Statistical planning and analysis of a randomized trial on genital erosive lichen planus

Background

- Genital erosive lichen planus (GELP) in women is a chronic inflammatory disease characterized by painful vulval and vaginal erosions
- A disease with few and unsatisfactory treatment options
- Topical photodynamic therapy (PDT) is increasingly used in premalignant and malignant diseases and may have an effect in inflammatory diseases

CLINICAL TRIALS

BJD
British Journal of Dermatology

Vulvovaginal photodynamic therapy vs. topical corticosteroids in genital erosive lichen planus: a randomized controlled trial

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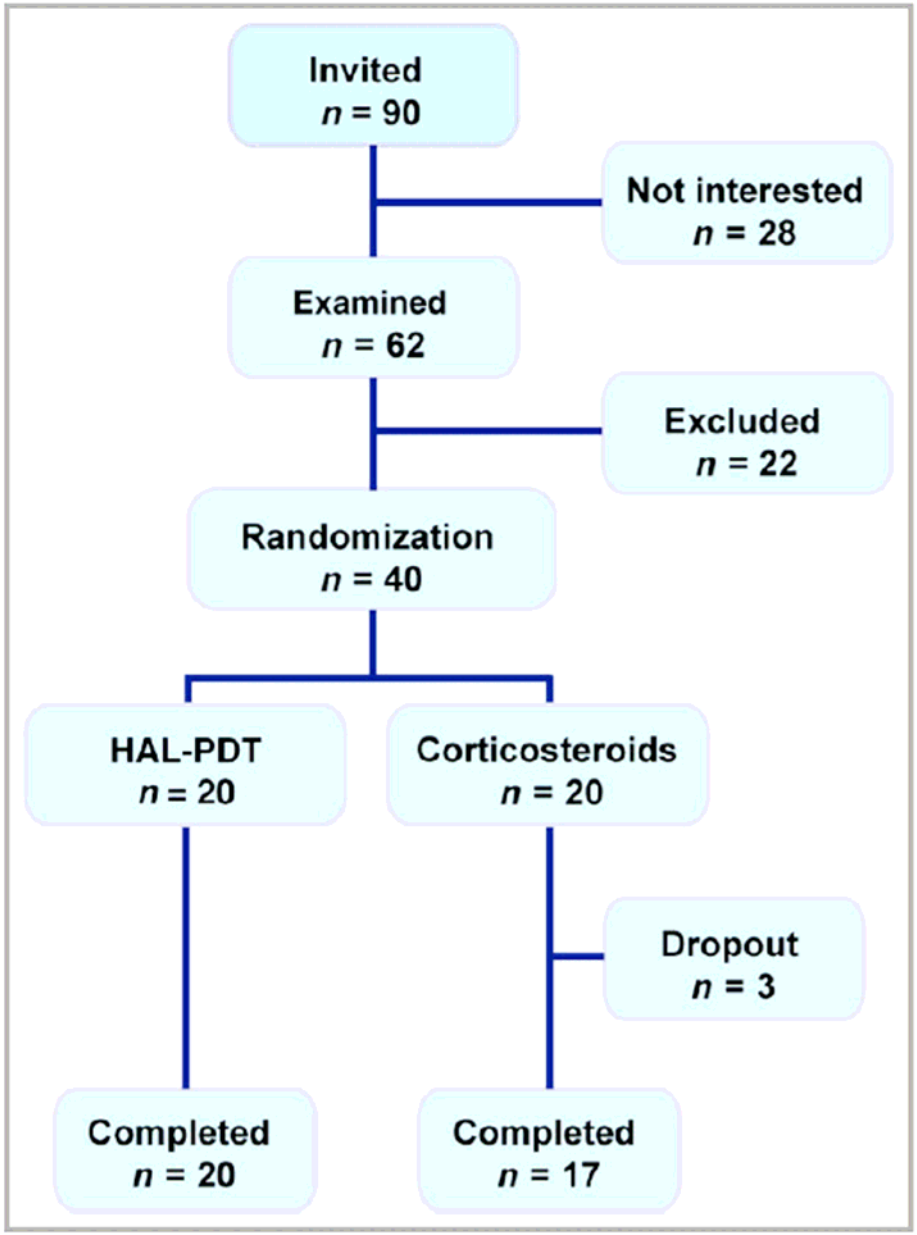
Objective and study design

