimulation (SNS) has been used for patients with constipation resistant to conservative treatment. A review of the literature is presented.

**Methods:** PubMed, MEDLINE and Embase databases were searched for studies demonstrating the use of SNS for the treatment of constipation.

**Results:** Thirteen studies have been published describing the results of SNS for chronic constipation. Of these, three were in children and ten in adults. Test stimulation was successful in 42–100 per cent of patients. In those who proceeded to permanent SNS, up to 87 per cent showed an improvement in symptoms at a median follow-up of 28 months. The success of stimulation varied depending on the outcome measure being used. Symptom improvement correlated with improvement in quality of life and patient satisfaction scores.

**Conclusion:** SNS appears to be an effective treatment for constipation, but this needs to be confirmed in larger prospective studies with longer follow-up. Improved outcome measures need to be adopted given the multiple symptoms that constipation may be associated with. Comparison with other established surgical therapies also needs consideration.

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# Randomised control trials

(Treatment Efficacy of sacral nerve stimulation in constipation)

Author	Lower bowel disorder	Study Design	Outcome measure
Kenefick, 2002	Constipation	RCT	Stool Frequency

- suggests that SNS can “reduce symptoms in some people with constipation”

Mowatt G, et al, Cochrane Review, 2007

- 14 constipated women with evacuatory dysfunction and rectal hyposensitivity; treatment with temporary sacral nerve stimulation (SNS)
  - in comparison to sham, SNS improve rectal sensitivity and percentage of successful defecating episodes.

Knowles CH, et al. *Ann Surg* 2012, **255**(4):643-649.

# AIMS

## ***Primary Aim:***

To assess, in patients with slow transit constipation, the clinical outcome in response to supra-sensory compared to sham stimulation

## ***Secondary Aim:***

To assess, in patients with slow transit constipation, the clinical outcome in response to sub-sensory compared to sham stimulation

# Outcome measures

## ***Primary Outcome Measure:***

Proportion of patients, who on more than 2 days per week for at least 2 of 3 weeks, report a bowel movement associated with a feeling of complete evacuation during supra-sensory stimulation.

## ***Secondary Outcome Measure:***

Proportion of patients, who on more than 2 days per week for at least 2 of 3 weeks, report a bowel movement associated with a feeling of complete evacuation during sub-sensory stimulation.

## ***Tertiary outcome measures:***

For both supra and sub sensory stimulation determine the effects of sacral nerve stimulation upon: Abdominal pain score, abdominal bloating score, laxative-free days, quality of life scores.

# Patient Eligibility

- Experience a feeling of incomplete evacuation on less than 3 days per week, for at least 2 of 3 weeks of the baseline/surveillance phase.

\*Dinning PG, et al. *BMC Gastroenterology* 2011, 11:121.

- Aged 18 – 75yrs
- Confirmed colonic slow transit
- Normal anorectal manometry
- Unsatisfactory symptomatic response to standard therapies including laxatives, dietary modification, biofeedback

# Patient Ineligibility

- Metabolic, neurogenic or endocrine disorder(s) known to cause constipation.
- Drugs which list constipation as a potential side effect deemed to be clinically relevant by the referring physician
- Prior abdominal radiotherapy
- Prior abdominal surgery (except cholecystectomy, appendicectomy, inguinal hernia repair, splenectomy, fundoplication; oophorectomy or hysterectomy)
- Current or planned pregnancy
- Co-morbidity considered by the clinician or the investigators to put the patient at risk from surgical electrode implantation
- Current or prior history of malignancy.

