Statistical properties of hypothesis tests using Goal Attainment Scaling

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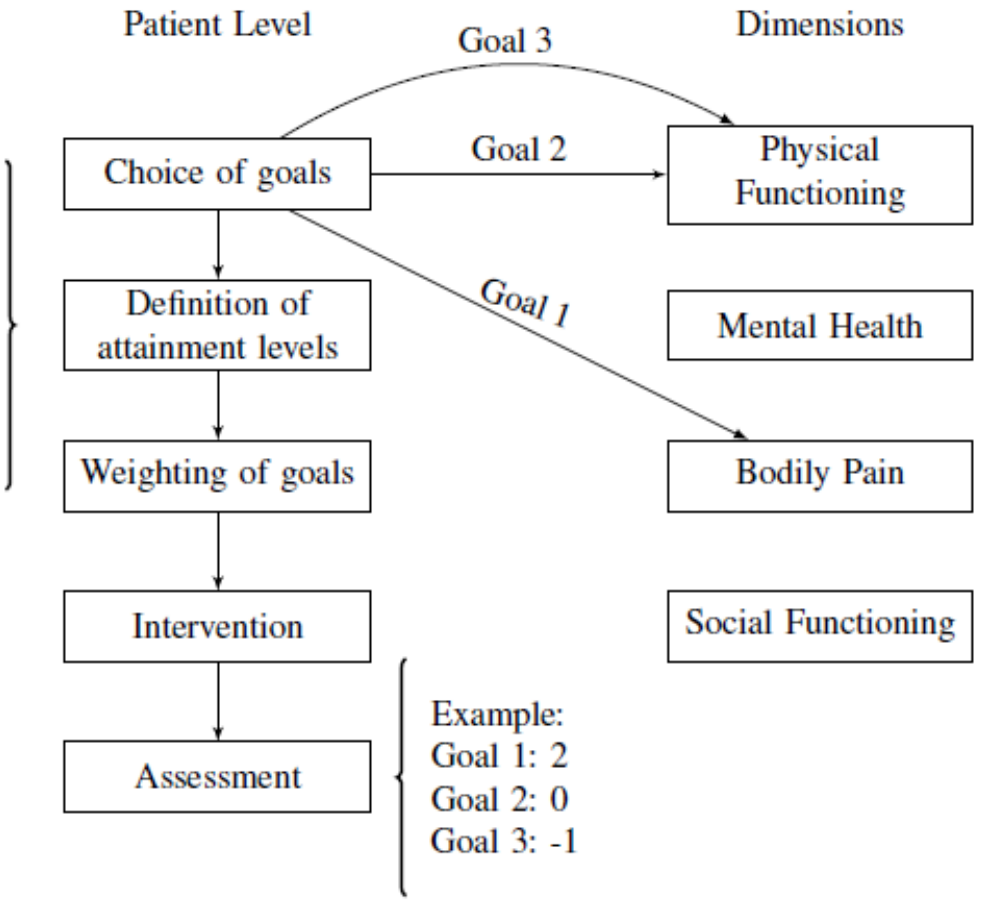
Process of goal setting and measurement

Example:
-2 unable to walk
-1 can walk for 3 steps
0 can walk for 5 minutes
+1 can walk for 15 minutes
+2 can walk for a longer period



Use of GAS for finding a treatment effect?

Advantages and disadvantages

- Advantages:
  - Relevance of the endpoint to the patient
  - Increasing the possible sample size for the clinical trial because not all endpoints are measurable in each patient affected by a certain disease

- Disadvantages and open questions:
  - Process of goal setting very time consuming
  - Not a validated measurement instrument
  - What concept does GAS measure? Treatment effect?
  - What kind of test should one perform with GAS data?
  - How can a significant hypothesis test be interpreted?
  - Clinical interpretation of estimated change?

Research questions

- Analyzing trials:
  - How to test for a treatment effect in an optimal way?
  - What kind of weights should be applied to the individual goals?
  - Interpretation of significant hypothesis test?