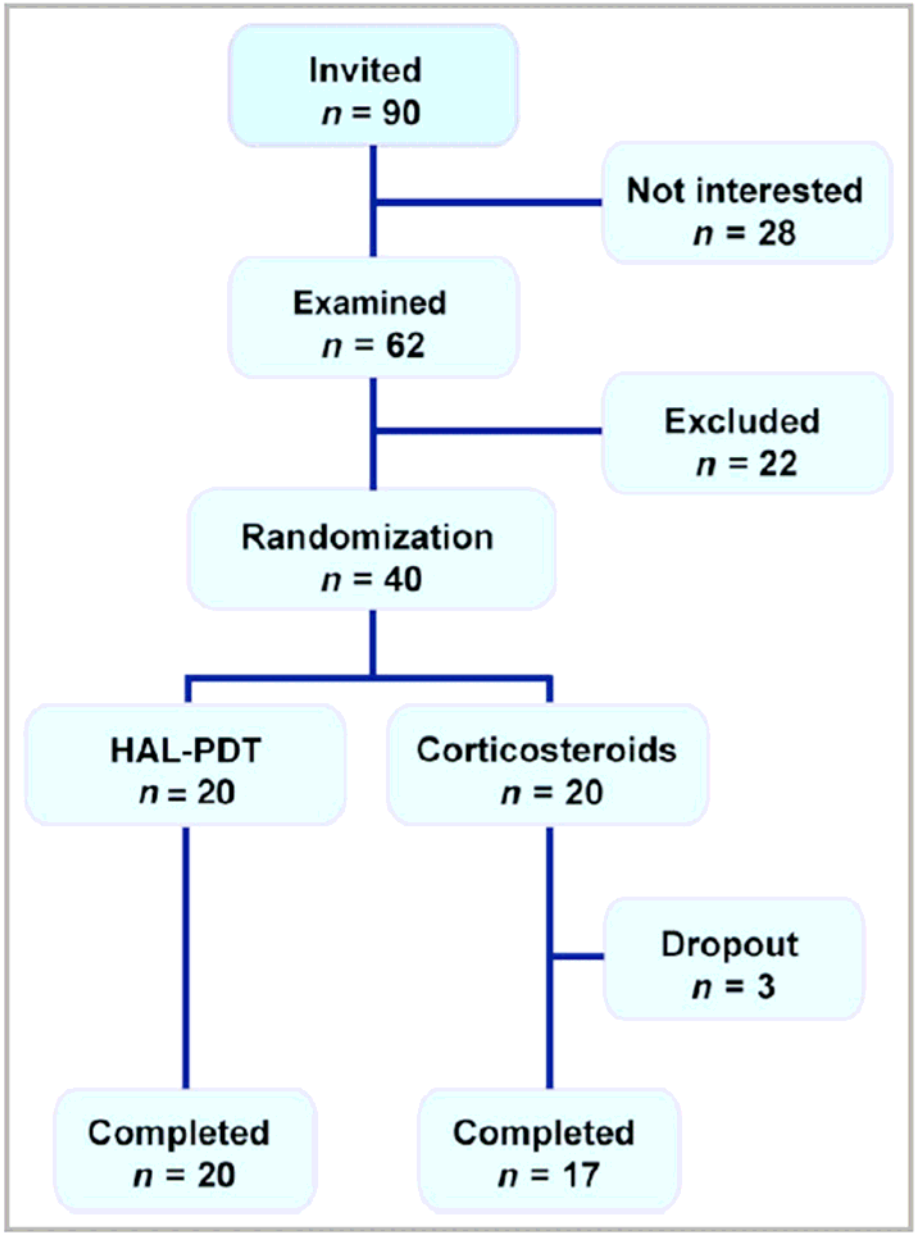
- To assess the feasibility, efficacy and safety of hexyl 5-aminolevulinate-hydrocloride-Photodynamic therapy (HAL-PDT)

