EFFECTS Efficacy oF Fluoxetine – a randomisEd Controlled Trial in Stroke

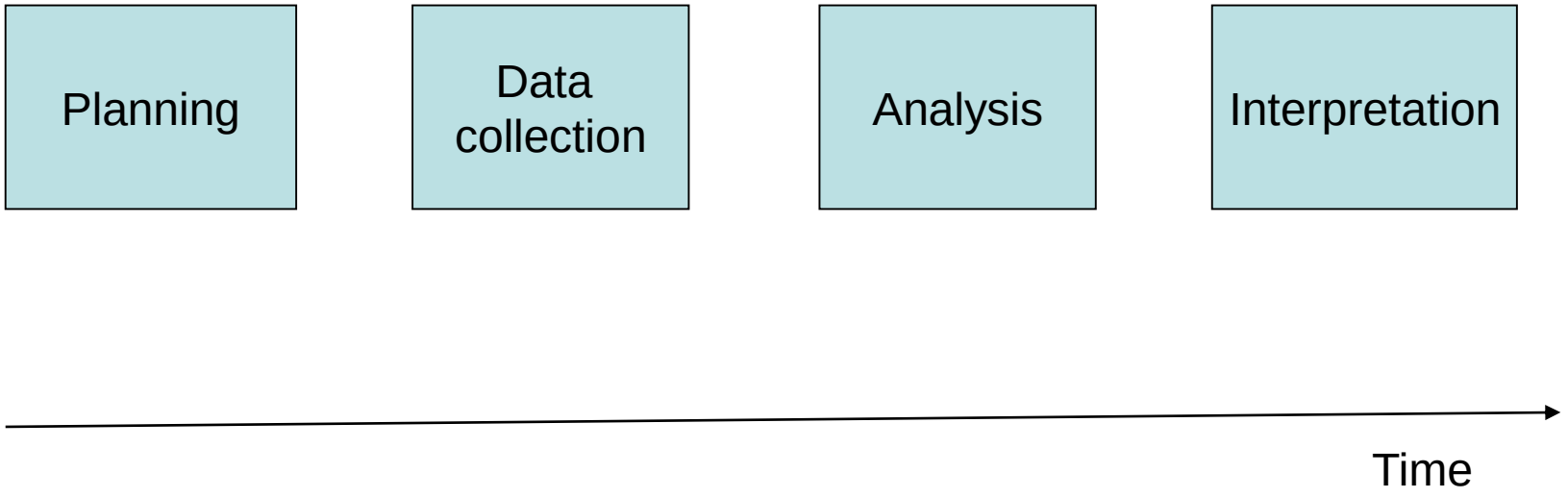
Statistisk utvärdering inom EFFECTS

Per Näsman

per.nasman@nasman.com

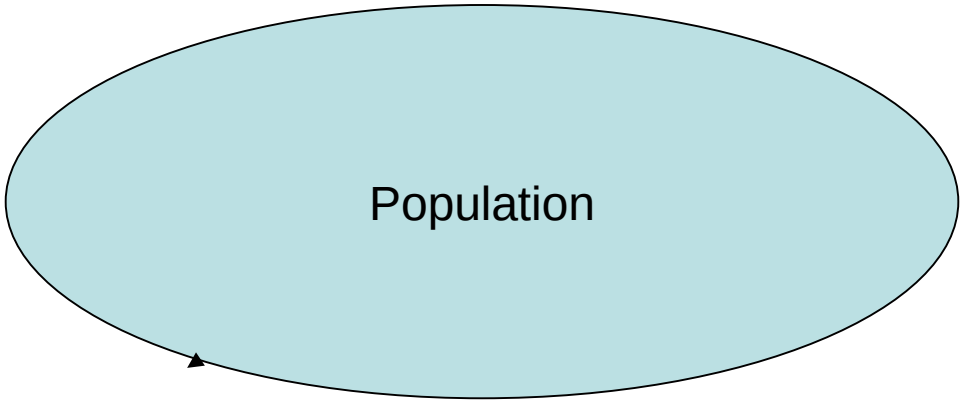
070 – 570 14 15