# Stool Diary

CODE NO. BL<sub>1</sub>

Baseline diary **Week 1**

Page 1 of 4

Patient ID: \_\_\_\_\_

Patient initials: \_\_\_\_\_  
 first mid last

Date of the first day of the week \_\_\_\_/\_\_\_\_/\_\_\_\_ (Investigator to insert start date)  
 Please complete one row at the end of each day Day Month Year

Day of the week	Actual Bowel Movement			Stool Form Refer to diagram on page 4	Abdominal pain/ discomfort?	Abdominal bloating?	Laxatives		
	Number of bowel movements 0 = None 1 = one 2 = two 3 = three >3 = more than three	Feeling of complete evacuation?	Straining?		0 = None 1 = Present but tolerable 2 = present and interfering with but not preventing normal daily activities like work and sleep 3 = preventing normal daily activities	Did you use a laxative today?	Drug name and form*?	Dose?	
1	0 1 2 3 >3 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	yes no <input type="checkbox"/> <input type="checkbox"/>	yes no <input type="checkbox"/> <input type="checkbox"/>	1 2 3 4 5 6 7 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	0 1 2 3 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	0 1 2 3 <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	yes no <input type="checkbox"/> <input type="checkbox"/>		
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At the end of the week please complete these questions

**How satisfied were you with your bowel habits over the past week?**

0 = a very great deal satisfied  
 4 = not at all satisfied

0 1 2 3 4

**How bothersome has your constipation been over the past week?**

0 = not at all  
 4 = a very great deal

0 1 2 3 4

\* tablets, granules, liquid, suppositories, enema.

# Stratification and randomisation

Patients were stratified on the basis of the following potential correlates to outcome:

- a) symptomatic response to PNE (defined as achieving > 2 days per week on which a complete bowel motion is experienced for 2 of 3 weeks);
- a) duration of constipation (<> 10yrs)
- a) prior hysterectomy
- b) study site (St.George Hospital or Concord Hospital; Sydney NSW).

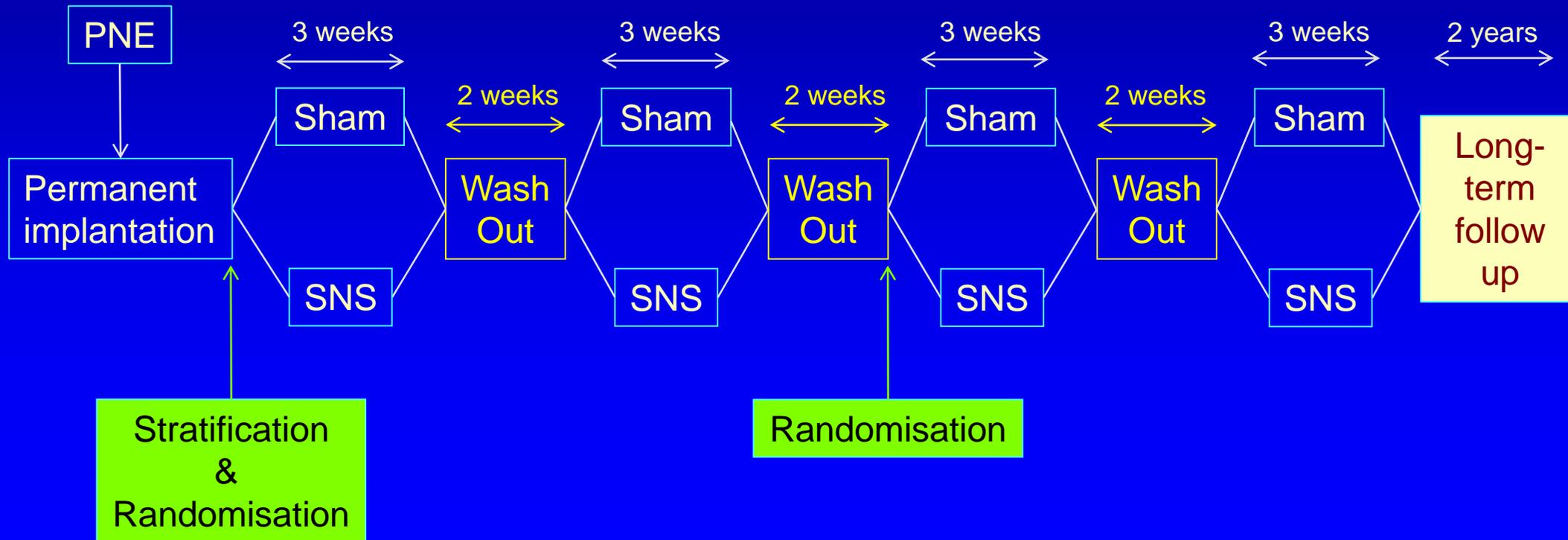
All randomisation was conducted by the NH&MRC clinical trial centre

