Probability of success in biomedical research

—

Instructor: Corine Baayen

Helping people live better lives

FERRING
PHARMACEUTICALS

Program for today/course objectives

Objectives:

- Understand how to obtain a probability of success estimate for a research project
- Ability to discuss various success criteria and their pros and cons
- Understand how to interpret and use a probability of success estimate

Program:

- Mix of lectures and exercises – discussion as we go along is very welcome!
- Two coffee breaks (morning and afternoon) and a lunch break in between

Consider how the material might apply to your own research and share if you like.

FERRING PHARMACEUTICALS

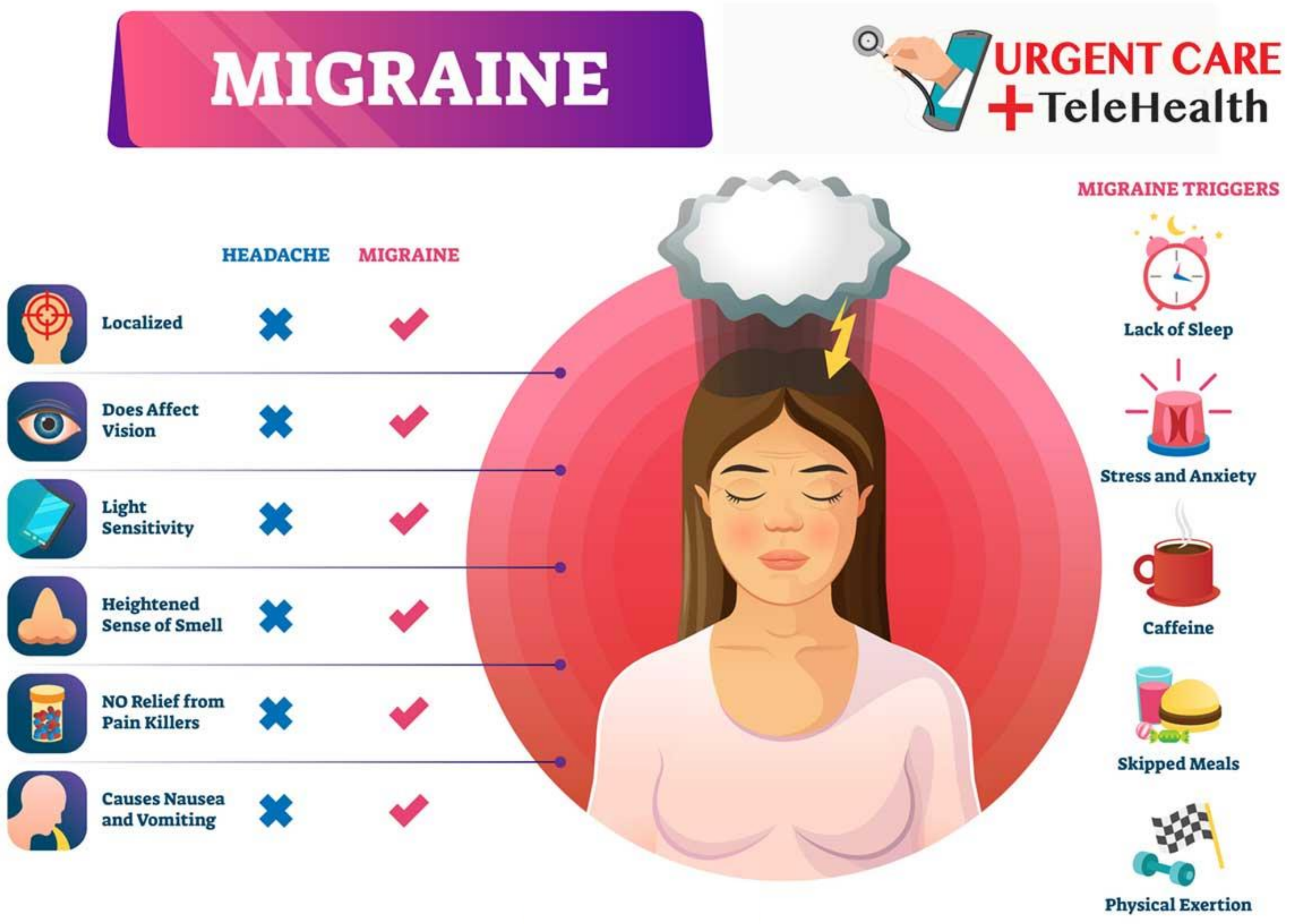
Case study

Loosely based on a real case

A drug is being developed to treat migraine

We have performed a small proof of concept study with positive results

Now we wish to design a large confirmatory trial to confirm that the drug works

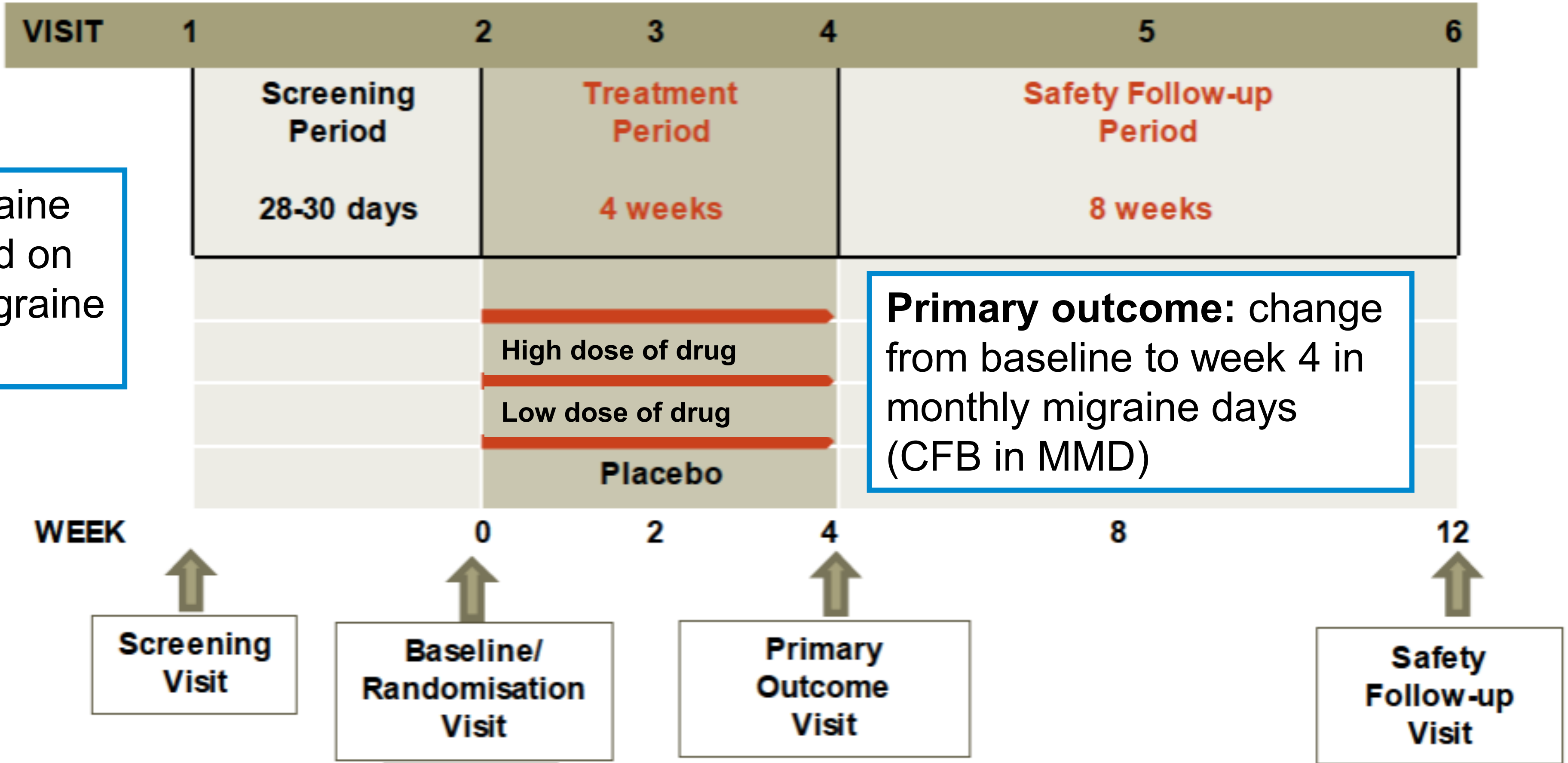


FERRING PHARMACEUTICALS

Design of the proof of concept study

A double-blind, parallel group, placebo controlled trial

Population: migraine patients who failed on 2-4 preventive migraine treatments



Primary outcome: change from baseline to week 4 in monthly migraine days (CFB in MMD)

