Randomized Trial of a Supportive Psychotherapy for Parents of Adolescents and Young Adults With Hematologic Malignancies

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ABSTRACT

Background: Cancer regularly disrupts health and developmental trajectories in adolescents and young adults (AYAs). Parents have been shown to have a substantial impact on the health and cancer survivorship activities of AYA patients in the form of symptom management. However, no randomized controlled trial has evaluated a coping support intervention (CSI) program for parents of AYAs with cancer aged 18 to 40 years. Patients and Methods: From November 30, 2012, to August 29, 2016, parents of AYAs with hematologic malignancies were randomized in a phase III controlled trial (1:1 ratio, stratified sampling) to either the research-based CSI AYA-Parents group (CSI group; n = 82) or the standard care (SC) group (n = 70). CSI consisted of 5 sessions to achieve the enhancement of parental adaptive coping as the primary outcome (per the adaptive coping scale of the 28-item Brief COPE, a validated multidimensional self-assessment-questionnaire recommended for clinical cancer research). Measures of adaptive coping, depression, and mental health were collected at pre-COI (measurement date T1), at the end of the intervention sessions (measurement date T2), and at follow-up (3 months). We calculated mean change scores in outcomes and estimated intervention effect sizes (Cohen’s d) for changes from T1 to T2/T3, with 0.2 indicating a small effect, 0.5 a medium effect, and 0.8 a large effect. All statistical tests were 2-sided. Results: In the intention-to-treat analysis, the CSI group significantly improved their adaptive coping compared with the SC group (95% CI, 0.30–2.54; P = .013; d = 0.405), whereas adaptive coping in the SC group deteriorated. The CSI group also experienced a significant decrease in depressive symptoms and improved mental health with clinical significance (95% CI, –1.98 to –0.30; P = .008; d = 0.433, and 95% CI, –0.19 to 3.97; P = .074; d = 0.292, respectively). Sensitivity analyses confirmed the robustness of the main intention-to-treat analysis. Conclusions: CSI improved effectively adaptive coping and depression in parents of AYAs with hematologic malignancies. It may represent a novel family-based approach in AYA oncology care.

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Background
Cancer in adolescents and young adults (AYAs; ages 15–40 years) leaves unique health and social disruptions in patients and their families for many years of survivorship even after completing successful cancer therapy.1–4 As vital key providers for several levels of care and support, parents of AYAs with cancer are “the unsung heroes” in these trying situations.6 With the onset of illness and treatment, a shift toward greater dependence on parents and healthcare providers occurs, and the tendency for many parents to become overly protective may interfere with normal psychosocial AYA development.4–7 Parents reassure their earlier parental roles, almost independent of the actual age of a child who has become an AYA patient with cancer. On the one hand, parents’ role changes in caring for an adult child with cancer.3–8 On the other hand, parents provide complex care at home (eg, symptom management, treatment monitoring, ensuring adequate nutrition and physical activity), maintain their child’s financial autonomy, and are both navigators for a complex and fragmented healthcare system and faithful companions in cancer therapy.2–21 Remarkably, the renewed reappearance of coping strategies and conflicts between parents and their adult child after cancer diagnosis happens regardless of the child’s age.4–7,16–20 In one study, almost 42% of children with cancer and their parents reported frequent conflicts about a variety of issues related to the illness.

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parents of AYA patients scored above a clinical cutoff score indicating posttraumatic stress symptoms, and nearly one-third reported moderate to severely elevated symptoms of anxiety and depression.16

In recent years, dramatic improvements in survival rates of patients with hematologic malignancies have been achieved through the introduction of molecular and personalized treatment approaches.22–27 Even so, AYAs with cancer have not, in general, attained the same improvements in overall survival as younger children or older adults.1 Currently, the care of AYAs with cancer under standard oncology care is seldom tailored to the specific needs of this particular patient population, tends to be incomplete and limited, and does not represent integrated medical care.4,5,9 There is a strong need for personalized AYA treatment and prevention approaches, and researchers and clinicians are just beginning to develop specific AYA health services.1,2,9,16 Recognizing and understanding AYA patients and their parents as primary caregivers as a functional coping dyad or an intertwined “psychological system” has essential clinical implications for effective cancer management, patient functioning, and cancer survivorship.3–20