# Study Outline

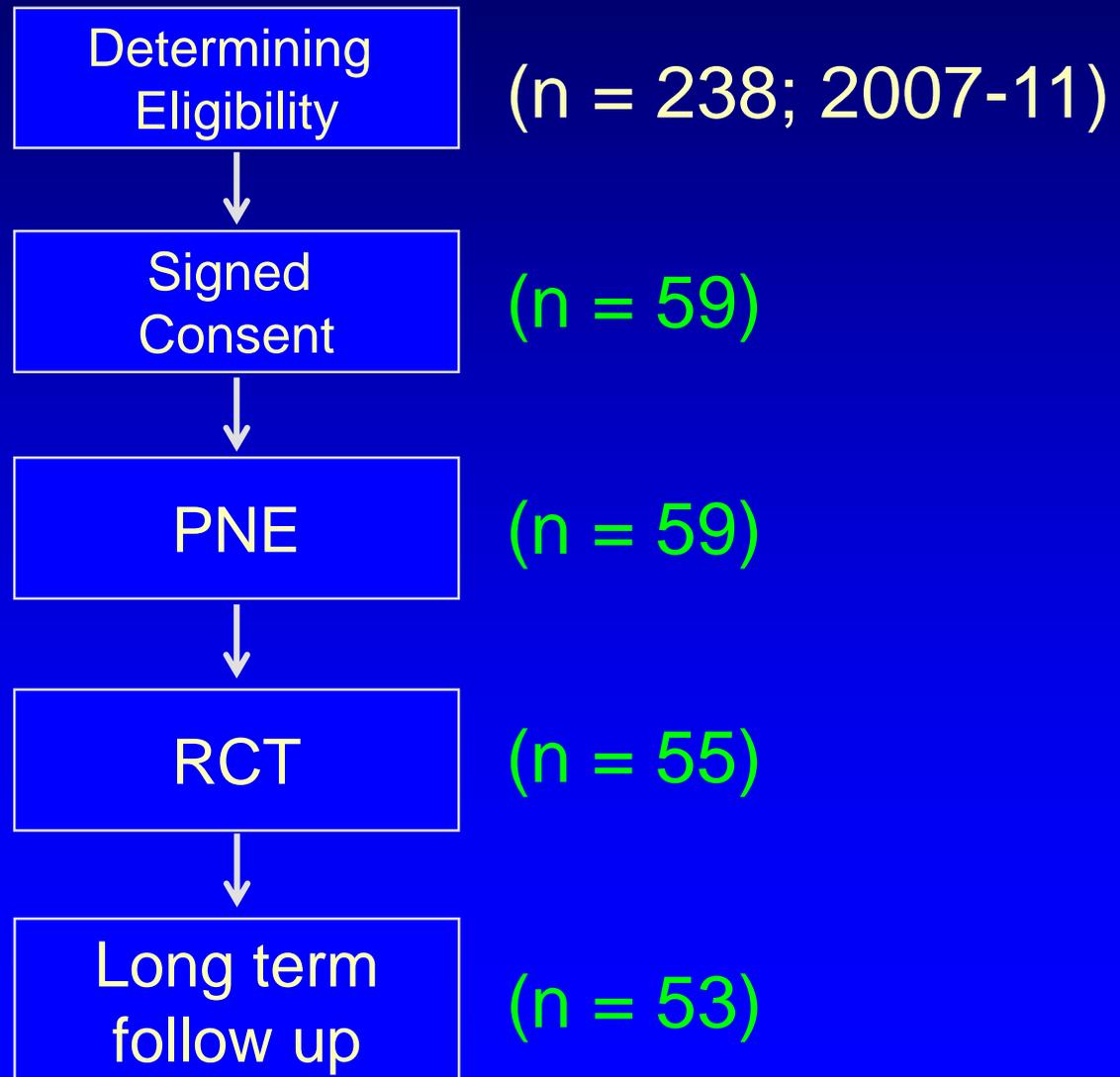
← 18 weeks →

Phase I:  
Subsensory v Sham

Phase II:  
Suprasensory v Sham



# CONSORT flow diagram



# Patient Demographics

## (RCT; n = 55)

- Age;  $44 \pm 15$  yrs (4 males)
- Duration of symptoms:
  - 1-2 yrs = 9%
  - 2-5 yrs = 7%
  - 5 -10 yrs = 13%
  - >10 yrs = 71%
- Laxative use:
  - 1- 3 d/w = 47%
  - 4 - 7 d/w = 53%
- Response to peripheral nerve evaluation
  - n = 16 (29%)

# Primary outcome: supra-sensory phase (n = 53)

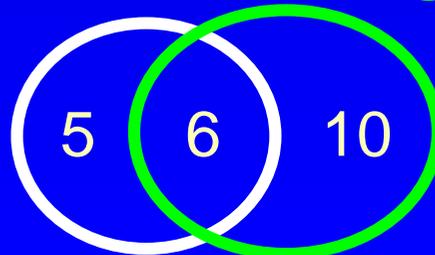
Table 1 – Response rate according to treatment arm – supra-sensory phase