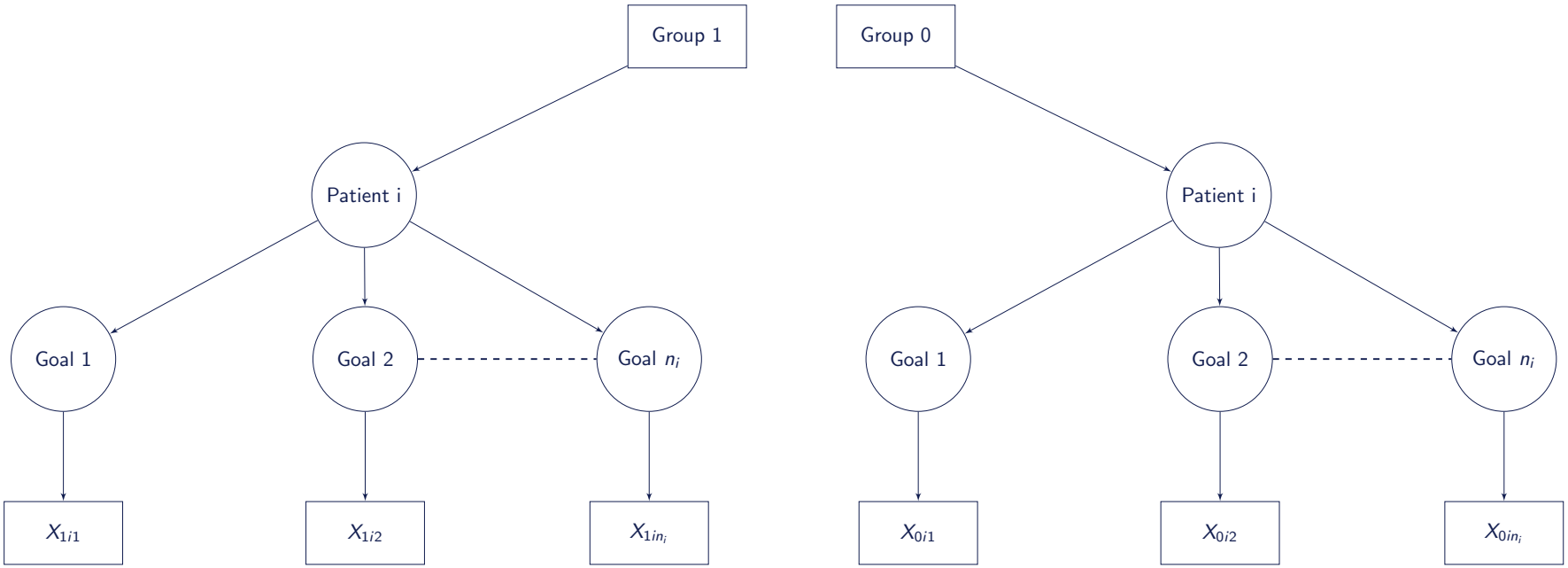
- Designing trials:

  How is a hypothesis test using a GAS endpoint affected by
  - Maximum number of goals
  - Correlation between the goals
  - Proportion of goals affected by the treatment
  - Number of attainment levels

Trial design assumptions

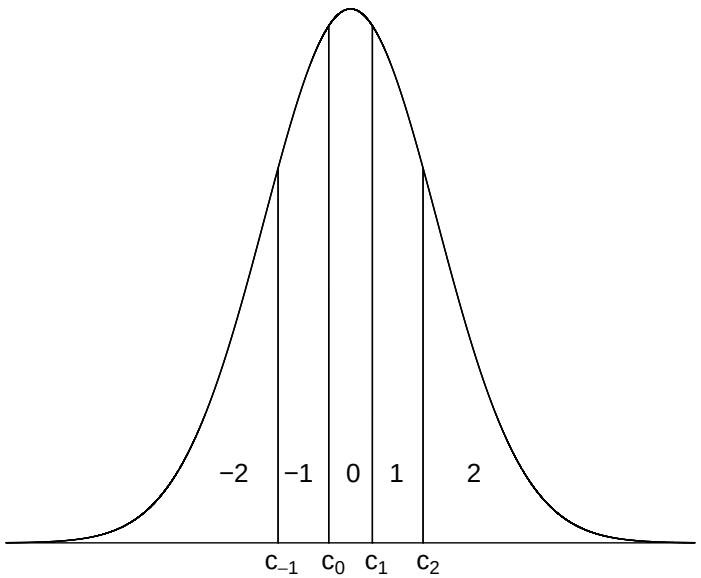
- The treatment affects the underlying mechanism of the disease and thereby several symptoms/goals.
- Randomized parallel group comparison between two arms.
- Goal outcomes are correlated within patients.
- Patients individually choose number and kind of goals.
- Same set of attainment levels for all goals, e.g. $\{-2, -1, 0, 1, 2\}$.

Multilevel hierarchical model



Discretization of continuous goal scores

- The observed ordinal goal attainment level X_{gik} for goal k of patient i in group g is the result of a discretization of a latent continuous normal variable Z_{gik}.
- The continuous variables are discretized based on thresholds c_j.



