Study Execution

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Spinal Cord Stimulation - RCT

SCS is a treatment for

- Pain
  - Neuropathic (nociceptive?)
  - Visceral pain
- Ischaemia
  - CCLI, vasospastic, cardiac, mesenteric
- Other
  - Cardiac dysrhythmia, heart failure
  - Spinal cord injury, Persistent vegetative states
  - Augment brain tumor chemotherapy

The Devil is in the Detail

- Equipoise
- Recruitment
  - Centre
  - Patient
- Patient Information
  - Written
  - Website
  - Social Media
- Randomisation
- Patient Education and Training in outcome measures
- Blinding
  - Patient, Clinical staff, Research staff, Programmer
- Programming
- The Sham
- Outcome measures

Clinical Equipoise in Neuromodulation RCTs

”Principle of research: Genuine uncertainty whether a treatment will be beneficial”

Freedman, B. (1987) 'Equipoise and the ethics of clinical research'. *The New England Journal of Medicine*, 317, (3):141–145.

Sources and Effects of Expectation Bias

- Subject expectation comes from:
  - Research staff expectation
  - Words, printed and on-line information
  - Other subjects, word of mouth
- Expectation bias can:
  - Bias studies to the null
  - Bias one treatment over another
  - Be at least as large as the effect of any pain treatment
  - Be long lasting – even indefinite
    (Quessy and Rowbotham, 2008)

Kam-Hansen et al., 2014
Kong et al., 2007
Rutherford & Roose, 2013
Schedlowski, Enck, Rief, & Bingel, 2015
Weimer, Colloca, & Enck, 2015

Recruitment and Research Centre

- GCP Training
- Skilled at Investigator procedure
- Skilled at Comparator procedure
- Skilled at Usual Care management
- Skilled at Outcome measures

- All personnel GCP trained?
- Eg. Spirit Trial- Refractory Angina
- Surgical, CMM, alternative SCS
- Able to provide all aspects of Usual Care
- Not just pain, but other disease specific primary and secondary measures

Patient Recruitment

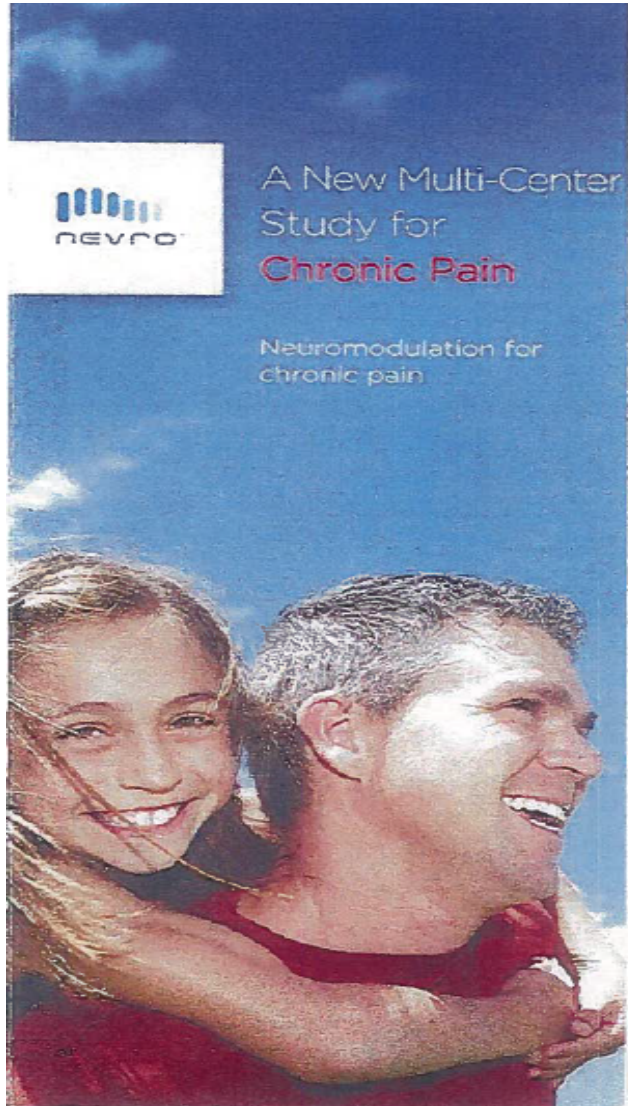
- Equipoise by referrer and centre
- Expectation Bias management
- Care NOT dependent upon research participation
- But SCS not universally available
- Patient should be equipoised

- Ideally referred for 2nd opinion not SCS, nor for interesting new therapy
- SCS should be universally available independent of trial participation
- Patient should be provided with factual and equipoised information and be indifferent to treatment randomisation

Patient Information

- Both Investigator and Comparator treatment(s) explained
- Equipoised information
  - Both Intervention AND Comparator
- PIS but also Website
- Social Media at the time?
- Should industry websites be suspended at time of recruitment?
- PIS examined by third party?
- Can you control social media?