Treatment arm for supra-sensory	No. of patients	No. of patients with a successful response	Success rate (%)	95% CI
Sham	53	11	20.8	12.0-33.5
Stimulation	54	16	29.6	19.1-42.8

The response rate was with 20.8% with sham and 29.6% with stimulation. **(p = 0.23)**

Sham

Supra-sensory

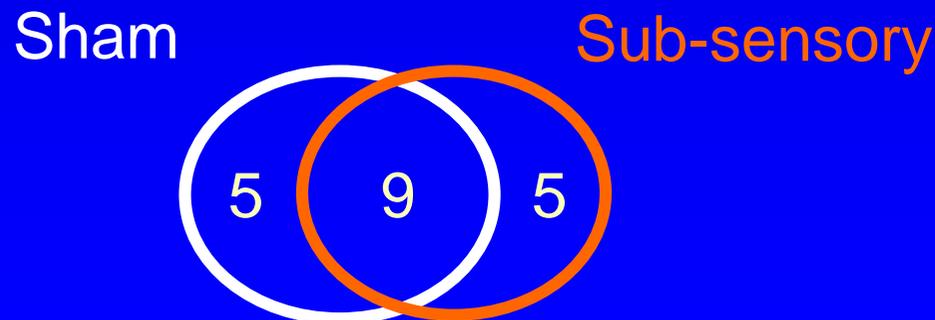


# Secondary outcome: sub-sensory phase (n = 55)

Table 4 – Response rate according to treatment arm – sub-sensory phase

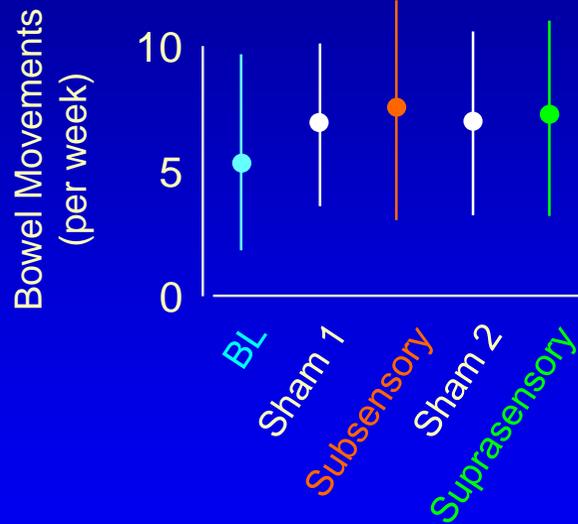
Treatment arm for sub-sensory	No. of patients	No. of patients with a successful response	Success rate (%)	95% CI
Sham	55	14	25.4	15.8-38.3
Stimulation	55	14	25.4	15.8-38.3