- 40 women randomized to
  - one session HAL-PDT in vulva and/or vagina

    or
  - daily applications corticosteroids in vagina for 6 weeks



- After 6 weeks, all patients were allowed to use topical corticosteroids as needed.
- Clinical examinations were performed at weeks 0, 6 and 24, using a clinical score developed for the study.
- All patients wrote a weekly log on pain, topical corticosteroid use and adverse events.



Primary outcome:

Percentage change of clinical GELP score at 6 and 24 weeks after start of treatment

GELP score based:

- Area of involvement
- Intensity of erythema
- Number of erosions
- Striae
- Pressure-induced pain

Statistical planning and background

- Medical hypothesis: Potential benefits of photodymaic therapy more on cost, adverse effects and patients compliance than specifically on the disease progression.
- Sample size and statistical planning initially based on a non-inferiority design

Non-inferiority margin

- How to assess if a test treatment is non-inferior to the control treatment
- A clinical and medical assessment
- However, it must not be equal to placebo.
  - If non-inferiority margin equal to effect of a placebo controlled trial, we say that our new treatment is not inferior to placebo!

(a) 1. Historical Effect of Active Control versus Placebo is of a specified size and there if belief that it is maintained in the present trial (C>P)

(b) 2. Trial has the ability to recognize when the test drug is within non-inferiority margin (M) of control