When is statistical issues relevant in a clinical trial

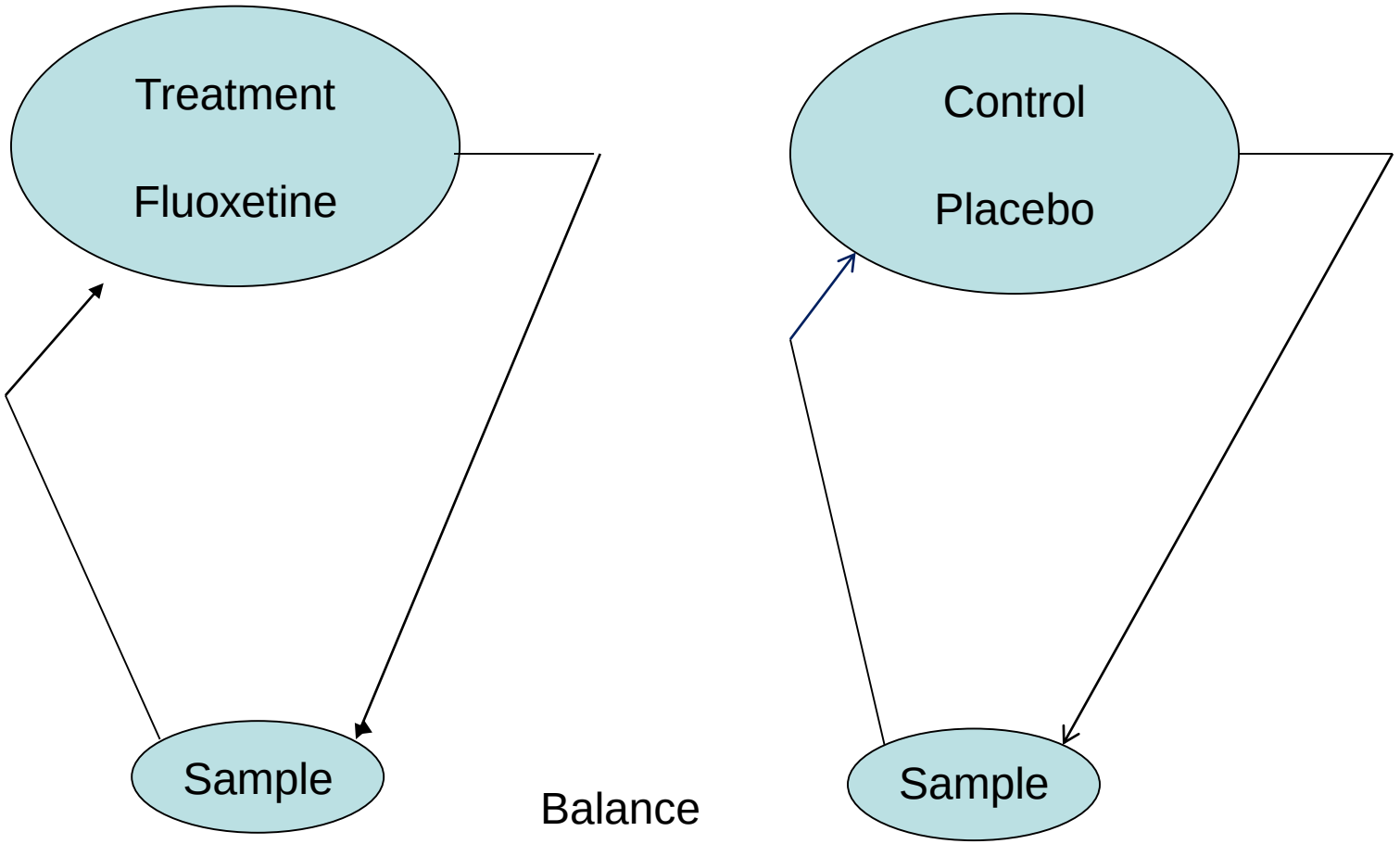


Selection of study population

Inclusion- and exclusion criteria



Randomisation



The system applies a minimization program to achieve balance for four factors:

Delay since stroke onset (2-8 vs. 9-15 days)

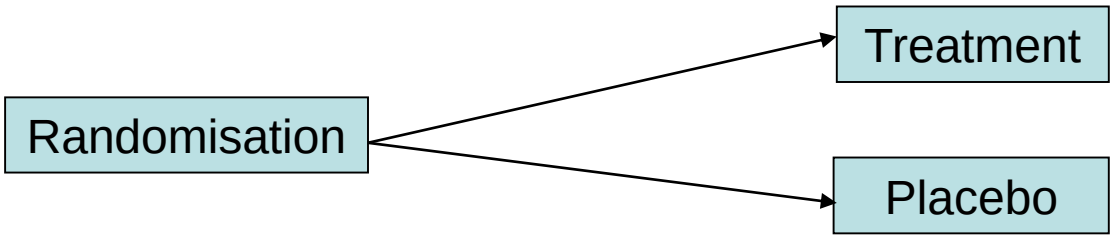
Predicted 6 month outcome (based on the six simple variable model)
(Counsell 2002).

Presence of a motor deficit (based on NIHSS)

Presence of aphasia (based on NIHSS)

Overall Study Design

- Parallell groups



Double-blind

Study objective

- Equivalence

EFFECTS is a Swedish multicentre, parallel-group, double-blind, placebo-controlled trial with broad entry criteria and follow-up to ascertain the primary and secondary outcomes at 6 and 12 months.

Primary efficacy variable

1) ”The primary variable should be the variable capable of proving the most clinically relevant and convincing evidence directly related to the primary objective”

2) ”There should generally be only one primary variable”

3) ”The selection of the primary variable should reflect the accepted norms and standards in the field of research”

4) ”The use of a reliable and validated variable with which experience has been gained is recommended”

The primary outcome is functional status, measured with the modified Ranking scale, mRS, at the 6-month follow-up.

We are using the simple modified Ranking scale questionnaire, smRSq, delivered by postal questionnaire, or via interview over the telephone or face to face face to determine the MRS.

Effektmått vid strokestudier

Score Definitionerna för de olika skalstegen i Modified Rankin Scale (mRS)

0 Inga symptom

1 Ingen signifikant funktionsnedsättning trots symptom. Klarar det dagliga livet som tidigare.

2 Viss funktionsnedsättning. Klarar det dagliga livet utan hjälp

3 Relativt uttalad funktionsnedsättning; kan gå, men behöver hjälp

4 Uttalad funktionsnedsättning. Kan inte gå utan hjälp

5 Kraftig funktionsnedsättning, sängbunden, inkontinent, i behov av hjälp dygnet runt

6 Död

Composite variable

”If a single variable cannot be selected from multiple measurements associated with the primary objective, another useful strategy is to integrate or combine the multiple measurements into a single or ’composite’ variable using a pre-defined algorithm”

”The primary endpoint was a composite of fatal and non-fatal myocardial infarction, stroke, and othe cardiovascular deaths”

(CAPPP studien, Lancet 1999, page 611)

Surrogate variables

”An efficacy variable is being used instead of the variable of intrest”

Due to for example expenses and difficulties in using the variable of interest.

For example tumor response as a surrogate variable for survival.

Cathegorised variables

It’s very common to dichotomize continues response variables into classes.

•Reduction in BMI	more than 5% =1	less than 5% = 0
•HB	above 120 = 1	below 120 = 0
•DBP	above 90 = 1	below 90 = 0
•Status	dead = 1	alive = 0

EFFECTS har dikotomiserat MRS-skalan i två grupper när det förväntade patientantalet beräknades, 0-2 versus 3-5.