The response rate was with 25.4% with both sham and stimulation. (**p = 0.95**)

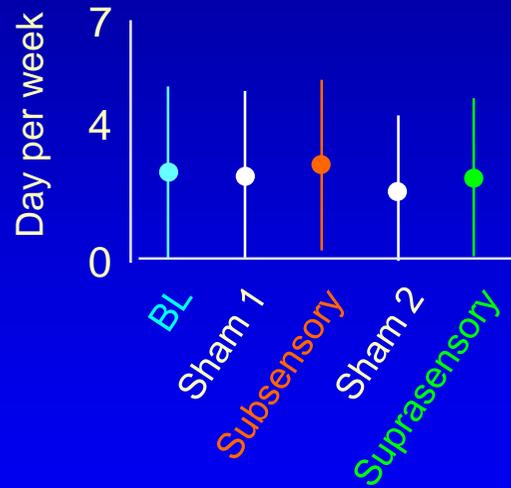


# Additional Measures

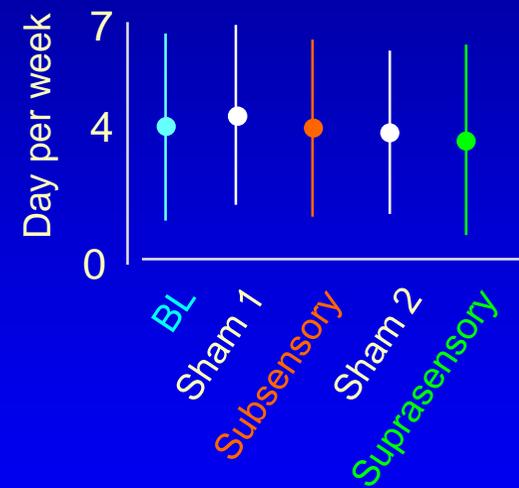
## Stool frequency



## Straining

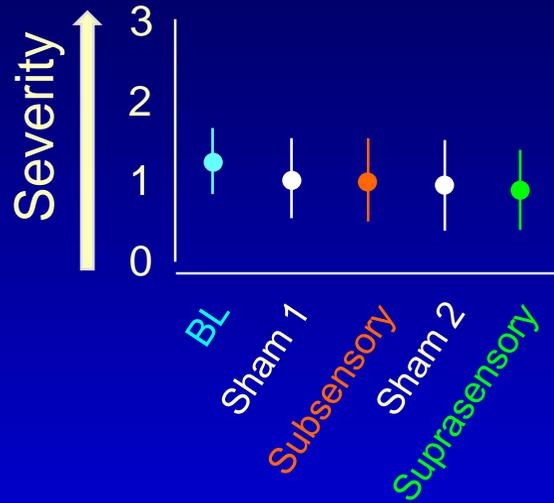