3. and Superior to a Placebo by a specified amount

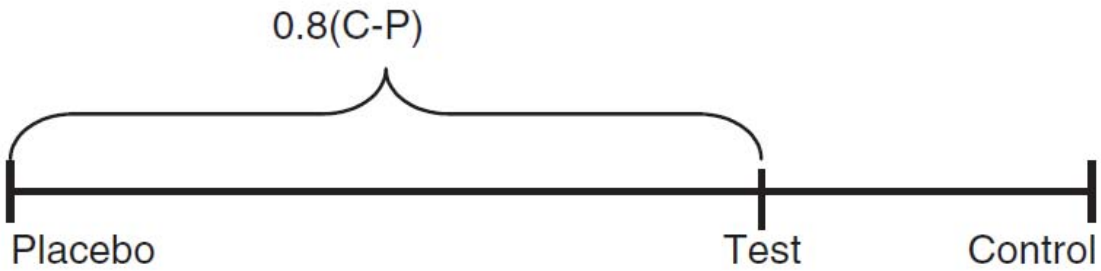
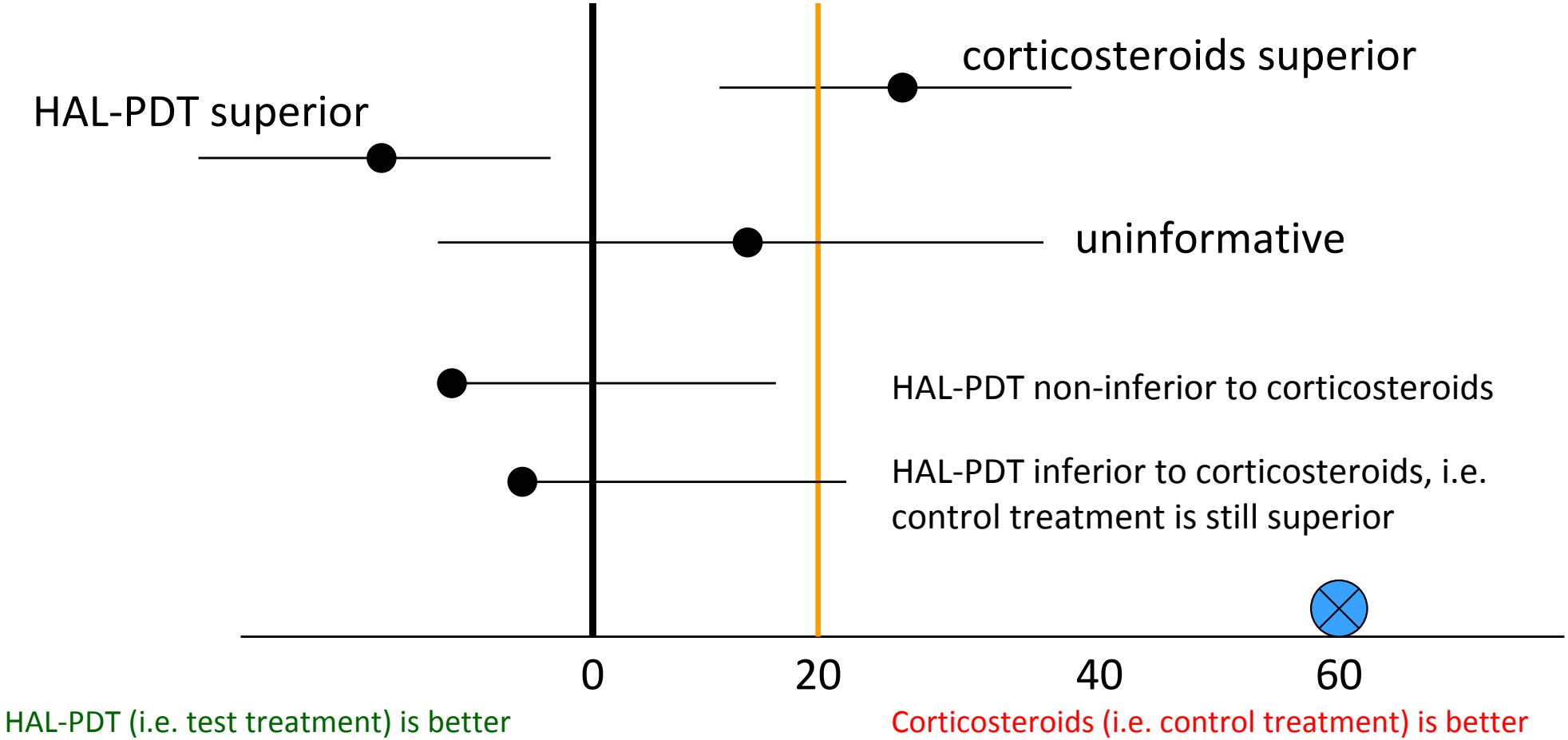


Illustration from D'Agostino RB et al. 2003. Non-inferiority trials: design concepts and issues – the encounters of academic consultants in statistics. Statist. Med. **22**: 169-186.

Non-inferiority margin and sample size

- A problem: There were no placebo controlled trials on Genitial erosive lichen planus in women
- Combining clinical knowledge and statistical intuition we assumed
  - Effect in placebo vs conticosterorid trial: 60
  - Non-inferiority margin: 20
  - Standard deviation: 25
  - Thus, 20 patients in each group to obtain 80% power

- Not realistic to expand sample size above 20 in each group due to small patient population