SENZA™ Study Patient Recruitment Brochure

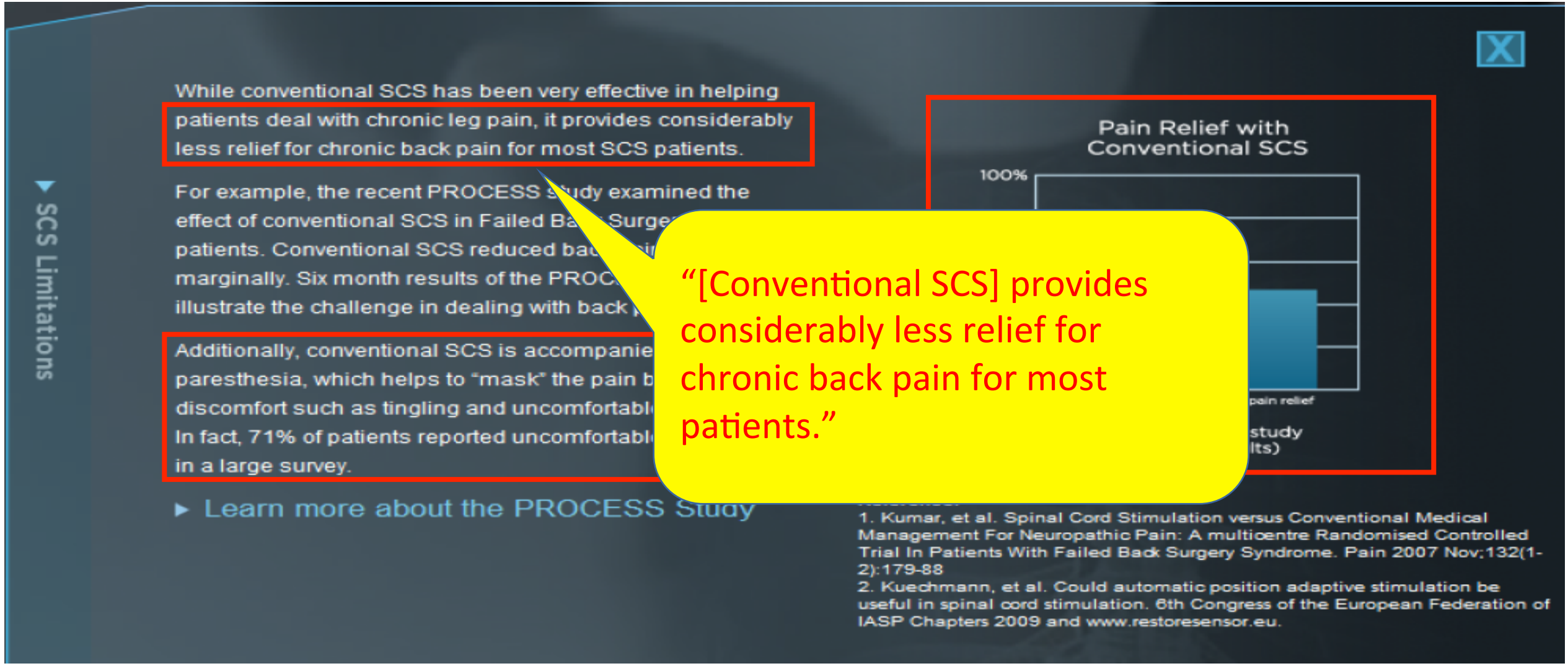


Clinical Study

The goal of the study is to evaluate the safety and effectiveness of a new SCS system called Senza™ made by the Nevro Corporation. The Senza™ system is designed to treat chronic pain in the trunk and/or limbs at least as effectively and without some of the potential side effects associated with currently available SCS systems.

"The Senza system is designed to treat chronic pain in the trunk or limbs without the need for a buzzing sensation"

Nevro's US Website at Time of Patient Recruitment
Section Title: "SCS Limitations"



Nevro's US Website at Time of Patient Recruitment
Section Title: "SCS Limitations"

▼ SCS Limitations

While conventional SCS has been very effective in helping patients deal with chronic leg pain, it provides considerably less relief for chronic back pain for most SCS patients.

For example, the recent PROCESS study examined the effect of conventional SCS in Failed Back Surgery (FBSS) patients. Conventional SCS reduced back pain only marginally. Six month results of the PROCESS study clearly illustrate the challenge in dealing with back pain.

Additionally, conventional SCS is accompanied by paresthesia, which helps to "mask" the pain but can cause discomfort such as tingling and uncomfortable stimulation. In fact, 71% of patients reported uncomfortable stimulation in a large survey.

▶ Learn more about the PROCESS Study

Paresthesia:
"In fact, 71% of patients reported uncomfortable stimulation in a large survey."

From PROCESS study
(6 month results)

Reference:
1. Kumar, et al. Spinal Cord Stimulation versus Conventional Medical Management For Neuropathic Pain: A multicentre Randomised Controlled Trial In Patients With Failed Back Surgery Syndrome. Pain 2007 Nov;132(1-2):179-88
2. Kuechmann, et al. Could automatic position adaptive stimulation be useful in spinal cord stimulation. 6th Congress of the European Federation of IASP Chapters 2009 and www.restoresensor.eu.