## Laxative Use

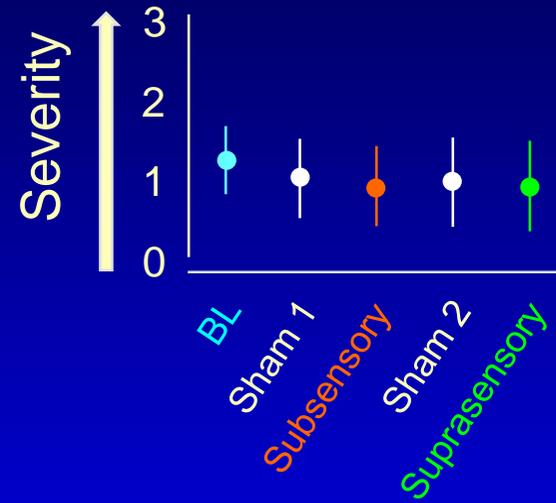


# Additional Measures

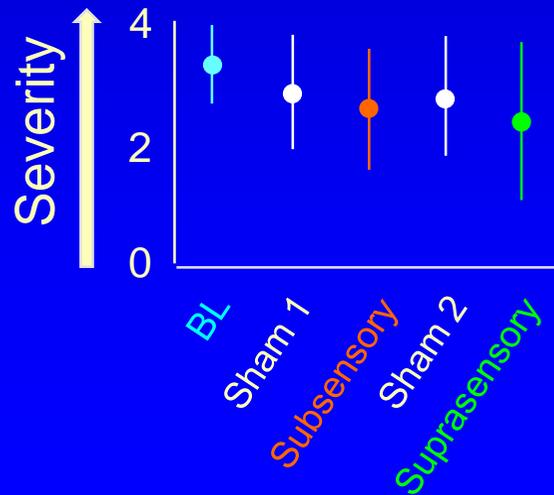
## Abdominal Pain



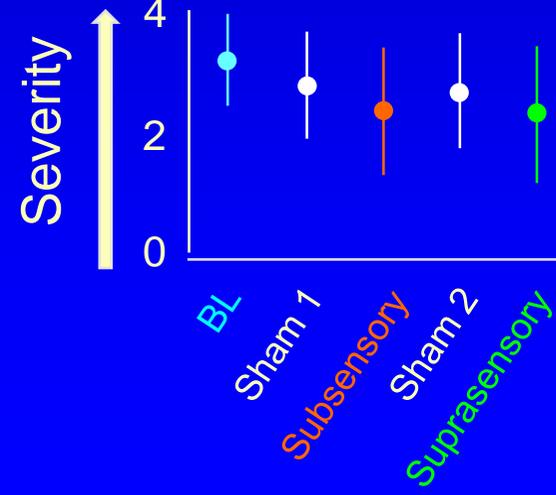
## Abdominal Bloating



## Satisfaction

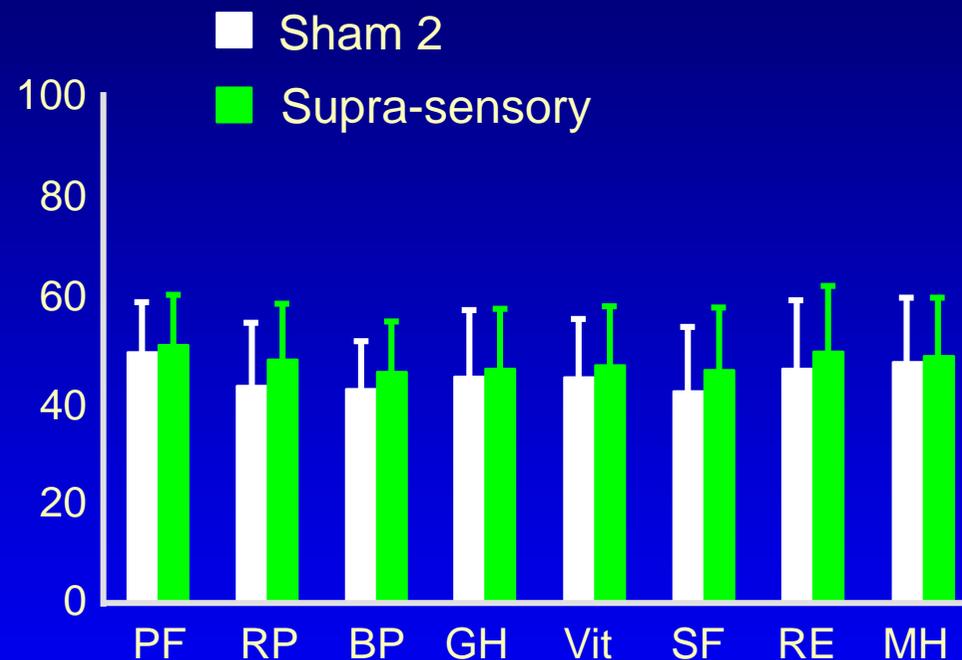