AYA patients’ and parents’ beliefs about the illness’s severity may not be based on clinical indicators often used by healthcare professionals. Overall, most patients’ and caregivers’ illness perceptions are not associated with risk prognosis, healthcare utilization, or treatment-related expenses.20,28 As parents are experiencing high levels of distress, feelings of guilt, and personal accountability, maladaptive coping and numerous time-consuming demands may negatively affect their own physical and mental health, and this in turn may negatively affect the health outcomes of AYA patients.2,7,16,20,29,30 Parents’ self-reported concepts of cancer and treatment (such as a self-reported theory on the causal attribution) may sometimes lead to irrational or maladaptive coping with their child’s cancer situation.6,7,16,20,28 However, no randomized controlled trial (RCT) has evaluated a psychosocial oncologic intervention program for parents of a child with cancer aged 18 to 40 years.2,7–21,31–34

We hypothesized that parents of AYAs with cancer who receive caregiver-centered special consultation in the setting of standard adult oncology care would have enhanced adaptive coping capabilities compared with parents who only receive standard care (SC). We evaluated changes in the rates of depressive symptoms and mental health as secondary clinical endpoints.

**Patients and Methods**

From November 30, 2012, to August 29, 2016, we enrolled mothers and fathers of AYAs with hematologic malignancies in a nonblinded, phase III RCT of the CSI AYA-Parents research-based coping support intervention (CSI group) compared with the SC group alone. The study was performed in accordance with the International Conference on Harmonization-Good Clinical Practice guidelines and preregistered on the German Clinical Trials Register (ID: DRKS0000425; UTN: U1111-1132-8011). The trial was planned and supervised based on process-oriented quality management (DIN ISO 9001) with the following implementations: process monitoring, data monitoring, data protection regulation, study protocol, failure management, accredited advanced training for oncologists and psychotherapists, and audible standard operating procedures. The protocol, including the statistical analysis plan, was approved by the ethics committee of the Otto-von-Guericke University, Magdeburg, Germany. All authors guarantee the completeness and accuracy of the data and attest to the fidelity of the trial with the protocol.

**Study Participants**

Eligibility criteria included parents of a child with a clinical diagnosis of a hematologic malignancy (initial manifestation between ages 15 and 40 years) with acute care or follow-up care after cancer treatment; an ECOG performance status of 0, 1, or 2; study inclusion between ages 18 and 40 years; and ability to comprehend, read, and respond to questions in German. Patients in a palliative care setting or on strongly sedating substances were ineligible for participation in the study.

**Screening and Randomization**

The developmental needs of AYAs with cancer along with changes that their families specifically experience are often a unique challenge in recruitment into and adherence to a clinical trial.2–15,36–39 Our research strategy was elaborated according to so-called pragmatic clinical trials for patients with rare cancers and included as a key principle the maximization of the usefulness of the data gathered in the trial (eg, to prevent missing data; see supplemental eAppendix 1, pages 9–10, available with this article at JNCCN.org).36–40 Pragmatic trials can emulate real-world experiences in the application of study findings with an increased external validity (generalizability in the real world).30,41 For example, we implemented this approach through high-frequency and personal onsite communication, the creation of a research network (the German Study Group AYA Cancer Network), and the foundation of the first regional patient advocacy group for AYAs with cancer.

Study participants were recruited via the cancer care situation of their children with cancer. Research staff queried the electronic health record documentation to identify potentially eligible patients and obtained permission from oncologists to approach patients at their upcoming clinic visits. We performed 2-tier recruitment by ad hoc
recruitment and systematic database queries to ensure homogeneous sampling (see supplemental eAppendix 1, pages 9–10). AYA patients were approached regardless of whether their parents were with them in the clinic. When parents were not present, AYA patients were asked to approach their parents to get in contact with the investigators. Parents who met prescreening criteria underwent an in-person evaluation and baseline assessment. Eligible participants were randomly assigned in a 1:1 ratio after enrollment using the minimization method of Pocock and Simon (randomization via Randomization in Treatment Arms [RITA] software, StatSol) as a highly effective allocation method42,43 with the stratification of parental emotional distress-coping (2 stages; measured using the Distress Thermometer, cutoff ≥4),44 treatment status (2 stages; present acute cancer treatment vs no treatment), and family situation (2 stages; single-parent vs 2-parent family). Outcome assessors were unaware of the group assignments.