Discretization

$$
\begin{aligned}
-\infty < Z_{gik} < c_{-1} &\rightarrow X_{gik} = -2 \\
c_{-1} \leq Z_{gik} < c_0 &\rightarrow X_{gik} = -1 \\
c_0 \leq Z_{gik} < c_1 &\rightarrow X_{gik} = 0 \\
c_1 \leq Z_{gik} < c_2 &\rightarrow X_{gik} = 1 \\
c_2 \leq Z_{gik} < \infty &\rightarrow X_{gik} = 2
\end{aligned}
$$

Generating clustered ordinal outcomes

Random effect model for latent continuous goal outcome

$$Z_{gik} = u_{gi} + \mu_{gik} + \epsilon_{gik}$$

Z_{gik} ... continuous outcome for goal k of patient i in group g=0,1
u_{gi} ... random patient effect in group g $\sim N(0, \sigma_u^2)$
μ_{gik} ... random treatment effect on goal k of patient i
with $E(\mu_{gik}) = \mu_g$ and $Var(\mu_{gik}) = \sigma^2_{\mu_g}$
ϵ_{gik} ... noise $\sim N(0, 1)$

- The difference in expected goal attainment across goals and patients between treatment and control group $\delta = \mu_1 - \mu_0$ can be interpreted as the average treatment effect.

Estimating $E(X_g)$ and testing $E(X_1) = E(X_0)$

Null hypothesis $H_0 : E(X_1) = E(X_0)$

The average goal attainment level $E(X_1)$ across patients and goals of the experimental group and $E(X_0)$ of the control group are the same.

- **Challenges:**
  - Clustered observations:
    Since goal attainment levels from within patients tend to be more alike than observations from different patients, those observations provide less information about a group.
  - Different number of goals per patient:
    Less correlated or more goals of a patient provide more information about the overall treatment effect.
- **Methods:**
  - Kiresuk and Sherman formula
  - Generalised estimation equation (GEE) approach

Kiresuk and Sherman formula and GEE approach

- Composite goal score ("T score") for patient i in group g:

$$T_{gi} = 50 + \frac{10 \sum_k (W_{gik} X_{gik})}{\sqrt{(1-\rho_{gi}) \sum_k W_{gik}^2 + \rho_{gi} (\sum_k W_{gik})^2}}$$

  $X_{gik} \ldots$ ordinal goal attainment levels
  $W_{gik} \ldots$ weigths for the individual goal attainment levels
  $\rho_{gi} = \rho = 0.3 \ldots$ weighted average correlation

- The T score is a standardized weighted average of the goal attainment levels. For testing $E(T_1) = E(T_0)$ a t test can be applied.

- Generalized estimating equation (GEE) approach is used to estimate the average goal attainment $E(X_g)$ in group g

Comparison of GEE and Kiresuk method

If we assume equal correlations ρ for all pairs $(X_{gik}, X_{gik'})$:

Kiresuk method

$$\frac{\bar{T} - 50}{10} = \frac{1}{m} \sum_{i=1}^{m} \sqrt{\frac{n_{gi}}{1 + (n_{gi} - 1)\rho}} \bar{X}_{gi}$$

Sum of the standardised mean goal attainment levels.

GEE method

$$J' \Sigma^{-1} X = \sum_{i=1}^{m} \frac{n_{gi}}{1 + (n_{gi} - 1)\rho} \bar{X}_{gi}$$

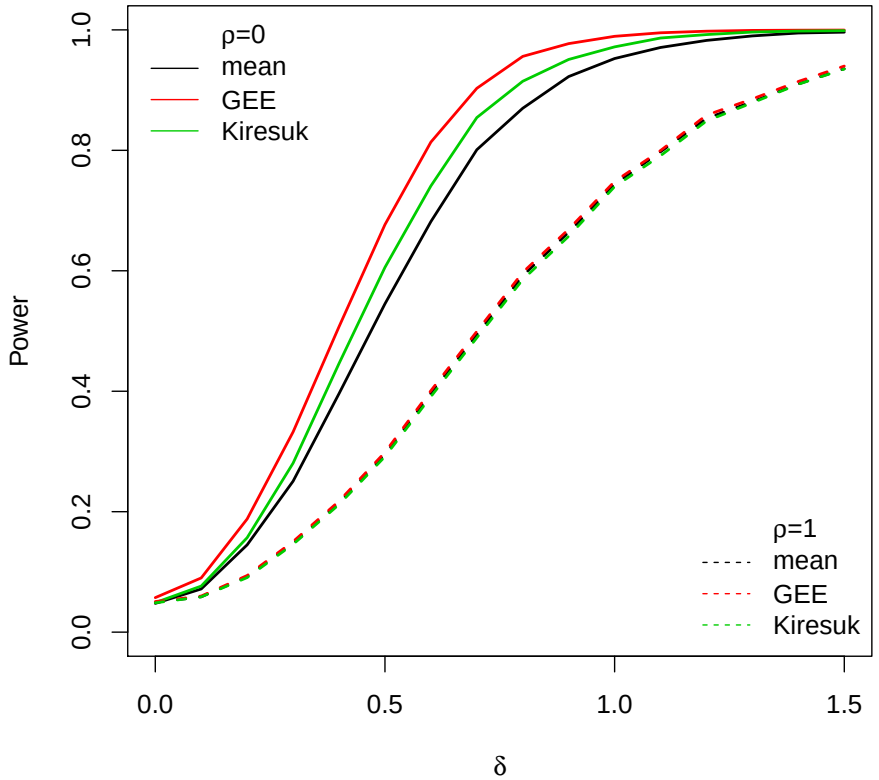
Weighting the goal attainment levels with the inverse of the covariance matrix Σ^{-1}.