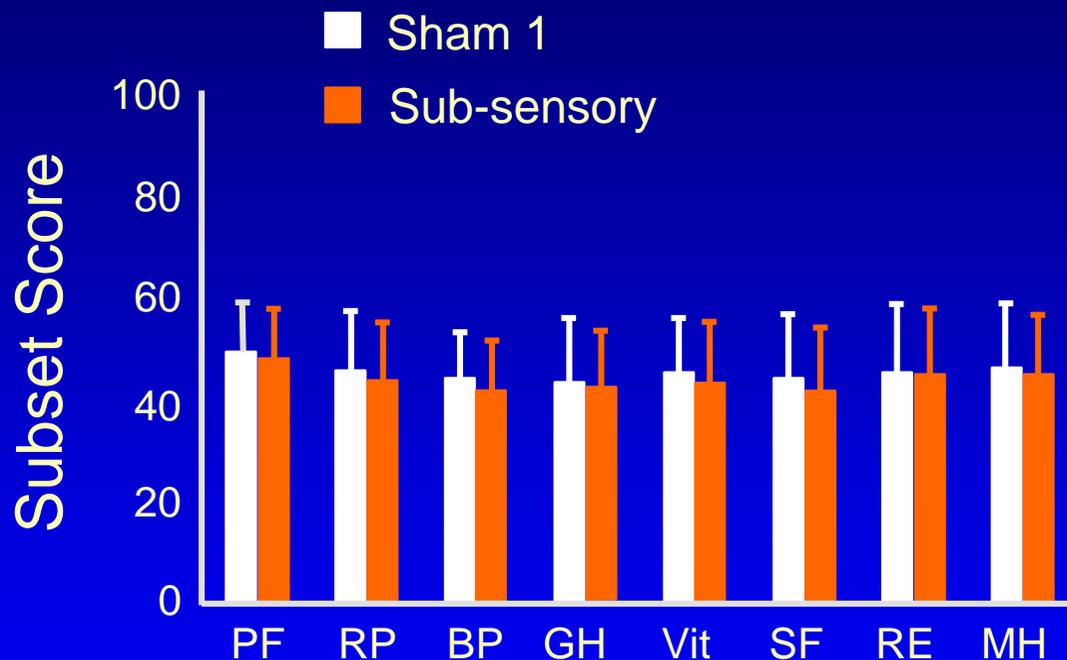


## Bothersome



# Quality of Life

(SF36)



PF = physical Function  
RP = role physical  
BP = body pain  
GH = general health

Vit = vitality  
SF = social functioning  
RE = role emotional  
MH = mental health