Statistical analysis plan (SAP)

Specify which comparisons, tests and analysis that we plan to do.

Determination of sample size

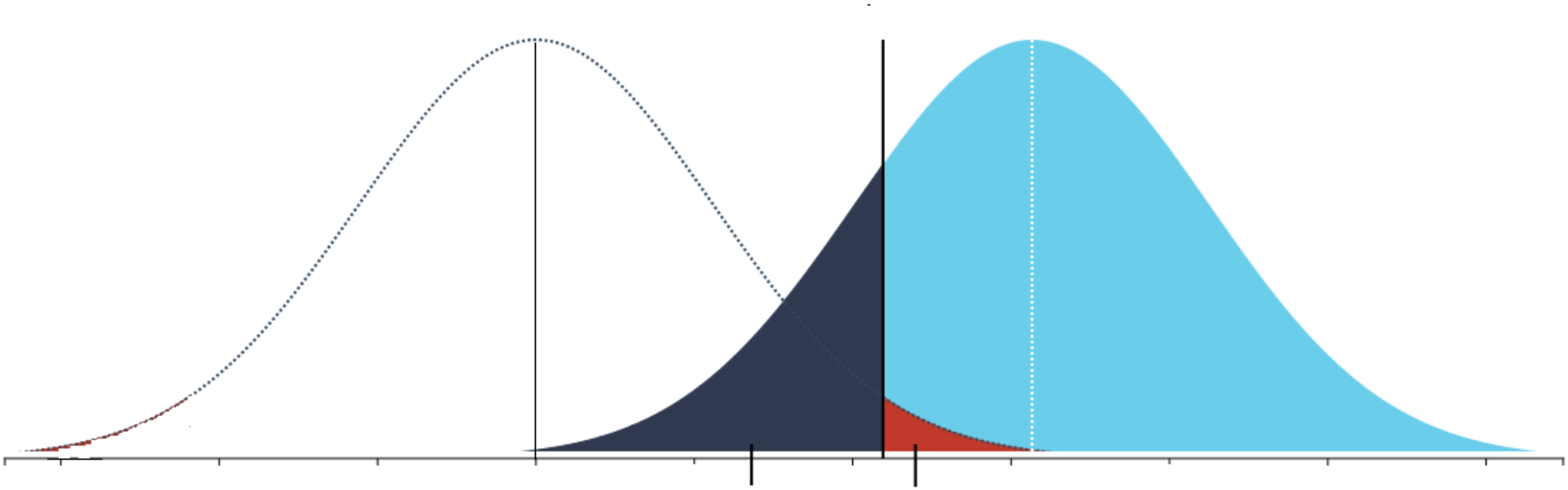
–

Hypothesis testing

The sample size in a study depends on:

- The objective
- The study design
- Ethical considerations
- Economy
- Access to patients
- Time aspect
- Choise of significance level
- Power
- Choice of primary efficacy variable
- Variation in the primary efficacy variable
- Choice of analysis method

		Decision	
		Not reject H_0	Reject H_0
Reality	$H_{0\ \text{true}}$	Correct (confidence) $1-\alpha$	Type I - error α Significance level p-value
	$H_{0\ \text{false}}$	Type II – error β	Correct (power)



How large risks should we take?

α = 0.05 ☆

= 0.01 ☆☆

= 0.001 ☆☆☆

β = 0.20 or 0.10 (Power = 0.80 or 0.90)

How to determine the sample size

- Decide the level of significance

- Decide the power

- Define (decide) the smallest difference that is considered clinical relevant (delta)
  Note: that is not the same as the expected difference

We are planning to enroll 1500 patients in the EFFECTS trial with equal number in each trial arm. This will provide 90% power to detect a 5.6% absolute increase in percentage with mRS 0-2 from 27.0% to 32.6% based on an ordinal analysis which is statistically more efficient than an analysis which dichotomizes the mRS.

