4.3 METHODOLOGICAL LIMITATIONS

While the studies presented in this dissertation certainly add to the existing literature, there remain some important limitations with regard to the methodologies applied.

Difficulties in observational studies

Cross-sectional design

In an effort to shed more light on the associations between cognitive functioning and HRQOL in LGG patients (chapter 2.1), a cross-sectional study design was applied. HRQOL in significant others of patients with brain tumors versus partners of patients with tumors outside the central nervous system (chapter 3.1) was also investigated cross-sectionally. Therefore, it was not possible to assess changes over time in the outcome measures; cognitive performance and HRQOL. In addition, causal relationships could not be examined. Applying a longitudinal study design in future efforts is therefore recommended.

Selected group of participants

The participants included in the study described in chapter 2.1 were all in a stable disease phase as defined by radiological and clinical observations. The selection of a specific subgroup of glioma patients hinders the generalizability of results. It is unclear if these findings apply to LGG patients in general, or if this is specific for patients who are in a stable disease phase. Moreover, the associations between cognitive functioning and HRQOL may be very different in HGG patients, as these patients seldom experience prolonged periods of stable disease.

A similar methodological limitation plays a role in chapter 3.1. The LGG and HGG patients of whom the significant others participated in this study, were in a stable disease phase or recently diagnosed, respectively. These groups are again selected and therefore, it is difficult to make any statement on the HRQOL of significant others per se. Therefore, it is advised that future studies aim to include study participants that represent a less selected group of glioma patients and/or their significant others.

Comparability of study populations

In the study on HRQOL in informal caregivers (chapter 3.1), there remain some issues regarding the comparability of the study populations. Although two groups of significant others of glioma patients (i.e., LGG and HGG partner samples) were presented in chapter 3.1, no statistical comparisons between these groups were made. The considerations for making this choice were that – because statistical comparison of the neuro-oncology partner samples was not appropriate – providing information on both samples in one chapter would lead to a greater understanding of the underlying concept, i.e., HRQOL in glioma patients’ informal caregivers. If chapter 3.1 had been restricted to a report on solely LGG and NHL/CLL caregivers, the conclusions would have been different, which does not do justice to the underlying problems. However, presenting the unrelated groups together in one report might be confusing to readers scanning chapter 3.1 for the main findings. The data used in chapter 3.1 were collected as part of a larger study, which
focused on two distinct groups of glioma patients (stable LGG patients and HGG patients in the acute disease phase) and their significant others. This contributes to the restricted comparability of the different study samples included in the chapter. In future studies, focus on informal caregiver’s HRQOL throughout the disease course of the patient is therefore recommended.

**Defining change in HRQOL**

In chapter 2.2, differences in HRQOL between LGG patients and healthy controls were presented alongside statistically significant change in HRQOL at group level and minimal detectable change in HRQOL at the individual patient level in a longitudinal sample. This makes it possible to evaluate whether HRQOL differs between patients and controls, as well as to evaluate the probability that change within the group occurred by random variation, and if changes found are larger than the measurement error of the instrument. Although valuable, these approaches may not directly reflect meaningful change (i.e., “change that results in a meaningful reduction of symptoms or improvement in function”274). Therefore, the methods applied in chapter 2.2 may not adequately reflect participants’ own view of whether their HRQOL has changed over time. A combination of distribution-based and anchor-based methods is therefore usually recommended.147, 274 Furthermore, when interpreting results from studies focusing on change in HRQOL, it is important to keep in mind the methods applied to determine change over time, as this can lead to different cut-off points and conclusions.

**Difficulties in intervention studies**

*Participation and retention rates*

Chapters 2.3, 2.4 and 3.2 are reports of randomized controlled trials. The study on the effect of modafinil on symptoms of fatigue (chapter 2.3) and the informal caregiver intervention study (chapter 3.2) both yielded relatively small sample sizes (N=37 and N=56, respectively). Although the internet-based intervention described in chapter 2.4 is still a work in progress, the recruitment of participants is slower than anticipated. After 32 months of patient inclusion, the glioma patient sample consists of two thirds the required sample size in this nation-wide study. Moreover, the informal caregiver intervention study (chapter 3.2) in particular had a high attrition rate (43%) which may be related to the longer period of follow-up: eight months in this intervention versus twelve weeks in the modafinil study (attrition 32%) (chapter 2.3).