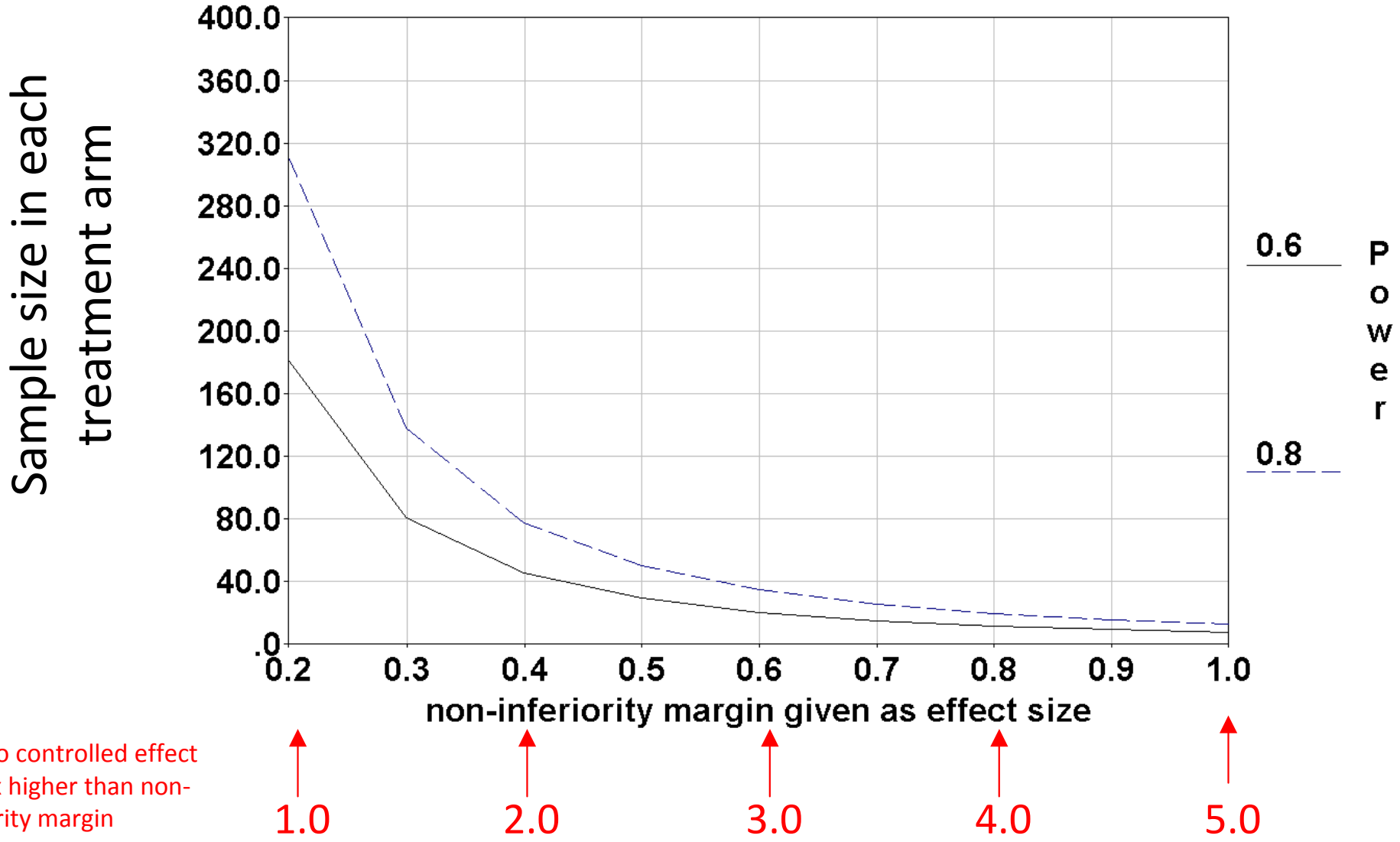


Confidence interval from different scenarios