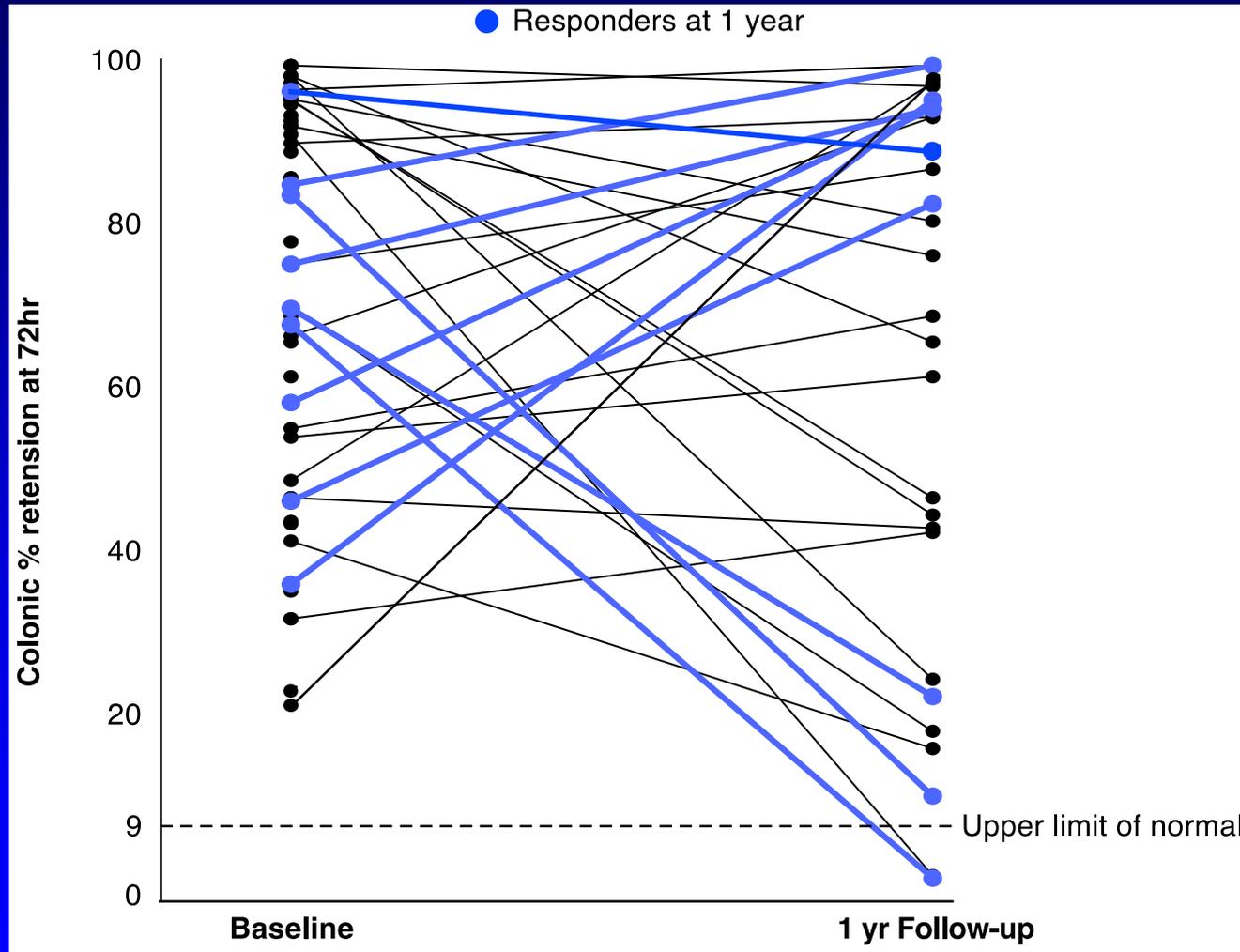
# Long-Term Follow-Up

## (1 year)

Fifty three patients that entered the long-term follow-up.

- Sixteen patients (30%) had had the sacral nerve stimulator explanted and had dropped out of the study.
- Fourteen patients (26%) still had the stimulating device implanted but the stimulation was turned off.
- Seven patients (13%) were still receiving stimulation but reported that they were not satisfied with the treatment.
- Seventeen (31%) reported some level of satisfaction and requested that the simulation remain on.
- Only nine patients (17%) met our primary endpoint.

# Colonic scintigraphy (Baseline vs 1 year)



# Conclusion

- In patients with slow transit constipation, in comparison to sham stimulation, sacral nerve stimulation had no significant effects upon
  - Frequency of complete bowel movements
  - Stool frequency
  - Straining
  - Quality of life
- These data suggest that sacral nerve stimulation is not an effective treatment for most patients with slow transit constipation

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A/Prof David Lubowski

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## Statistical analysis

Prof Val Gebski

Prof Mike Jones

## Patient Selection & Study Design

Prof Ian Cook

Prof Val Gebski

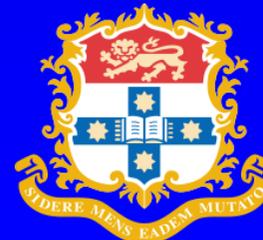
## Trial maintenance

Ms Linda Hunt

Ms Vicki Patton

## Supported by

- NHMRC
- Medtronic



# Is PNE a predictor of treatment outcome?