Nevro's US Website at Time of Patient Recruitment
Section Title: "SCS Limitations"

▼ SCS Limitations

PROCESS Study Results:

Poor back pain relief

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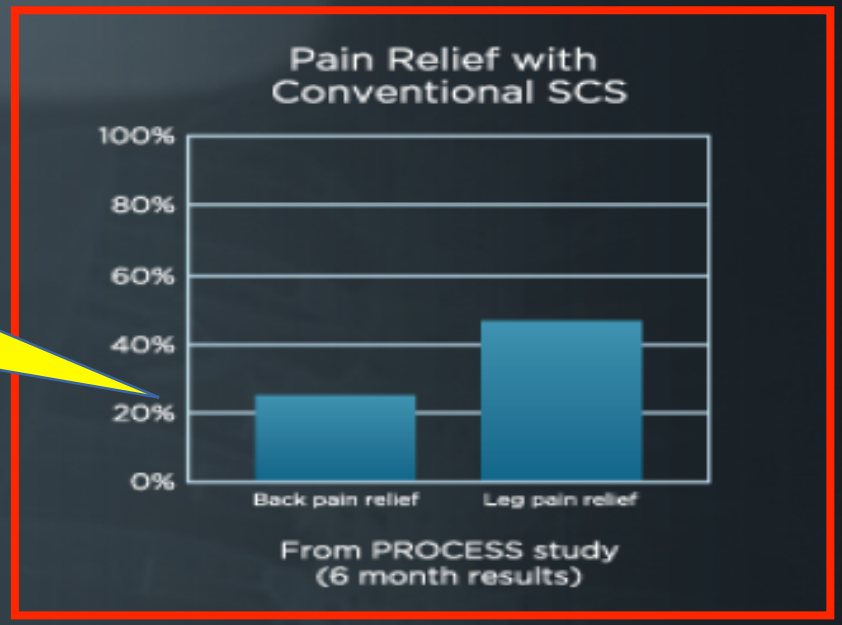