Test Procedures
The Computer-Based Health Evaluation System (CHES)45,46 was applied using self-assessment questionnaires and 2 external assessments at 4 measurement dates: T0 (baseline), T1 (pretreatment), T2 (posttreatment), and T3 (follow-up, at most 3 months after T0).

Intervention
Successful coping strategies develop based not only on objective but also on self-reported evaluation mechanisms. Coping with illness is generally modulated by patients’ subjective theories of illness (STOI),6,7,16–20,28 STOI are defined as the cognitive constructions that people with illness make regarding (1) the nature of their disease, (2) its source, and (3) its treatment.28 We assumed that maladaptive coping results from maladaptive STOI. For example, there is excessive strain on a daughter (age 28 years, Hodgkin lymphoma) as an integral part of the mother’s STOI regarding the source of the daughter’s cancer. As a result, the mother behaves in an overprotective manner. The mother shows “love” with anxiety and fails to honor the daughter’s boundaries (physical, emotional, social, and psychological boundaries). Thus, she provokes both further serious conflicts with the young adult daughter striving for autonomy and further problems in the daughter’s cancer survivorship. For example, the daughter engages in emotional eating in response to these negative effects and conflicts, leading to grade 3 obesity.16–20,28,47,48

CSI AYA-Parents was a 5-session 1-on-1 therapy employing a supportive-psychodynamic approach.21,28–34,49 As in other supportive-psychoanalytic approaches, the central elements were (1) the support of psycho-oncologic information processing, (2) the reflection and modification of the parents’ STOI and the individual coping strategies for dealing with cancer situation, and (3) the reflection and verbalization of role changes within the family system and changes in the relationship to the child with cancer (see supplemental eAppendix 1, pages 6–7).21–46 The primary therapeutic focus of the intervention was parental self-support. CSI AYA-Parents consisted of the following elements:

- Communication of objective information relevant to cancer and cancer treatment using information from recognized cancer counseling services. By using verified information, we achieved standardization of the basic information.
- Verbalization of self-reported illness concepts regarding the nature of the illness and nature of the treatment, self-reported attribution of causes and prognosis estimation, and cognitive-affective evaluation and modification.
- Development of individual (especially functional) aspects of coping with illness and clarification of approaches for the development of problem-oriented strategies.
- Considering the effects of the current illness situation on the parent–patient relationship from the point of view of the developmental psychosocial situation of the AYA patients and pointing out change options taking into account the emotional coping with the illness. The fifth treatment session was conducted together with the parents and their AYA patients in order to deeply assess changed relationship aspects and their effects on subjective regulation based on the cancer diagnosis.

Based on extensive preliminary work and given the research desiderata, CSI AYA-Parents was developed and clinically tested with parents of AYAs with hematologic malignancies between 2009 and 2011 within the outpatient supportive care clinic at the University Hospital of Magdeburg.28,31 The 5 sessions were offered once weekly. One treating psychotherapist was trained and supervised by 3 experienced psychotherapists/physicians. To assure treatment integrity, the treating psychotherapist presented each participant at 2 time points under individual supervision (after the first session with M. Koehler and before the fourth session with J. Frommer and H.H. Flechtn). Parents of AYA patients randomly assigned to the SC group were not invited to a special counseling session unless a standard of care consultation was requested by the AYA patient, parent, or oncologist (“as usual”). However, this situation was never encountered in our clinical trial. All SC parent–child dyads continued to receive routine oncologic care throughout the study period without any special counseling.
Evaluation Strategy for the Primary Endpoint
As the primary outcome, we defined the change score using the adaptive coping (AC) scale of the 28-item Brief COPE instrument (change in AC score from T1 to T2), a validated multidimensional self-assessment questionnaire recommended for clinical cancer research that assesses 14 coping strategies using conceptually different subscales with 2 items per scale (internal consistency, $\alpha=0.58$).\textsuperscript{50} Scores on the AC scale range from 4 to 32; higher scores indicate more frequent use of AC strategies. To achieve clinical validity and adequate reliability, the construction of the AC scale followed a research-based 3-step evaluation strategy (see supplemental eAppendix 1, page 4). The resultant AC scale used 8 items with 4 subscales (use of emotional support, active coping, use of instrumental support, and planning; Table 1).