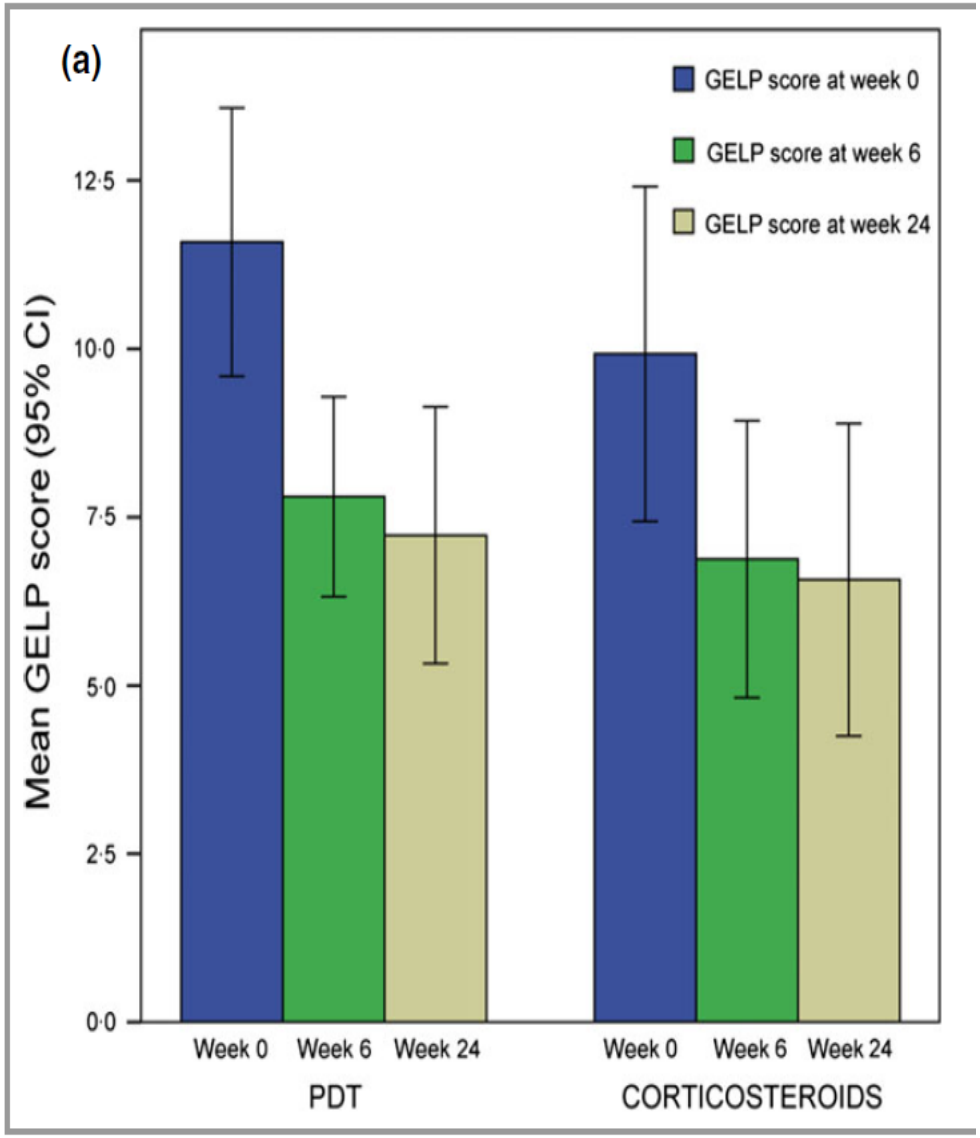
Non-inferority margin in our trial

