IMPERIAL

Causal inference methods to account for compliance in trials of device interventions

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Background

Noncompliance to a treatment intervention can affect the power for analysis and the interpretation of the estimate of treatment effect.

In a systematic review of the statistical methods used to handle compliance to a device intervention in Randomized Control Trials (RCTs) we found:

- Post hoc stratification
- Alternative analysis populations

Causal inference models have not been well adopted in device trials.

Objective

Using the data from the NESIC randomised controlled trial, we explore two common causal inference methods to account for compliance in the analysis of a device intervention: Compliance Average Causal Estimate (CACE) and Instrumental Variable (IV).

We compare the results from these two methods to results from Intention to Treat (ITT) and Per-Protocol (PP) analyses.

Methods

The NESIC Trial

Does Neuro-muscular Electrical Stimulation (NMES) improve the absolute walking distance in patients with Intermittent Claudication compared to standard of care?

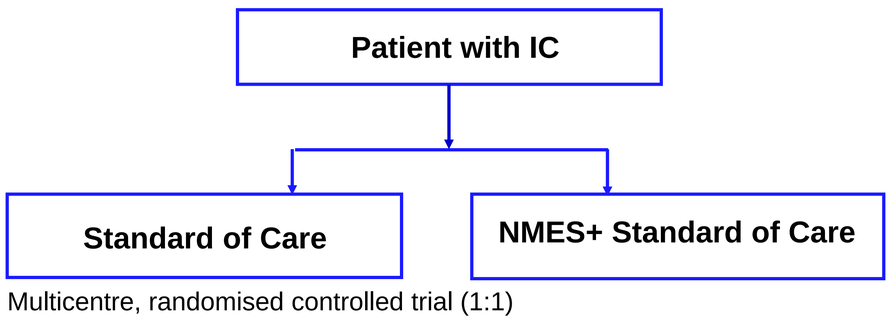
PICO

Population: Patients with Intermittent Claudication

Intervention: NMES + Local Standard of Care

Comparator: Local Standard of Care (Exercise Advice (EA) or EA + Local Supervised Exercise Therapy (SET))

Outcome: Absolute Walking distance (AWD) at 3 months, censored at 790m



Multicentre, randomised controlled trial (1:1)

Statistical Analysis Plan: Methods for censoring data (Tobit regression for ITT, PP)

The Causal Inference Methods

1. Compliance Average Causal Estimate (CACE)

This method considers two latent classes of participants (compliers/non-compliers)

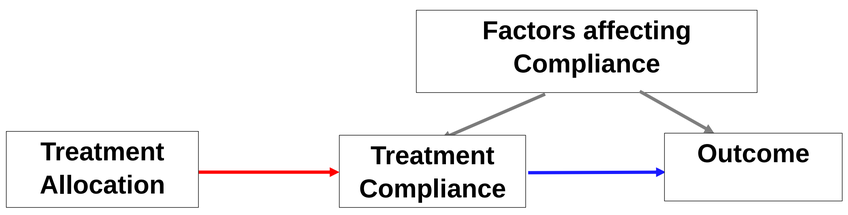
Assumptions:

- Proportion of compliers is the same in both arms
- The outcome for non-compliers is not influenced by the offer of treatment itself

	Compliance=1	Compliance=0
Treatment =1	Complier	Non-complier
Treatment =0	Would-be complier	Non-complier

2. Instrumental Variables (IV)

An instrumental Variable (IV) only influences the probability of being treated with an intervention but is not otherwise associated with the outcome or with any of the confounder measurements.



Compliance Definition

Prespecified threshold was set for compliance to:

- EA + SET
- EA alone
- NMES + EA + SET
- NMES + EA alone

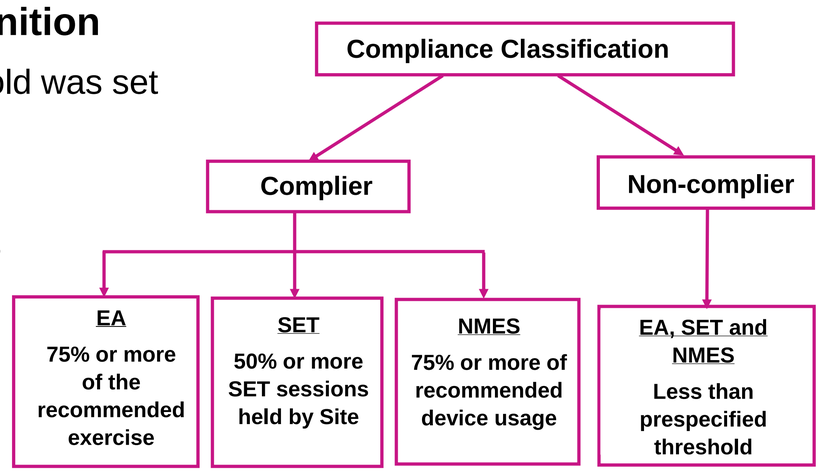


Table 1: Compliance classification for the ITT population by treatment and control

Classification	Treatment: NMES + EA and NMES+EA+SET	Control: EA and EA+SET	Total	
	N=74	N=74	N=148	P-value
Non-Complier	34 (45.9%)	28 (37.8%)	62 (41.9%)	0.32*
Complier	40 (54.1%)	46 (62.2%)	86 (58.1%)	

*P-values for the difference between groups was computed using Pearson's chi-squared

Results

- All the models showed no evidence of a significant difference between the study groups
- Magnitude of the treatment effect varies widely
- Very evident for results using untransformed data (for easier interpretation)

Table 2: Output (Coefficient [95% CI] p-value) for Tobit (ITT and PP), IV and CACE models - Transformed data

	Tobit Regression	Tobit Regression	IV	CACE (gsem)
	ITT (Model 1)	PP (Model 2)	Model 3	Model 4
Treatment	0.83 [-0.67,2.34] p=0.28	0.32 [-1.23,1.88] p=0.68	1.85 [-1.12,4.82] p=0.22	1.58 [-1.65,4.81] p=0.34

Table 3: Output (Coefficient [95% CI] p-value) for Tobit (ITT and PP), IV and CACE models - Untransformed data

	Tobit Regression	Tobit Regression	IV	CACE(gsem)
	ITT (Model 1)	PP (Model 2)	Model 3	Model 4
Treatment	27.18 [-26.92,81.28] p=0.32	10.05 [-45.88,65.98] p=0.72	55.82 [-50.79,162.43] p=0.31	44.17 [-83.43,171.77] p=0.5

Key points

- Causal inference models like Compliance Average Causal Effect (CASE) or Instrumental Variable (IV) approaches have not been adopted in RCTs of device interventions.
- Causal inference methods should be used to account for compliance in the analysis of device trails.
- When selecting the causal method, it is important to be aware of their assumptions and limitations.

Conclusion

- Causal inference methods should be used to account for compliance in the analysis of device trails
- We recommend considering planning the analysis of compliance from the early stages, considering thresholds for compliance, definitions of populations and statistical methods for handling compliance when developing Protocols and Statistical Analysis Plans (SAP)