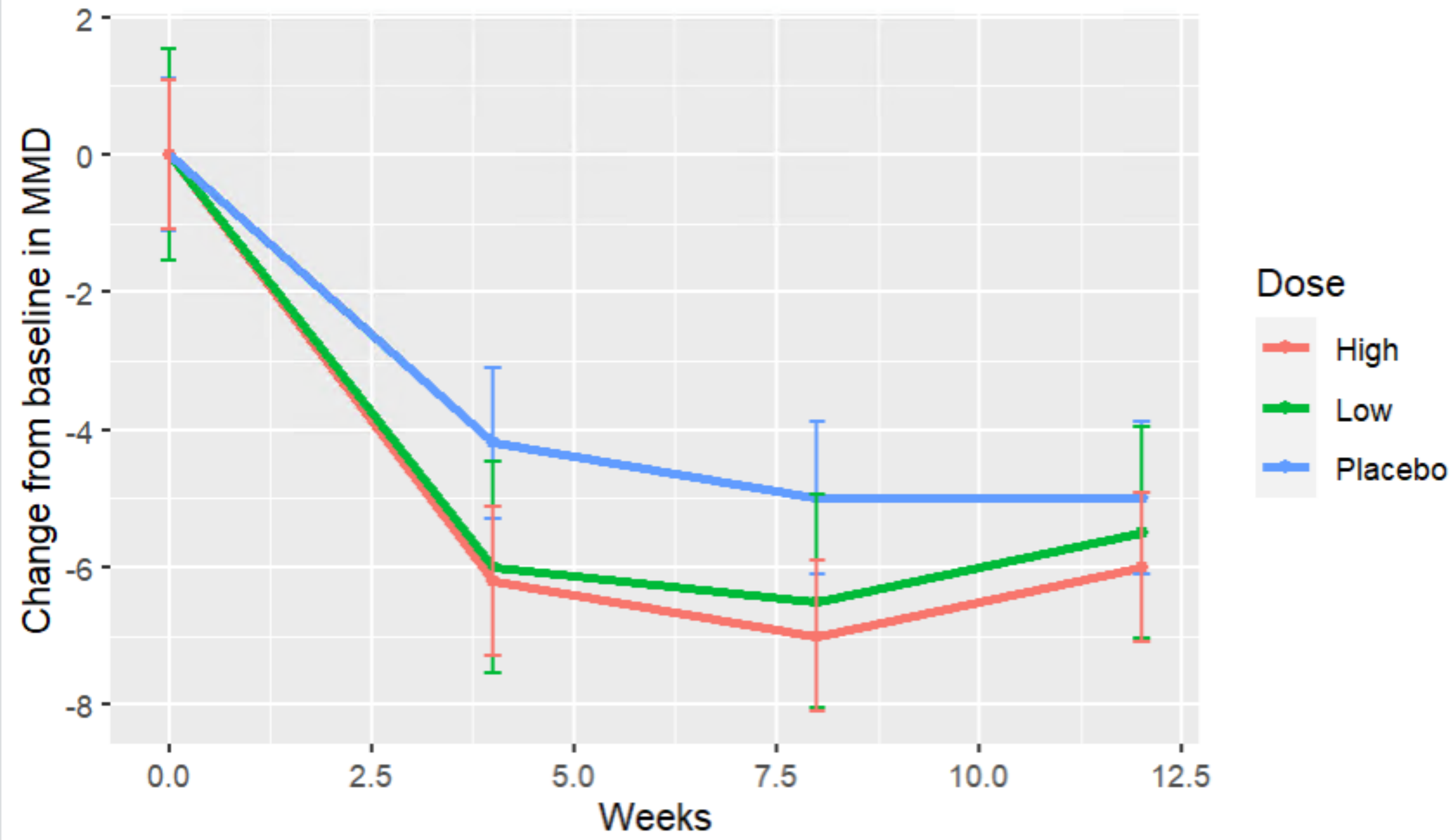
Mode of administration: Single intravenous infusion

IMP = investigational medicinal product.