Secondary Endpoints
Depressive symptoms were measured using the Patient Health Questionnaire-9 (PHQ-9; internal consistency, $\alpha=0.88$) per the DSM-IV criteria.\textsuperscript{51,52} Validated for clinical cancer research, total severity scores according to the PHQ-9 range from 0 to 27, with a higher score indicating worse depressive symptoms. The PHQ-9, scored as a continuous measure, has performed well in identifying minor depressive disorder in patients and is considered a valid screening instrument (cutoff score of $\geq5$ in identifying minor depressive disorder).\textsuperscript{51,52} We defined the change of the PHQ-9 score from T1 to T2 as a secondary outcome.

Mental health was recorded using the 36-Item Short-Form Health Survey (SF-36),\textsuperscript{53,54} a compact, reliably developed, and well-tested instrument with an international standardized implementation (internal consistency, $\alpha=0.70$). This 36-item instrument assesses 8 dimensions separated as summary scores in physical health and mental health (mental component score [MCS]), with higher total scores indicating better quality of life. Scores range from 0 to 100; higher scores indicate better mental health. We defined the change of the MCS score from T1 to T2 as a secondary outcome.

Parental emotional distress/coping was measured as a stratified variable with the use of the Distress Thermometer as a 1-item-scale (2 stages; cutoff $\geq4$).\textsuperscript{44} The Distress Thermometer is a compact, reliably developed, valid instrument for screening family members of patients with cancer for clinically significant distress in the form of symptoms of depression and anxiety (construct validity, $r$ of 0.65–0.69; discriminative validity, area under the curve of 0.81–0.85). Participants were asked to rate how distressed they felt in the previous week on a single-item scale ranging from 0 (not distressed) to 10 (extremely distressed).

Statistical Analysis
The primary endpoint was the change score of the AC scale from T1 to T2. Secondary endpoints included an evaluation of the change of depression and mental health scores from pretreatment to posttreatment (T1 to T2), and the effect sizes. All analyses were performed on an intention-to-treat (ITT) basis. We followed the rules and checklist of the CONSORT statement and used the 4-point ITT analysis strategy for trials with incomplete outcome data according to White et al.\textsuperscript{55} Parents in the same household were considered as individual participants in the randomization. We had to maximize the recruitment by including mothers and fathers in the same household. This broadening of eligibility criteria had to be balanced against the possibility of dilution of the treatment effect.\textsuperscript{39} However, with this decision we achieved an increase in external validity (generalizability to the real world). If we had strictly focused on maximizing internal validity and ignored external validity, we would have had to focus strictly on recruiting mothers.\textsuperscript{40,41} Randomized participants were included in the ITT analyses, if T2 data assessment of these participants was completed disregarding intervention-related protocol

| Table 1. AC Scale With 8 Items and 4 Subscales of the 28-Item Brief COPE$^{50}$ |
|---------------------------------|--------------------------------------------------------------------------------|
| Subscale                        | Items                                                                 |
| Use of emotional support        | I have been getting comfort and understanding from someone             |
|                                 | I have been getting emotional support from others                      |
| Active coping                   | I have been concentrating my efforts on doing something about the situation I’m in |
|                                 | I have been taking action to try to make the situation better          |
| Use of instrumental support     | I have been trying to get advice or help from other people about what to do |
|                                 | I have been getting help and advice from other people                  |
| Planning                        | I have been trying to come up with a strategy about what to do          |
|                                 | I have been thinking hard about what steps to take                      |

Abbreviation: AC, adaptive coping.
deviations in the CSI group (90% of participants with 5 sessions). Due to CHES-based assessment, all questionnaire sets were completed (assessment completion rates of 100%). Because of the low proportion of withdrawal by parents or refusal to participate (<5%), we omitted these participants from the dataset (listwise deletion). We performed sensitivity analyses (eg, using methods based on multiple imputations or likelihood-based methods, including intrafamily correlation) to explore the impact of possible departures (parental sex, participants as a parent couple) from the assumptions made in the main ITT analysis. Concerning the outcome data, the statistical significance was tested at a significance level of .05 using 2-tailed independent t tests.

Baseline data were compared using Pearson chi-square tests or 2-tailed independent t tests. Effects of potential covariates were examined using univariate analyses of variance (ANOVs). We calculated mean change scores in outcomes and estimated intervention effect sizes (Cohen’s d and dcov as the corrected effect size per Klauser and Phye, considering baseline mean differences and differences in standard deviation, representing a more conservative method compared with Cohen’s d), with 0.2 indicating a small effect, 0.5 a medium effect, and 0.8 a large effect. As additional measures of clinical benefit, we calculated the number needed to treat, the risk difference, and the binomial effect size display.