Data from FOCUS and AFFINITY, the trials with which we share the minimal data set, aim to enroll 3000 + 1500 respectively, in all 4500 which if added to the EFFECTS inclusion will yield 6000 patients and provide 90% power to detect a 4.6% absolute improvement in percentage with mRS 0-2 from 27.0% to 31.6%.

Dataset to be analysed

- **ITT (Intention to treat)**

- **PP (Per protocol)**

Eligibility criteria not fullfilled

No dose taken

No data after randomization

Per protocol population

- No protocol violations or deviations
- Relevant measurements for primary variable
- Taken medication

Missing values or outliers

”Unfortunately, no universally applicable methods of handeling missing values can be recommended”

1. Let them be missing losing information
2. Impute mean value based on data from other patients
3. Impute ”worst case” or ”best case”
4. Regression models
5. Last observation carried forward (LOCF)

Interim analyses

- **For safety reasons**
- **For efficacy reasons**
- **For sample size adjustments**

Statistical analysis

- Descriptive statistics - always look at your data

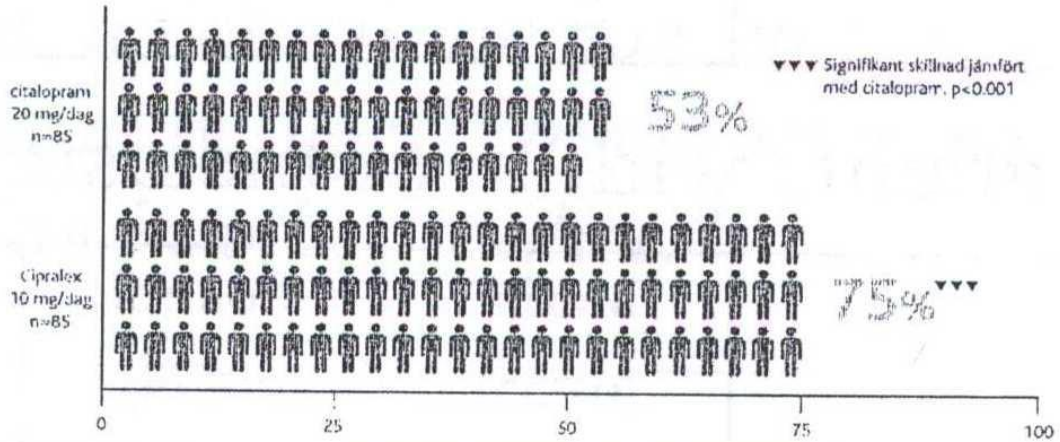
- Inferential statistics

Subgroup analyses

Beware!

Av 100 behandlade patienter förväntas 22 fler bli återställda* med Cipralex jämfört med citalopram.

- Av 100 behandlade deprimerade patienter förväntas 22 st fler bli återställda* efter 8 veckors behandling med Cipralex än med citalopram.[1]
- Patienterna blir återställda cirka 2 veckor tidigare med Cipralex 10 mg jämfört med citalopram 20 mg.[1]



Data från en subanalys av patienter med medelsvår depression (MADRS ≥ 22 och < 30 poäng). Från en dubbelblind, randomiserad, multinationell, multicenterstudie bland primärvårdspatienter med egentlig depression (MADRS ≥ 22 och < 40 poäng). Patienterna fick Cipralex 10 mg/dag (n=85) eller citalopram 20 mg/dag (n=85) i 24 veckor.

*återställd definieras som < 12 poäng på MADRS-skalan.

Nämnden för Bedömning av Läkemedelsinformation

Ärende 705/04

I broschyren presenteras en subanalys av patienter med svår depression som skall visa att Cipralex® är effektivare än Citalopram. Detta är en subanalys som inte är prespecificerad, vilket innebär att den saknar vetenskapligt bevisvärde. Läkemedelsverket anser därför att påståendena är osakliga.