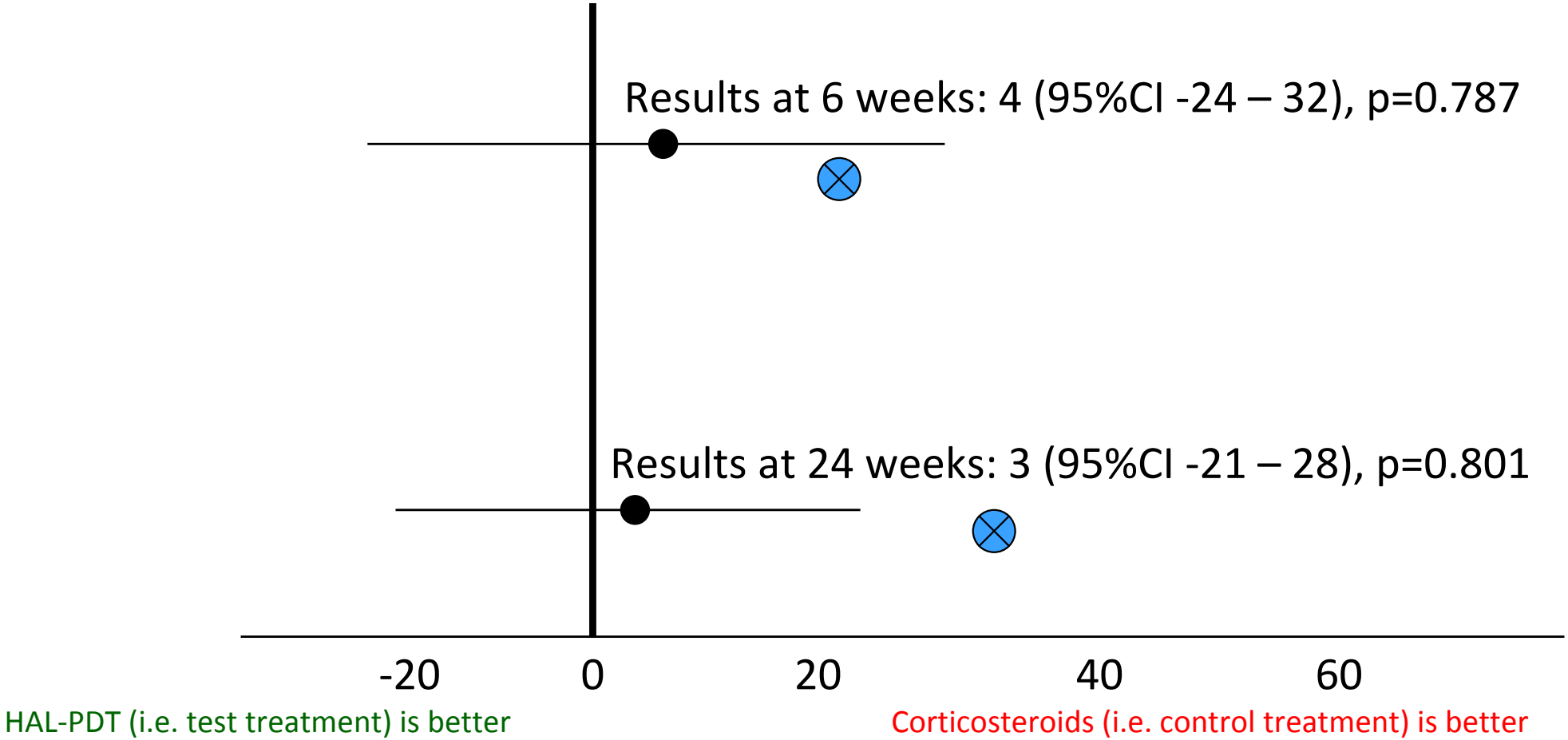
Our assumed effect in a steroid vs placebo trial

