

APPENDIX: SOFTWARE

Cox proportional hazards regression for recurrent events was performed in STATA with the *stcox* procedure. Before this procedure can be used, first the survival nature of the data must be defined. This is done by the procedure *stset*.

```
stset weeks, id(patient_number) failure(success) time0('start of time period')
stcox therapy1 therapy2, robust
```

GEE-analysis was also performed in STATA with the procedure *xtgee*.

```
xtgee success therapy1 therapy2 time, i(patient_number) fam(binomial)
link(logit)
corr(unspecified)
robust
```

Random coefficient analysis on the other hand was performed in MLwiN. Although syntax can be used to perform a random coefficient analysis in MLwiN, it is highly recommended to use the menu options. Within MLwiN, there are several estimation procedures available to analyse recurrent event data, but it is recommended to use a so-called 'second order penalised quasi likelihood' estimation procedure.[22]

Although in the present paper, MLwiN is used, a random coefficient analysis of recurrent event data is also possible in STATA with the 'generalised linear and latent mixed models' (*gllamm*) procedure.[23] Although the *gllamm* procedure is very flexible, it has some disadvantages: 1) It is not available in the standard package, but it should be downloaded from the internet. 2) it is very time consuming, and 3) it is difficult to use for non experienced users.

```
gen con=1
eq int:con
eq slope:time
gllamm success therapy1 therapy2 time, i(id) fam(binomial) link(logit) nrf(2)
eqs(int slope) nip(12)
adapt
```

All three longitudinal techniques discussed in the present paper can also be performed within SAS. Cox proportional hazards regression for recurrent events can be performed with the PROCEDURE PHREG, while GEE-analysis can be performed with the PROCEDURE GENMOD. Random coefficient analysis for recurrent event data can be performed with the PROCEDURE NLMIXED. [24]

22 Goldstein H, Rasbash J. Improved approximation for multilevel models with binary responses. *J Royal Stat Soc* 1996;**159**:505-513.

23 Rabe-Hesketh S, Skrondal A, Pickles A. *GLLAMM Manual*. U.C. Berkeley Division of Biostatistics Working Paper Series (paper 160) [<http://www.bpress.com/ucbbiostat/paper160>], 2004.

24 SAS Institute Inc. *SAS/STAT software: changes and enhancements through release 6.12*. Cary, NC: SAS Institute Inc, 1997.