A composite score that combines response and remission

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Background

All studies in the depression initiative have the same design. There are four administration points ($T_1 \ldots T_4$) after baseline (T_0) with three months intervals between time points.

The basic dependent variable was the PHQ-9, and remission and response were defined in terms of this variable. Response was defined as a 50% decrease in the value of the PHQ-9 compared to baseline, remission was defined as a PHQ-9 score less than 5. Since patients with a PHQ-9 < 10 at baseline where excluded from the trial, remission could not occur at baseline and remission at any later administration point involves response by definition.

Note that *first* remission/response observed at some administration point indicates that the patient is in remission or responds to treatment at that point in time or before but not earlier than at the previous time point.

From a substantial point of view, remission indicates full recovery of a patient while response but no remission indicates a more moderate recovery. To obtain a plausible composite score which combines remission and response but favours remission and which enables to compare development over time between treatment groups, the following scoring scheme was used:

1: First remission at T_1 (three months);
2: First remission at T_2 (six months);
3: First remission at T_3 (nine months);
4: First remission at T_4 (twelve months);
5: No remission during the observation period but first response at T_1 (three months);
6: No remission, but first response at T_2 (six months);
7: No remission, but first response at T_3 (nine months);
8: No remission, but first response at T_4 (twelve months);
9: No response during the observation period.

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The resulting score was labeled **remres** since it combines remission and response.

Note that this 9-point score consists of three parts: (i) scores which apply when patients are in remission (1–4), (ii) scores which apply patients respond (5–8), and (iii) a score (9) which indicates that a patient did not respond during the observation period. In the model, three dummy variables (**inremission**, **response** and **noresponse**) are used to indicate in which part of the trajectory a patient's score is situated.

Multilevel models

Two multilevel models were used.
The first one is a logistic multilevel model with **noresponse** as a dependent variable. It provides information on possible different response rates in the two treatment groups. For instance, in the primary care trial, the fixed part of this logistic multilevel model was[1]:

$$\begin{aligned} \text{noresponse} &\sim \text{Binomial}(\text{denom}, \pi) \\ \text{logit}(\pi) &= 0.454(0.293) - 0.176(0.761)\text{propensity} \\ &\quad -0.379(0.444)\text{CC-screened} - 0.421(0.425)\text{CC-GP}. \end{aligned} \tag{1}$$

Numbers in parentheses indicate standard errors. Standardized parameter estimates are normally distributed. For instance, the standardized estimate for the screened CC group is $\frac{0.379}{0.444} < 1.96$ and is therefore not significant at $\alpha = 0.05$-level.

The second multilevel model that is used, is a linear model in which **remres** is the dependent variable. For instance, for the primary care study, the following multilevel model was fitted:

$$\begin{aligned} \text{remres} &\sim N(XB, \Omega) \\ \text{remres} &= 9.006(0.110) - 0.153(0.244)\text{propensity} \\ &\quad +0.136(0.168)\text{CC-screened} - 0.151(0.161)\text{CC-GP} \\ &\quad -6.858(0.211)\text{inremission} - 2.545(0.239)\text{response} \\ &\quad -0.428(0.301)\text{CC-screened} \times \text{inremission} - 0.365(0.274)\text{CC-GP} \times \text{inremission} \\ &\quad -1.137(0.344)\text{CC-screened} \times \text{response} + 0.093(0.329)\text{CC-GP} \times \text{response}. \end{aligned} \tag{2}$$

Remarks:

1. By including in the model the dummy variables **inremission** and **response** and their interaction with the treatment groups we can estimate the contributions to the remission and response trajectories of **remres** separately.
2. the constant term is the estimate of the **noresponse** category in the CAU group. The estimates for **inremission** (-6.858) and **response** (-2.545) are the offsets for patients in remission and patients who respond compared to patients in the **noresponse** group.

[1] For clarity the random part of the multilevel model is left out, since it is not relevant for the discussion.

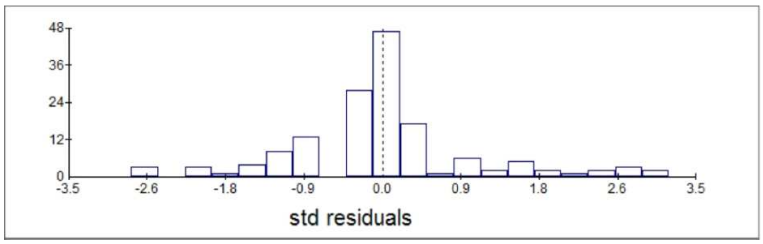

Figure 1: Distribution of the standardised residuals in the Collaborative Care trial in primary care.

3. Only the term CC-screened $\times$ response has a significant (negative) parameter estimate indicating that patients in the screened treatment group have their first response earlier than patients in the care-as-usual group.

It is now possible to calculate the estimated **remres** scores in the individual treatment groups from model (2). We restrict the calculation to the significant interaction term in the response trajectory:

$$\begin{aligned}
\text{CAU} &= 9.006 - 2.545 \\
&= 6.461 \\
&\approx 3 \times (6.461 - 4) \\
&\approx 7.383\text{months} \\
\text{CC-screened} &= 9.006 + 0.136 - 2.545 - 1.137 \\
&= 5.460 \\
&\approx 3 \times (5.460 - 4) \\
&\approx 4.38\text{months}.
\end{aligned}$$

In sum, in this example the screened Collaborative Care group responds $7.383 - 4.380 = 3.003$ months earlier than the Care-as-usual group.

Caveat

It may be argued that **remres** is an ordinal variable which should be modelled with an ordinal regression model, but since the time lags between observation points are equal (three months), **remres** can be considered to have ratio schale measurement level on the separate remission and response trajectories of the score. But an additional check on the distribution of the residuals is necessary to make sure the normality assumption of a linear regression model is defendable.

The distribution of the standardised residuals is given in Figure 1. There seems no reason to question the applicability of the linear model.

As Rasbash, Steele, Browne, and Goldstein (2009, Chapter 11) state, ordered category scales are often analysed using a linear regression model. However, they offer

alternative modelling strategies when it is questionable if the dependent variable can be modelled as a linear scale. We only mention the first one here, which is based on Darlington (1997). In this approach, the dependent variable (in our case **remres**) is transformed to Normal scores. To each response category, this transformatipon assigns the value from the inverse of the standard (0,1) Normal cumulatieve distribution for the estimated proportion of patients from the response variable's original distribution. The multilevel program `MLwiN` (Version 2.10), provides a command **NSCO** that performs this transformation.

In cases in which the residuals of the linear multilevel model are clearly not normally distributed, we wil use this transformation and use the resulting model to assess treatment effects on first response.

Conclusion

The newly defined composite score offers an informative way to combine the states of remission and response based on a basic linear dependent variable with which disease severity can be reliably be assessed.

As an outcome in a clinical trials in which groups have to be compared, the administration point at which a patient first responds, be it by reaching full recovery (remission) or considerable reduction in disease severity is relevant to measure effectiveness.

If the time points at which measurements are taken are not equaly spaced as in the present example, coding of the variable **remres** should be properly weighted to be able to apply a linear model.

As we saw, if the distribution of the residuals in the linear model is clearly not normal, special provisions should be made.

References

Darlington, R. (1997). *Transforming a variable to a normal distribution or other specified shape.* Available from `http://comp9.psych.cornell.edu/Darlington/transfrm.htm` (Retrieved 21st June 2003)

Rasbash, J., Steele, F., Browne, W. J., & Goldstein, H. (2009). A user's guide to MLwiN. version 2.10 [Computer software manual]. University of Bristol, UK: Centre for Multilevel Modelling.