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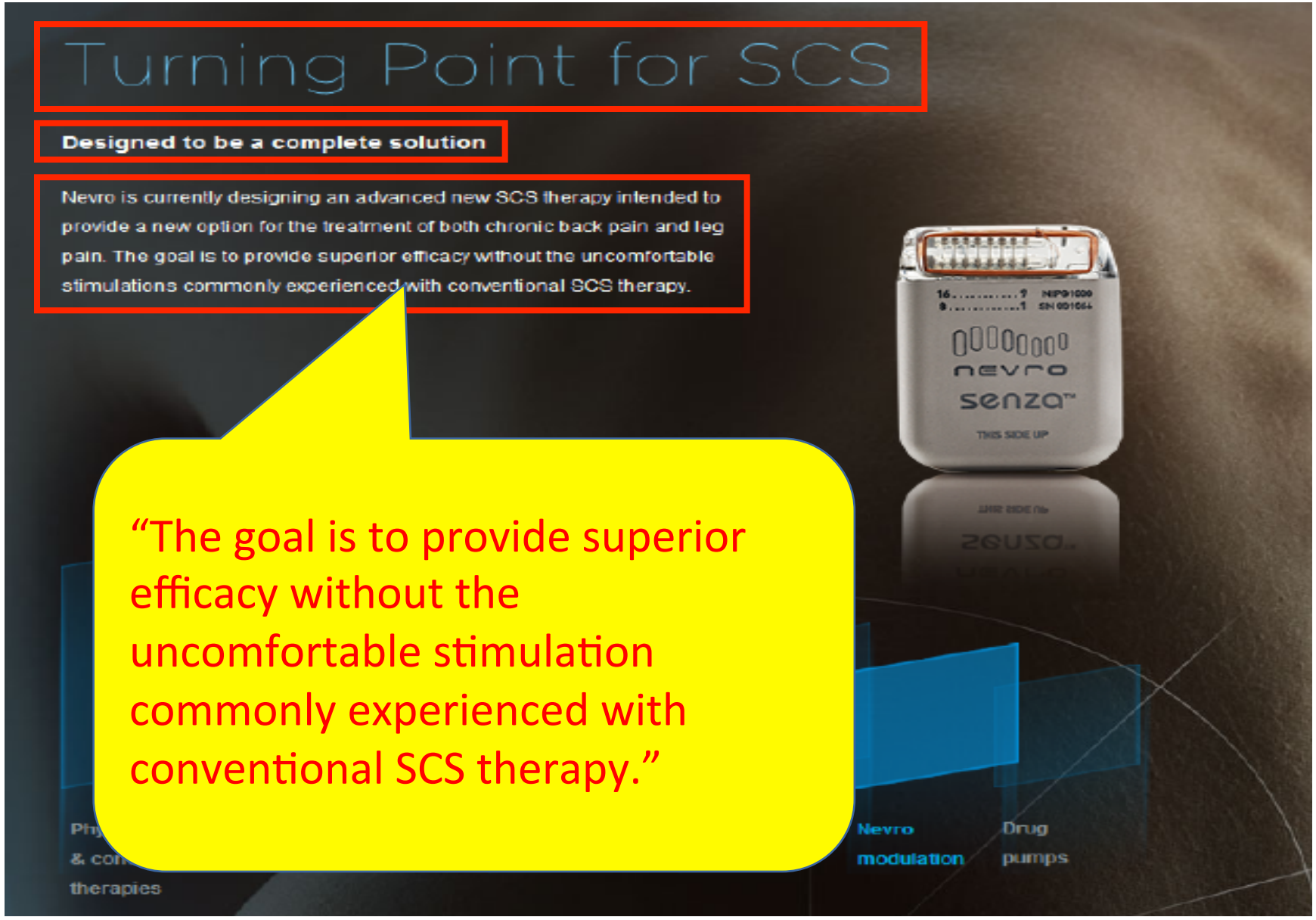
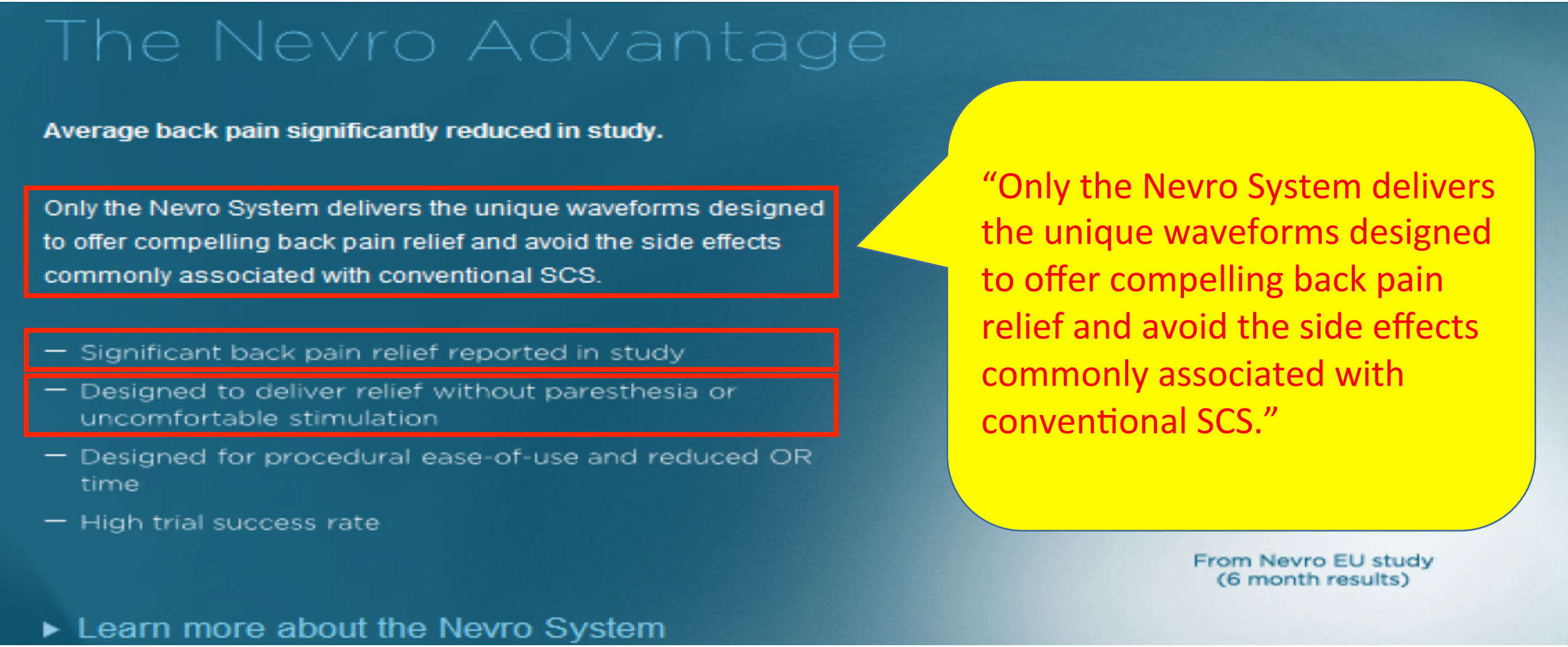
Nevro's US Website at Time of Patient Recruitment
Section Title: "The Challenge"