These relatively small sample sizes and high attrition rates, given the high prevalence of symptoms of fatigue, anxiety and depression and high caregiver burden, were surprising and indicate that the identification of barriers and facilitators of patient and informal caregiver participation is essential. A previous report on informal caregiving in the palliative care setting indicated that those caregivers experiencing relatively low levels of distress are less inclined to participate in interventions.305 In addition, those who were younger, more familiar with social and professional support, or whose loved one was treated at the same facility where the intervention took place, were more likely to participate.305 In an observational longitudinal study among brain tumor patients and their caregivers, demographic characteristics (e.g. age, gender, educational
level, marital status) and patient characteristics (cognitive status, severity of symptoms, tumor type) did not appear to influence participation in the study. Throughout the study, younger caregivers, with a higher educational level, of whom the patients had better cognitive functioning were less likely to drop out, indicating that higher burden can influence the willingness to continue participation in observational studies. Furthermore, recruiting brain tumor patients and their informal caregivers shortly after diagnosis can hamper participation rates, as the most frequently reported reasons for non-participation were that eligible participants felt overwhelmed and stressed. Instead of focusing on barriers to and facilitators of participation, the needs and preferences in support opportunities can also be investigated, as was recently done in a North-American study. On group level, most interest was expressed in education about the disease and the potential negative cognitive effects of treatment, whereas subgroups of patients and informal caregivers showed very high interest in specific brief supportive interventions. Means to identify members of these subgroups remain, however, undetermined.

As often suggested, it seems worthwhile to routinely screen both patients and informal caregivers for HRQOL issues and distress, as well as the wish for supportive care. Patients or informal caregivers at risk can then be identified (chapter 1.2). When initiating intervention studies in these vulnerable groups, it is pivotal to prepare a randomized controlled trial by first performing a pilot study. This will provide insight into the prevalence and magnitude of the problems experienced by patients or informal caregivers, the experienced need for an intervention, and the barriers to and facilitators of participation. After pilot testing, realistic power calculations can be performed and a tailored recruitment procedure can be started.

**Dealing with missing data and dropout**

In the informal caregiver intervention study (chapter 3.2), an eight month follow-up period was scheduled, but not all participants completed all assessments due to dropout (43%). In order to analyze the follow-up data, we used the last observation carried forward technique. With this technique, the value of the last available assessment is used for each missing value afterwards (it is therefore ‘carried forward’), which implies the assumption that the score remains stable from the point of dropout until trial completion. As this is consistent with our null hypothesis, we felt confident in using this method. However, this technique evidently has its downsides, especially when missing values are unevenly distributed across the intervention group and the control group. It could lead to an overestimation of the effect of the intervention, for example, if the outcome measure is expected to show regression towards the mean with multiple assessments and if there are more missing values in the control group than in the intervention group. In the caregiver intervention study, there were more missing data in the intervention group, leading us to conclude that in this case, last observation carried forward was indeed a conservative approach.

In those who retain in the intervention studies, not all assessments were completed throughout follow-up (chapters 2.3 and 3.2). Given the high symptom and caregiver burden of our target population, this is not surprising. Various methods for dealing with missing data are available. However, all these methods have implications for the interpretation of the results. In chapter 3.2, we chose not to impute missing data from incomplete assessments. In
chapter 2.3, we used mean imputation, replacing missing values from incomplete self-reported assessments and neuropsychological assessments with the mean of observed values for that variable. Although not changing the mean for that variable, using this method can distort the variables’ distribution, leading to an underestimation of the standard deviation. Moreover, mean imputation can have consequences for correlations between variables, as in those cases with imputation, there will be no relationship between the imputed variable (which is not as reported by the participant) and other measured variables (which are reported by the participant).307

To summarize, each method for dealing with missing values has its advantages and disadvantages. Imputed data are never as good as fully completed assessments. The participants, whether they be patients or caregivers, suffer from high burden, and much of the attrition and missing data can be attributed to the additional burden of participating in (intervention) studies. Therefore, it is worthwhile to decrease this burden - after all, these intervention studies were initiated to help the participants, rather than to cause further burden. It is recommended to reduce the length of assessments as much as possible. If short versions of questionnaires are available and have adequate psychometric properties, these should always be chosen over the longer version. Moreover, a member of the research team could help complete the questionnaires during a routine visit to the clinic or through a telephone interview. This way, participants are supported during the completion of the assessment, and missing values can be avoided as much as possible.