With 146 participants, we estimated that the study would have 80% power at a one-tailed alpha level of 0.025 to detect a significant between-group difference in the change in AC score from pretreatment (T1) to posttreatment (T2) with an effect size of g=0.47. All data analyses were conducted using SPSS Statistics, version 24 (IBM Corp), and SAS 9.4 (SAS Institute Inc).

Results
Between November 30, 2012, and August 29, 2016, our study enrolled 106 families of AYAs with cancer and 182 parents; 29 parents declined to participate (Figure 1), resulting in a total of 153 parental caregivers recruited for assessment and randomization.

Patient- and disease-related characteristics were distributed equally between the study groups (Tables 2 and 3). There were no significant differences in baseline demographic variables or the primary and secondary outcomes between participants who completed the trial and those who did not. Despite randomization, we found significant between-group differences indicating higher distress in the CSI group related to distress level. Of note, 53.5% of participants in the SC group and 75.6% of participants in the CSI group indicated high-level emotional distress as measured with the Distress Thermometer (Table 3). Two-factor ANOVAs did not reveal any main or interaction effect of the baseline distress level on each outcome measure. Thus, no further subgroup analyses were necessary.

Primary Outcome
The comparison of the change score of the AC scale from T1 to T2 (Table 4, Figure 2A) showed that the parents assigned to CSI AYA-Parents had significantly increased scores than did those assigned to the SC group (P=.013; d=0.405). Using the corrected effect size dcov per Klauser and Phye, we achieved a robust clinically significant improvement of AC in the CSI group (dcov=0.345).

Participants in the CSI group had a clinically relevant AC improvement of 10.74% in contrast to the SC group, whose AC deteriorated (~0.61%). In other words, parents in the CSI group used statistically significant more instrumental support or emotional support compared with the SC group. The sensitivity analysis for exploring significant group differences of AC scores at T1 (pretreatment) revealed a significant influence of the T1 AC scores on the outcome scores at posttreatment; the effect of group assignment remained significantly detectable.

An analysis of clinical benefits (Table 5) revealed a significantly higher proportion of parents showing an AC increase in the CSI group compared with the SC group (P<.001), documenting a clinically significant improvement (d=0.698). Table 5 shows that using CSI AYA-Parents lowered the risk of maladaptive coping by 28% (binomial effect size display; Figure 3A). In other words, 28 out of 100 parents of an AYA with cancer were spared maladaptive coping if they were assigned to the CSI program.

The 4 sensitivity analyses for exploring the impact of possible departures from the assumption confirmed the robustness of the main ITT analysis (P=.032; intra-class correlation coefficients =0.348; Table 6).

In addition, Figure 4 shows the secondary evaluation of the mean change scores between the 2 study arms from pretreatment to follow-up (T1–T3; T3 completers, n=142) with a clinically but not statistically significant AC improvement for the parents assigned to CSI AYA-Parents (dcov=0.24). However, the follow-up analysis was less robust because of the expected loss of participants and therefore the loss of power.

Secondary Outcomes
Depression
The evaluation of the depressive symptoms (PHQ-9 change score) from T1 to T2 (Table 4, Figure 2B) showed that the parents assigned to the CSI group had significantly decreased scores compared with those assigned to SC (P=.008; d=0.433). Analysis of clinical benefits indicated a
significantly higher proportion of parents showing a depressive symptom decrease in the CSI group compared with the SC group ($P<.006$; Table 5), documenting a clinically significant improvement ($d=0.517$). Using CSI AYA-Parents, we achieved a clear reduction in the risk difference of the proportion of clinically relevant depression between the 2 study arms from pretreatment (30%) to posttreatment (13%; Table 5, Figure 3B).

**Mental Health**

The evaluation of mental health (SF-36 MCS change score) from T1 to T2 (Table 4, Figure 2C) showed that the
parents assigned to CSI AYA-Parents had clinically significant increased scores compared with those assigned to SC ($P=.07; \, d=0.292$).