Nevro's US Website at Time of Patient Recruitment
Section Title: "The Solution"



Nevro's US Website at Time of Patient Recruitment
Section Title: "The Nevro Advantage"



"Only the Nevro System delivers the unique waveforms designed to offer compelling back pain relief and avoid the side effects commonly associated with conventional SCS."

North et al 2005

Clinical Equipoise

"The study was presented to candidates as a comparison of two standard, non-experimental procedures, SCS and reoperation, to determine whether SCS should be offered as an FBSS treatment before or after exhausting all reoperation treatment options"

Extract from Patient Information Sheet

PROCO equipoise

- ***Why is this study being done?***
- Standard SCS uses stimulation frequencies between 40 and 100 Hz. In recent years a SCS device capable of giving frequencies of stimulation as high as 10 KHz has been used with claims of improved back pain relief and without the patient being aware of the stimulation. However the science to support this claim is not adequate. Furthermore it is not known if such high frequencies are required to achieve the pain relief.

Expectation: Considerations for Guidelines

- Document efforts to balance researcher and subject expectation between groups
- Measure expectation of benefit at baseline and endpoint for researchers and subjects
- Make all materials available
  - Patient Information sheets
  - Website information

Randomisation

- Robust transparent randomization methodology
- Recruit – randomization equipoise
- Reports of recruit distress after randomization – Senza trial
- Consider measures to record randomisation satisfaction

Research Patient education and training

- Educate patients in intervention AND Comparator therapies
- Educate patients in outcome measures
- Educate patient in blinding procedures

- SCS is complex but usual care
- Therapies and outcomes within the RCT are complex (compared to pharmacological therapies)
- Learning burden for patients
- Physical burden
  - eg. electronic watch strap for pain scoring

Blinding

- Most RCT in SCS have no blinding
- Single Blind
- Double Blind

- Not only do they know what treatment but also its effects!
- Unblinded and Blinded
  - Clinical and Research teams
- Maintaining blinding discipline

Outcome Measure Collection

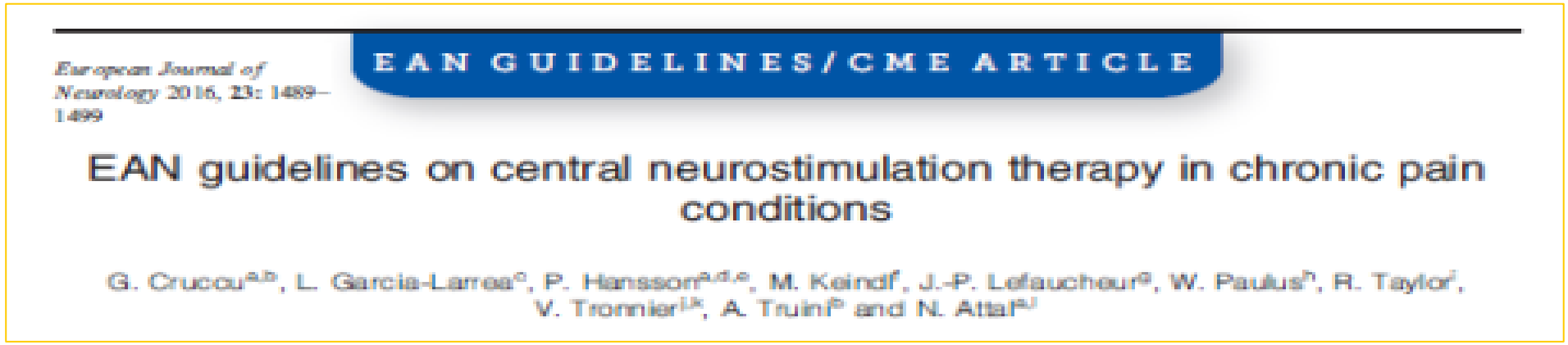
Blinding of outcome measure collectors

Subjects, investigators, and study site staff were not blinded to subjects' assigned therapy.

Due to practical considerations (see Limitations section), study subjects and investigators were not masked to the assigned treatment group.

Given the nature of the intervention, it was impossible to blind patients and difficult to blind investigators during the trial.

SCS for CLBP - EAN Recommendation



European Journal of Neurology 2016, 23: 1489–1499

EAN GUIDELINES/CME ARTICLE

EAN guidelines on central neurostimulation therapy in chronic pain conditions

G. Cruccu[a,b], L. Garcia-Larrea[c], P. Hansson[a,d,e], M. Keindl[f], J.-P. Lefaucheur[g], W. Paulus[h], R. Taylor[i], V. Tronnier[j,k], A. Truini[b] and N. Attal[a,l]

	Intervention	Comparator	GRADE quality of evidence	GRADE recommendation
Post surgical chronic leg and back pain	SCS (+ CMM)	CMM alone	**++, low**	**Weak** recommendation **for using** intervention

Blinding SCS

- Few studies are double blind
  - PROCO RCT – Thomson et al 2018
  - Alkaisy et al 2018 – 37.5% patients felt 1kHz parasthesia
- But
  - They could be single blind
    - Blinded data collector
    - De Andres et al., Conventional vs. High frequency SCS. Pain Medicine 2017
- Could have scripted, monitored and documented interaction with programmer

Device Programming in Neurmodulation RCT

A Pragmatic Approach?

Both devices were programmed by separate technicians for each arm such that the programming was performed by experienced personnel for the specific device to achieve optimal analgesia.

- **Frequency of reprogramming**
- **Duration**
- **Setting**
- **Scripted programming in Placebo controlled trials**

Programming

- Dichotomy
- Clinical Team
  - Sub-optimal programming
- Industry Research Scientist
  - New device
- Commercial Team
  - Usual Care

- Efforts to control interaction
  - Monitoring by research team
  - Scripting
- Programming sessions
  - How long, How often
  - Timing with outcome data point

The Sham

- Purpose of Sham
  - Efficacy
  - Influence of non-treatment effects
  - Non-inferiority
    - Both treatments work/don't work

- Parasthesia based
  - Unilateral treatment for bilateral pain
  - Red Light on box – Tesfaye 1998 PDPN
  - Ultra Low dose SCS – Placebo?
- Sub-perception programming
  - Maintain sub-p – Alkaisy et al 2018 – 37.5% at 1kHz felt parasthesia
  - Battery depletion/drain