Sample size calculations based on effect size $= \frac{\mu_1 - \mu_2}{\sigma}$



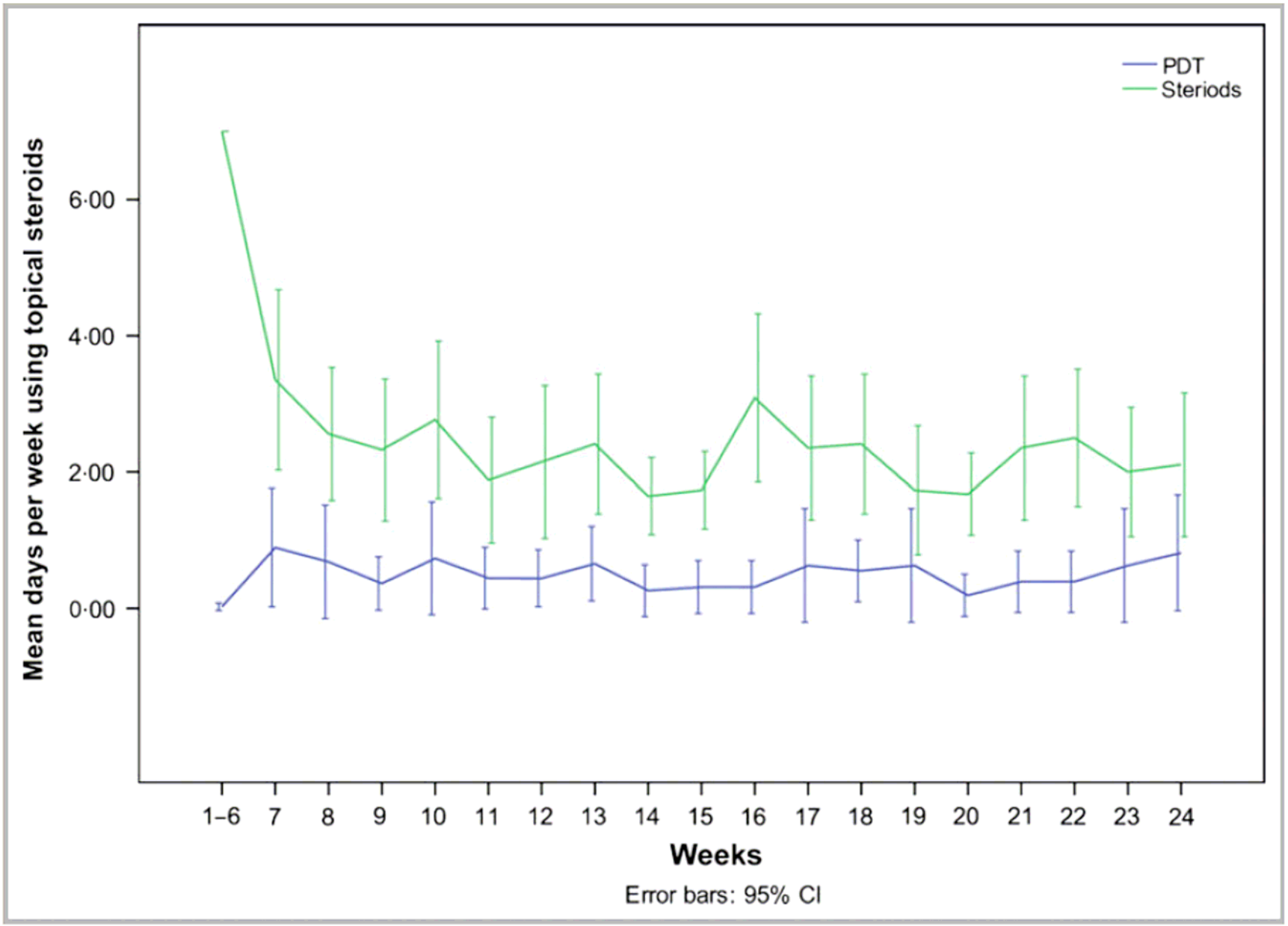
- Results
  - Not presented and published as a non-inferiority trial
  - No statistical difference between HAL-PDT and Corticosteroids





Confidence interval

Corticosteroid vs placebo trial if assumed no effect in placebo group


PDT
Steriods
Mean days per week using topical steroids
6·00
4·00
2·00
0·00
1–6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
Weeks
Error bars: 95% CI

Conclusion

- Clinical conclusion based on ”statistical gutfeeling” and medical knowledge
  - Photodynamic therapy (HAL-PDT) give equal effect on GELP than control treatment with corticosteroids
  - HAL-PDT can replace corticosteroids and thereby be beneficial concerning cost, compliance and adverse effects
- However, we still lack a statistical significant ”proof” that HAL-PDT should be the recommended treatment for these women

Some points for discussion

- Non-inferiority and equivalence studies in small patient populations
- How to choose primary outcome in such studies
- Sample size calculations in small patient population