**Discussion**

In this RCT, we found that a research-based CSI (CSI AYA-Parents) for parents of AYAs with hematologic malignancies was effective in enhancing parents’ AC and depressive symptoms. In addition, there was a trend toward improvement in mental health. In follow-up analyses, we found no significant between-group differences in effect, except for a significant improvement in depression in the intervention group compared with the control group ($P=.04; \, d_{Cohens'=0.35; \, d_{Carr}=0.22}$). However, the follow-up analyses were less reliable because of the expected loss of n and therefore the loss of power. Thus, further studies should be conducted that are powered to detect changes in

<table>
<thead>
<tr>
<th>Strata variables</th>
<th>SC Group n (%)</th>
<th>CSI Group n (%)</th>
<th>$P$ Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total, n</td>
<td>71</td>
<td>82</td>
<td></td>
</tr>
<tr>
<td>AYA treatment status</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>In active treatment</td>
<td>15 (21)</td>
<td>25 (31)</td>
<td>.19</td>
</tr>
<tr>
<td>Status posttreatment</td>
<td>56 (79)</td>
<td>57 (70)</td>
<td></td>
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<tr>
<td>Family situation</td>
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<tr>
<td>One-parent family</td>
<td>4 (6)</td>
<td>9 (11)</td>
<td>.24</td>
</tr>
<tr>
<td>Two-parent family</td>
<td>67 (94)</td>
<td>73 (89)</td>
<td></td>
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<tr>
<td>Parental distress levelb</td>
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<tr>
<td>Low (&lt;4)</td>
<td>33 (47)</td>
<td>20 (24)</td>
<td>.004</td>
</tr>
<tr>
<td>High (≥4)</td>
<td>38 (54)</td>
<td>62 (76)</td>
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</tr>
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<tr>
<td>Mean age [SD], y</td>
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<td>29.7 [6.8]</td>
<td>.58</td>
</tr>
<tr>
<td>Female sex</td>
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<td>36 (44)</td>
<td>.62</td>
</tr>
<tr>
<td>Diagnosis</td>
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<tr>
<td>Acute leukemia</td>
<td>24 (39)</td>
<td>28 (34)</td>
<td>.96</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>42 (59)</td>
<td>49 (60)</td>
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<tr>
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<td>2 (2)</td>
<td></td>
</tr>
<tr>
<td>MPN</td>
<td>2 (3)</td>
<td>3 (4)</td>
<td></td>
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<tr>
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<td>62.8 [45.0]</td>
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</tr>
<tr>
<td>ECOG performance statusc</td>
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<tr>
<td>0</td>
<td>55 (78)</td>
<td>52 (63)</td>
<td>.10</td>
</tr>
<tr>
<td>1</td>
<td>11 (16)</td>
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<td></td>
</tr>
<tr>
<td>2</td>
<td>5 (7)</td>
<td>5 (6)</td>
<td></td>
</tr>
</tbody>
</table>

The pattern of between-group baseline data comparisons was not affected by dropout and persisted across all analyzed populations (baseline completers, T1 completers, T2 completers; see also Figure 1 and Table 3 for further details, including dropout analysis). Sum of percentages may slightly differ from 100 due to rounding. Abbreviations: AYA, adolescent/young adult; CSI, coping support intervention; MPN, myeloproliferative neoplasm; SC, standard care; T1, pretreatment; T2, posttreatment.

*P values derive from between-group comparisons (from either the independent t test for time data or the chi-square test for categorical data).

**Distress level was evaluated using the Distress Thermometer score with a cutoff point of ≥4 indicating clinically relevant distress.**

**An ECOG performance status of 0 indicates that the patient is asymptomatic, a status of 1 indicates that the patient is symptomatic but fully ambulatory, and a status of 2 indicates that the patient is ambulatory and capable of all self-care but is unable to carry out any work activities; the patient is awake for >50% of waking hours.**
longer-term follow-up. Although families of AYAs with cancer are confronted with high rates of mental and psychosocial concerns, the results of this trial indicate that they benefit from a supportive-psychodynamic and family-based approach in AYA oncology care.