Outcome Measures

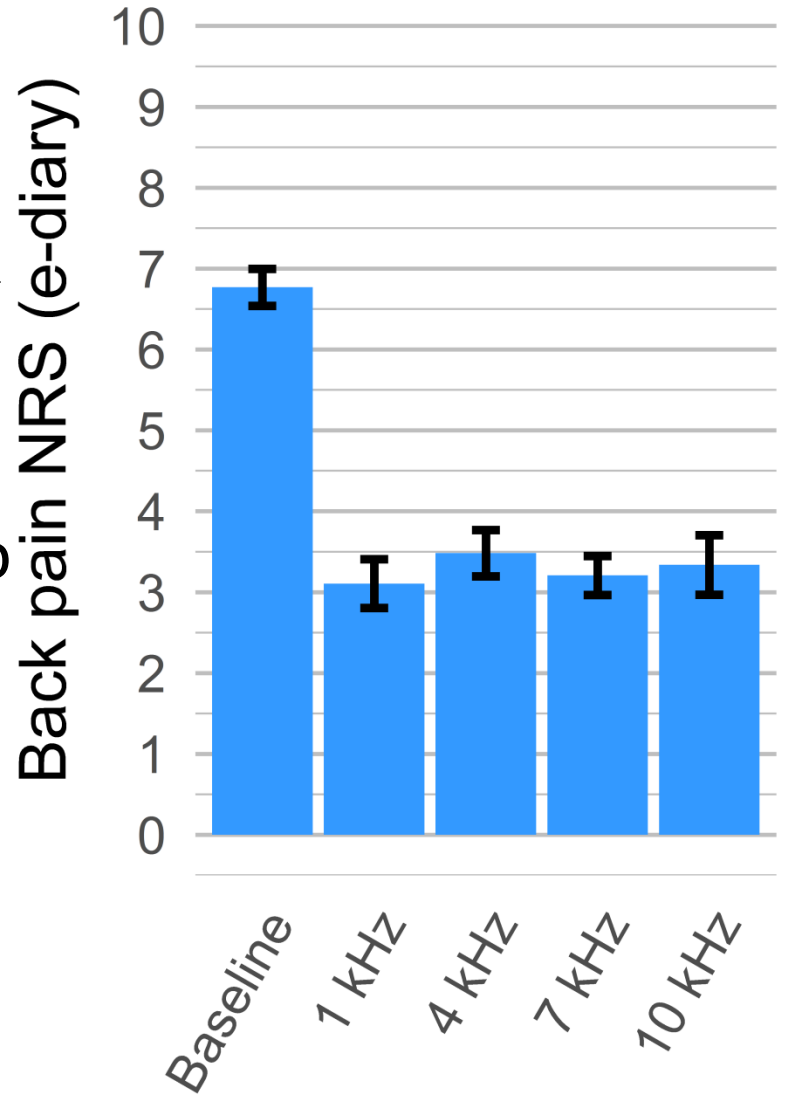
- Depends upon indication
- But Chronic Pain
- What are we treating in long term?
- Pain? HRQoL? Function? Medication reduction?
- Primary and Secondary outcome measures
- Choosing the Primary Outcome
- What is the scientific question?
  - Regulatory demands
  - Clinical demands

The Pain Score

- Percentage Pain Relief
- NRSPI or VASPI change expressed as % change
- Single pain score looking back over 1 day, week
  - Worst, Average (usual) or Best
  - Night/Day (PDPN − Slangen et al)
- Mean of pain scores in data collection window over several time points and days
  - Paper Diary
  - E-Diary (FBSS PROCO − Thomson et al 2018)
- Management of omissions

Primary Outcome measure

- Compliance with paper diaries is only 11%[1]
- Many studies just collect VAS or NRS at clinic visit → 1 data point per patient per evaluation period
  - Memory of pain intensity is unreliable[2]
- PROCO - Real-time E-diary prompted each patient fo 180 pain scores over the rate randomisation phase
  - Larger sample size → More accurate results[3,4]
  - Pain scores 24/7 on several days of evaluation period
  - Eliminates Observer Bias



Single-point VAS scores ≠ Paper diary scores ≠ Real-time e-Diary Scores

SENZA Study Results (Primary Endpoint)

	Test
Responder rates (% of subjects)	
Back pain - VAS	78.3%
Back pain with rest - diary	66.7%
Back pain with activity - diary	71.3%
Back pain - PPR	79.3%

Δ = - 11.6%

Source: SENZA Summary of Safety & Effectiveness Data (SSED), p.44

Which pain score rating method?

Subject GIC = 52.2% (better or great deal better)

Despite 78.3% responder rate – Single VAS

Or 66.7% responder rate – Pain Diary

Which score best describes the outcome?

SENZA study - FDA SSED (page 45)

	Test
Opioid change (% increased)	6.0
Opioid change (% maintained)	73.5
Non-Opioid Pain Medication (% increase for > 5 days)	2.2
ODI (% minimal to moderate disability)	64.1
GAF (% no symptoms to transient symptoms)	56.5
Subject GIC (% better or a great deal better)	52.2
Clinician GIC (% better or a great deal better)	68.5
Subject Satisfaction (% very satisfied)	54.1

Variation in outcome by pain scoring methodology

DRG for pain relief
FDA SSED Page 50 to 51

Table 29: Average VAS Scores Based on Subject Diary Responses – 3 Months

	Baseline		1 Month		3 Months	
	Axium	Control	Axium	Control	Axium	Control
Number of Subjects	**76**	**76**	**61**	**54**	**59**	**54**
Average Pain 'Right Now' Per Subject Diary						
N	76	76	56	53	54	51