FERRING PHARMACEUTICALS

Results from the proof of concept study

A positive study



Significant difference at week 4 of -2 (SE=0.89) MMD on high dose compared to pbo (p=0.01)

Standard deviation of CFB in MMD to week 4 of 6.5

Based on Results Posted | A Study With Lu AG09222 in Adults With Migraine Who Have Not Been Helped by Prior Preventive Treatments | ClinicalTrials.gov (data after 4 weeks is fictional)

SE = Standard Error

Study design for the confirmatory trial

A double-blind, parallel group, placebo controlled trial

VISIT	1	2	3	4	5	6	7
WEEK		0	4	8	12	16	20

Population:
migraine patients who failed on 2-4 preventive migraine treatments

Screening Period
28-30 days

Treatment Period
12 weeks

Safety Follow-up Period
8 weeks

High dose of drug

Placebo

Primary outcome: change from baseline to week 12 in monthly migraine days (CFB in MMD)

Screening Visit (Week –4, Visit 1)

Baseline/ Randomisation Visit (Week 0, Visit 2) – **IMP**

Week 4 (Visit 3) – **IMP**

Week 8 (Visit 4) – **IMP**

Primary Outcome Visit (Week 12, Visit 5)

Safety Follow-up Visit (Week 20, Visit 7)

Mode of administration:
Monthly subcutaneous injections

IMP = Investigational Medicinal Product

FERRING
PHARMACEUTICALS

Distribution of the difference in means

Suppose patients are randomised to one of two treatments, with n_i patients allocated to Treatment i

Suppose that the *j*th patient receiving Treatment i will yield a continuous response y_{ij} with

$$Y_{ij} \sim N(\mu_i, \sigma_i), \text{ independent.}$$

Then the distribution of the difference in means $\bar{y}_1 - \bar{y}_0 = \frac{1}{n_1}\sum_{i=1}^{n_1} y_{1i} - \frac{1}{n_0}\sum_{i=1}^{n_0} y_{0i}$ is

$$\bar{y}_1 - \bar{y}_0 \sim N(\mu_1 - \mu_0, \sqrt{\frac{\sigma_1^2}{n_1} + \frac{\sigma_0^2}{n_0}})$$

Where $\sqrt{\frac{\sigma_1^2}{n_1} + \frac{\sigma_0^2}{n_0}}$ simplifies to $\sigma\sqrt{\frac{2}{n}}$ in case $\sigma_1 = \sigma_0$ and $n_1 = n_0$.

FERRING
PHARMACEUTICALS

Deciding on a sample size

Power calculation (continuous endpoint, assuming known variance)