Table 3. Pattern of Between-Group Differences of Baseline Characteristics in Dependence on Dropout

<table>
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<tr>
<th>Strata variables</th>
<th>SC Group (n=71)</th>
<th>CSI Group (n=82)</th>
<th>P Value*</th>
<th>SC Group (n=70)</th>
<th>CSI Group (n=82)</th>
<th>P Value*</th>
<th>SC Group (n=69)</th>
<th>CSI Group (n=77)</th>
<th>P Value*</th>
<th>SC Group (n=67)</th>
<th>CSI Group (n=75)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>In active treatment</td>
<td>15 (21.1)</td>
<td>25 (30.5)</td>
<td>.14</td>
<td>14 (20)</td>
<td>25 (30.5)</td>
<td>.13</td>
<td>18 (24.6)</td>
<td>21 (27.3)</td>
<td>.11</td>
<td>16 (23.9)</td>
<td>20 (26.7)</td>
<td>.14</td>
</tr>
<tr>
<td>After end of treatment</td>
<td>56 (78.9)</td>
<td>57 (69.5)</td>
<td>.25</td>
<td>56 (80)</td>
<td>57 (69.5)</td>
<td>.56</td>
<td>58 (81.2)</td>
<td>56 (72.7)</td>
<td>.56</td>
<td>58 (83.6)</td>
<td>55 (73.3)</td>
<td>.25</td>
</tr>
<tr>
<td>Family situation</td>
<td>.24</td>
<td>.25</td>
<td>.31</td>
<td>.17</td>
<td>.24</td>
<td>.25</td>
<td>.31</td>
<td>.17</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-parent family</td>
<td>4 (5.6)</td>
<td>9 (11.0)</td>
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<td>4 (5.7)</td>
<td>9 (10.9)</td>
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<td>4 (5.8)</td>
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<td>.64</td>
<td>67 (95.5)</td>
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<td>.003</td>
<td>.006</td>
<td>.005</td>
<td>.004</td>
<td>.003</td>
<td>.006</td>
<td>.005</td>
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<td>67 (85.6)</td>
<td>.36</td>
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<td>67 (85.3)</td>
<td>.34</td>
<td>33 (50.7)</td>
<td>67 (85.3)</td>
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<td>.74</td>
<td>.74</td>
<td>.73</td>
<td>.73</td>
<td>.74</td>
<td>.74</td>
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<td></td>
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</tr>
<tr>
<td>In remission</td>
<td>1 (1.4)</td>
<td>1 (1.2)</td>
<td>.73</td>
<td>1 (1.4)</td>
<td>1 (1.2)</td>
<td>1 (1.45)</td>
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</tr>
<tr>
<td>In active treatment</td>
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<td>1 (1.2)</td>
<td>.73</td>
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<td>1 (1.2)</td>
<td>1 (1.45)</td>
<td>1 (1.3)</td>
<td>1 (1.5)</td>
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<td>.67</td>
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<td>Cancer history</td>
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<td>.73</td>
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<td>.74</td>
<td>.74</td>
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<tr>
<td>In remission</td>
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<td>1 (1.2)</td>
<td>.73</td>
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<td>1 (1.45)</td>
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<tr>
<td>In active treatment</td>
<td>1 (1.4)</td>
<td>1 (1.2)</td>
<td>.73</td>
<td>1 (1.4)</td>
<td>1 (1.2)</td>
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<td>1 (1.3)</td>
<td>1 (1.5)</td>
<td>1.3</td>
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<tr>
<td>No cancer</td>
<td>69 (97.2)</td>
<td>81 (98.8)</td>
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<td>68 (97.2)</td>
<td>81 (98.8)</td>
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<td>67 (97.1)</td>
<td>74 (98.7)</td>
<td>.65</td>
<td>69 (97.0)</td>
<td>74 (98.7)</td>
<td>.73</td>
</tr>
</tbody>
</table>

To reduce the risk of bias due to dropout, we investigated the significance levels between-group differences of baseline characteristics and dropout rates at each measurement time. The pattern of differences was not affected in terms of shifts in significance levels. Abbreviations: AYA, adolescent/young adult; CSI, coping support intervention; MPN, myeloproliferative neoplasm; PS, performance status; SC, standard care; T0, follow-up.

*Two-tailed P values derive from either the chi-square test (categorical data) or the t test (metric data).
bSum of percentage may slightly differ from 100 due to rounding.
cParental emotional distress-coping (2 stages; measured with the use of the Distress Thermometer, cutoff $\geq 4$).

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*Two-tailed P values derive from either the chi-square test (categorical data) or the t test (metric data).
**Sum of percentage may slightly differ from 100 due to rounding.
**Parental emotional distress-coping (2 stages; measured with the use of the Distress Thermometer, cutoff $\geq 4$).