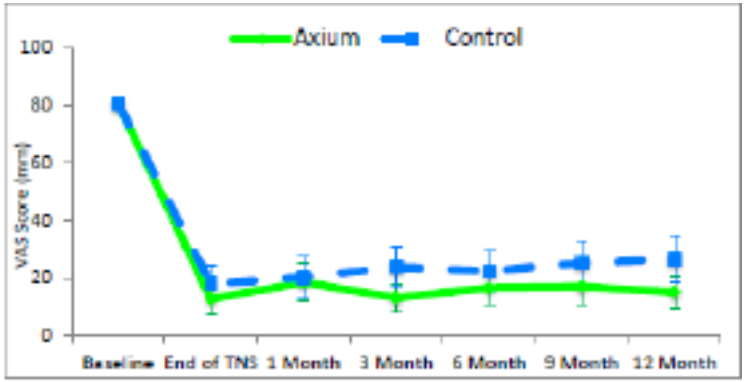
	Baseline		1 Month		3 Months	
	Axium	Control	Axium	Control	Axium	Control
Mean	68.5	65.6	22.0	18.9	17.8	23.0
SD	19.3	17.5	22.2	18.4	18.4	22.0
Median	73.3	65.9	13.5	10.9	13.9	14.0
Min	13.3	13.1	0.0	0.0	0.0	0.0
Max	100.0	100.0	81.6	75.0	75.6	72.9
Average 'Worst Pain' Per Subject Diary						
N	76	76	56	53	54	51
Mean	80.8	78.6	32.3	33.1	28.6	36.8
SD	13.8	13.6	25.9	24.4	24.6	27.1
Median	81.6	78.5	26.8	30.1	24.8	36.6
Min	40.4	40.4	0.0	0.0	0.0	0.0
Max	100.0	100.0	87.7	89.6	96.9	100.0

Mean Diary VASPI at 3 mos.

- DRG = 17.8
- SCS = 23.0

Table 24: Primary Composite Endpoint Treatment Success through 3 Months

Primary Endpoint Component	Axium	Control
Number of Subjects - MITT analysis data set	**73**	**73**
Number of Subjects-Primary endpoint analysis	**69**	**70**
Overall primary endpoint success		
n/N (%)	56/69 (81.2)	39/70 (55.7)
95% CI	(69.9, 89.6)	(43.3, 67.6)
Success rate difference (%) and 95% CI (Blackwelder)	25.4 (13.0, 100.0)	
P-value (non-inferiority δ = 10%)	<0.0001	
P-value (superiority)	0.0004	



Single point VAS at 3 mos.

- DRG = 13.1
- SCS = 23.8

Composite Responder rate 81.2% versus 55.7%

Variation of subject satisfaction appears less evident than difference composite responder rates derived from Single Point VAS

Table 34: Subject Satisfaction through 12 Months

	Axium			Control		
	3 Months	6 Months	12 Months	3 Months	6 Months	12 Months
Subject Satisfaction						
How likely you would undergo the therapy again[1]	9.0	8.7	8.9	9.1	8.7	8.5
Change in your pain as compared to before the device was implanted[2]						
Much Worse	0.0	0.0	0.0	0.0	0.0	2.1
Worse	0.0	1.7	1.8	1.9	0.0	0.0
A Little Worse	1.7	0.0	0.0	1.9	1.9	0.0
No change	0.0	5.1	3.6	3.7	5.8	4.2
A Little Better	6.8	6.8	3.6	11.1	9.6	12.5
Better	27.1	20.3	25.5	14.8	19.2	20.8
Much Better	64.4	66.1	65.5	66.7	63.5	60.4

DRG for pain relief - FDA page 54 SSED

The FDA SSED: DRG ACCURATE study – Adverse Events

Table 17: Definitely Related Adverse Event Rates – ITT Population

	Axium N=76		Control N=76		
Adverse Event Characteristic	**Events**	**Subjects n (%)**	**Events**	**Subjects n (%)**	**P-value**
Relatedness to Neurostimulator System/ Device	39	28 (36.8%)	24	20 (26.3%)	0.2217
Relatedness to Implant Procedure	52	35 (46.1%)	29	20 (26.3%)	0.0177
Relatedness to Stimulation Therapy	10	8 (10.5%)	10	10 (13.2%)	0.8025

AE's related to Implant Procedure are statistically more in DRG Axium group than SCS group

- DRG = 46.1%
- SCS = 26.3%

P-value of 0.0177 → Difference is statistically significant

Published Manuscript: DRG ACCURATE study – Adverse Events

From the ACCURATE study manuscript abstract:

"Device-related and serious adverse events were not different between the 2 groups."

From SSED Table 19:

Lead / Breakage	DRG	SCS
Through TNS Phase	0	0
INS to 30 days	0	0
>30 days to 3 Months	1	0
>3 Months to 6 Months	3	0
>6 Months to 12 Months	2	0
>12 Months	0	0
Sub-total	***6***	***0***

Table 23: Subsequent Replacement, Revision, or Explant Procedures through 12 Months