H_0: null hypothesis - no effect

H_1: alternative hypothesis – the effect equals δ

μ_0: true mean CFB in MMD on placebo

μ_1: true mean CFB in MMD on drug

σ: standard deviation of CFB in MMD

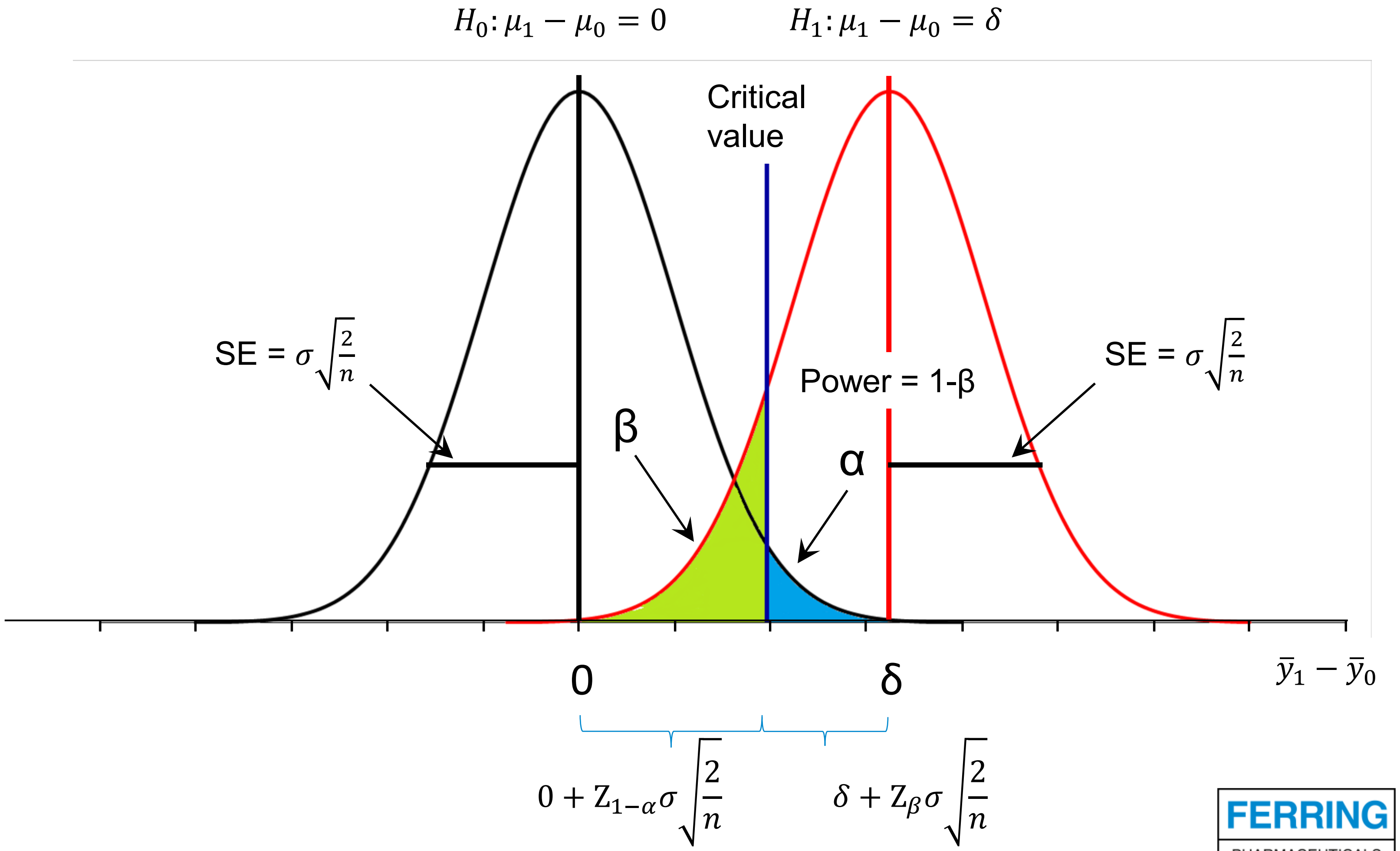
β: level at which to control the false negative rate

α: level at which to control the false positive rate

Z_q: q[th] quantile of the standard normal distribution

The sample size can be calculated by finding *n* such that $0 + Z_{1-\alpha}\sigma\sqrt{\frac{2}{n}} = \delta + Z_{\beta}\sigma\sqrt{\frac{2}{n}}$:

$$n = \frac{2\sigma^2\left(Z_{1-\alpha} + Z_{1-\beta}\right)^2}{\delta^2}$$



FERRING PHARMACEUTICALS

SE = Standard Error

Exercise 1 – propose a sample size for the confirmatory trial

You are very welcome to work together

Requirements/assumptions:

- We would like to have a power of 90%
- We would like to control the false positive rate at a one-sided 2.5% level
- Make appropriate assumptions about:
  - the expected difference δ in mean CFB in MMD at week 12
  - the standard deviation σ for the CFB in MMD at week 12

Hints:

- make use of the results from the proof of concept study
- In R Z_q can be obtained using `qnorm(q)` and x^2 by `x^2`

FERRING PHARMACEUTICALS