Similarities between the GEE and Kiresuk method

- The means are weighted accounting for the different numbers of goals and the correlation between them.
- If the number of goals n_{gi} are independent of the goal attainment levels, it holds that $E(T_1) = E(T_0) \Leftrightarrow E(X_1) = E(X_0)$.

Power of the hypothesis test: GEE vs Kiresuk

The GEE approach has better power for testing $E(X_1) = E(X_0)$:



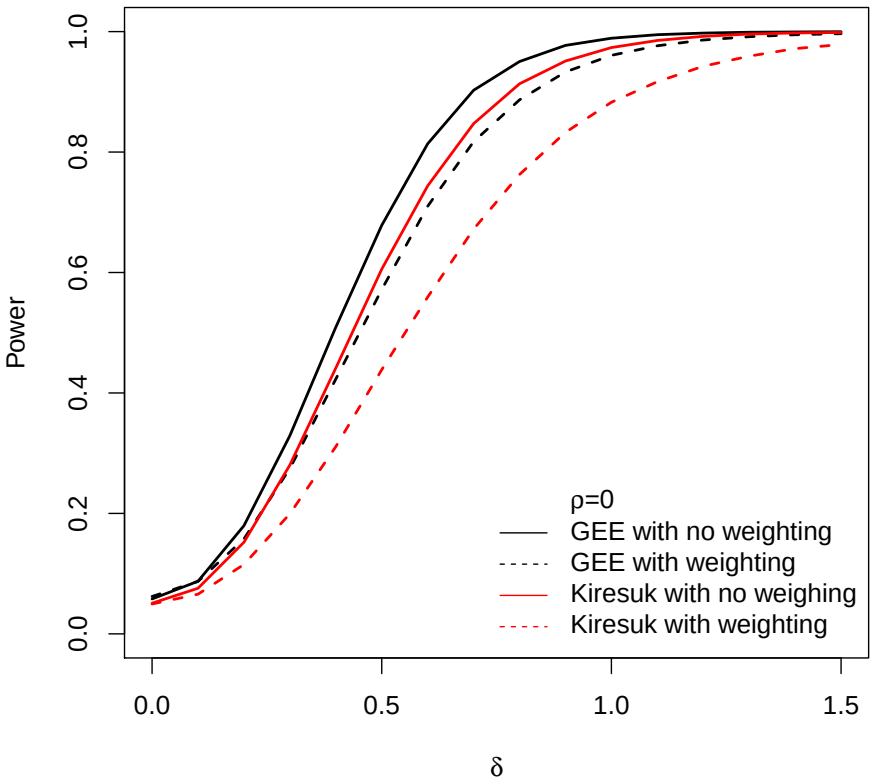
Power, $\delta = 0.5$

GEE: 68%
Kiresuk: 61%
mean: 55.4%

m=20, $n_{max} = 5$, $c_j = \Phi^{-1}(p_j)$, $p = (0.2, 0.4, 0.6, 0.8)$
$n_{gi} \sim U\{1, \ldots, n_{max}\}$, $\mu_{gik} \sim U(0, 2\mu_g)$, $\delta = \mu_1 - \mu_0$

Weighting of goal attainment outcomes

If the weights are not correlated with the treatment effect on the goals, weighting leads to a substantial loss in power.



Power, $\delta = 0.5$, $\rho = 0$

GEE no weighting: 68%
GEE with weighting: 57%
Kiresuk no weighting: 61%
Kiresuk with weighting: 43%

Impact of design aspects on power

- The power increases with the number of goals affected by the treatment, but the increase levels off: For weak correlation between goals, there can be substantial power increase up to about 5 goals.
- If goals chosen by a patient are very similar, the gain in power by adding goals is small.
- Including goals that are not affected by the treatment can lead to a substantial loss in power.
- A scale with 5 levels appears to be sufficient. Further increasing the number of level has little influence on the power.

Conclusions

- The optimal way to test for a change in average goal attainment levels between groups would be to use the GEE approach ($m \geq 20$).
- Using weights for the goal attainment levels which are not correlated with the treatment effect reduces power.
- The statistical implications of design choices (as, e.g., the maximum number of goals) should be considered.
- Clinical interpretation of a significant hypothesis test: There is a difference in the average attainment of goals.
- When presenting the results, the individual goals chosen should be investigated as well, maybe for certain domain clusters.

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