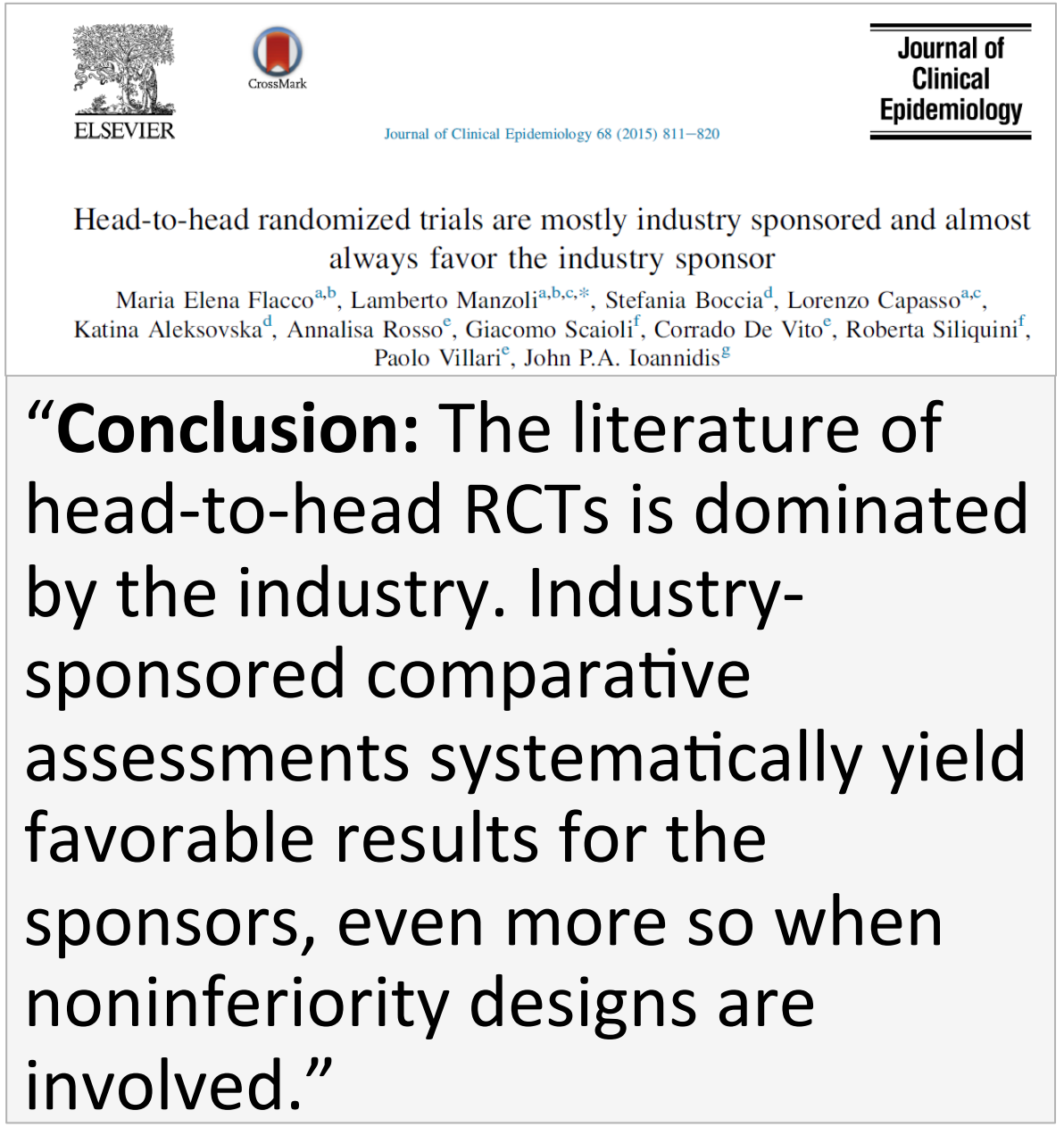
	Axium	Control
INS or INS Lead Replacement/Revisions	8	4
TNS Lead Revision	0	1
INS System Replacement/Revision	5	1
TNS System Replacement/Revision	4	3
INS/TNS Lead Addition	4	0
INS System Explant	5	4
Total:	26	13

Per SSED, DRG Incidents Significantly Higher vs. SCS for:

- Lead Breakage (6 DRG vs. 0 SCS)
- Lead Replacement/Revision (8 vs. 4)
- IPG Replacement/Revision (5 vs. 1)
- Lead Addition (4 vs. 0)

Why Important?

- Senza and Accurate studies are market access studies for FDA
- Funded by sponsor
- Non-inferiority designed
- Unblinded
- Expectation bias
- Possible Observation bias
- SSED provide a more complete reporting than published articles
- Marketing messages exploit data presentation



ELSEVIER

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Journal of Clinical Epidemiology 68 (2015) 811–820

Journal of Clinical Epidemiology

Head-to-head randomized trials are mostly industry sponsored and almost always favor the industry sponsor

Maria Elena Flacco[a,b], Lamberto Manzoli[a,b,c,*], Stefania Boccia[d], Lorenzo Capasso[a,c], Katina Aleksovska[d], Annalisa Rosso[e], Giacomo Scaioli[f], Corrado De Vito[e], Roberta Siliquini[f], Paolo Villari[e], John P.A. Ioannidis[g]

"**Conclusion:** The literature of head-to-head RCTs is dominated by the industry. Industry-sponsored comparative assessments systematically yield favorable results for the sponsors, even more so when noninferiority designs are involved."

Conclusions

- Study execution should include transparent methods to reduce expectation and observer bias
- Role of the clinical, research and sponsor teams must be documented and managed by Trial Management Group with Independent members
- Will a pain score always be the primary outcome?
- Multiple methods of pain scoring
- Which one?