**An ECOG performance status of 0 indicates that the patient is asymptomatic, a status of 1 indicates that the patient is symptomatic but fully ambulatory, and a status of 2 indicates that the patient is ambulatory and capable of all self-care but is unable to carry out any work activities; the patient is awake for >50% of waking hours.
A psycho-oncologic intervention can effectively improve mental health in parents of AYAs with hematologic malignancies. In a short-term study, 65.4% of parents of AYA patients (75.6% of patients in the CSI group vs 53.5% of participants in the SC group) reported Distress Thermometer scores within a clinically significant range. Two-factor ANOVAs did not reveal any main or interaction effect of the baseline distress level on each outcome measure. However, we hypothesize that the 5 inherent treatment building blocks that constitute evidence-based practice led to enhanced AC and mental health parameters. However, the mechanisms behind the therapeutic change in participants’ subjective conceptions and coping skills (mind and behavior) remain less understood and necessitate future investigations. Along these lines, note that the treatment response observed was influenced by the recruitment of a highly affected study population. We found that 65.4% of parents of AYA patients (75.6% of participants in the CSI group vs 53.5% of participants in the SC group) reported Distress Thermometer scores within a clinically significant range. Two-factor ANOVAs did not reveal any main or interaction effect of the baseline distress level on each outcome measure. However, compared with other patient age groups and peer control groups, AYAs with cancer are highly vulnerable to long-term medical and psychosocial complications, are often more dependent on parents, and are more likely to fill antidepressant prescriptions.2,15,59-61 On the other hand, parents have significant potential to positively or negatively impact their child’s adjustment to daily demands and survivorship activities post cancer therapy.2,4,16-20,62 However, no clinical trial has shown the efficacy of an intervention program in reducing rates of depression and enhancing AC and mental health in this specific population. Thus, this study adds to the pediatric and adult cancer care literature by showing that a short-term psycho-oncologic intervention can effectively improve mental health in parents of AYAs with hematologic malignancies.

The CSI AYA-Parents protocol focused on a supportive-psychoanalytic approach for changing problematic behaviors, feelings, and thoughts by disclosing parents’ (occasionally unconscious) meanings and motivations.49
we believe that using the minimization method of Pocock and Simon is a very suitable configuration with regard to typical quality criteria and with regard to the high level of distress in the study population. Minimization as a highly effective allocation method is recommended for wider adoption in the conduct of RCTs.42–43

The construction of the AC scale followed a research-based 3-step evaluation strategy in our study. We achieved clinical validity and adequate reliability with the AC scale. However, the interpretation of an AC composite score is an area of debate. According to the current literature, a research-based calculation of composite subscales or a selection of coping strategies is a valid strategy.63–66

Our phase III RCT has a number of strengths: a 4-point AYA-Parents recruitment and data strategy according to recommendations for research methods to change clinical practice for patients with rare cancers (see supplemental eAppendix 1, pages 9–10)36–41; representative, homogeneous sampling with inclusion of mothers and fathers (with 36.6% fathers) for which we obtained a high agreement with family responsibility realities; <5% withdrawal rate of participants for the primary outcome analysis; and assessment completion rates of 100%. The study was planned and supervised based on standardized, process-oriented quality management (DIN ISO 9001) and was adequately powered to detect relevant changes in both AC and mental health. Compared with recruitment rates of approximately 10% in other cancer clinical trials in an AYA setting, the recruitment of 23% supports the credibility of the results obtained.36–37

However, we also acknowledge the limitations of this study. First, this RCT was conducted by a specialized team. This particular setting may limit the generalization of the results to other care settings or parents of AYAs with other types of cancer. Second, participants were aware of their randomized intervention assignment. This awareness may have initiated biases in the treatment courses and trial results. Third, parents in the same household were considered as individual participants in the randomization. We allowed both parents to be included based on practical recruitment considerations. The developmental needs of AYAs with cancer along with changes that families of AYAs with cancer specifically experience are often a unique challenge to recruitment into a clinical trial and adherence to the trial.2–15,36–39 Our research strategy was elaborated according to so-called pragmatic clinical trials for patients with rare cancers and included as a key principle the maximization of the usefulness of the data gathered in the trial. Despite their strengths, RCTs have substantial limitations. Although they can have strong internal validity, RCTs sometimes lack external validity (generalizability in the real world); generalizations of findings outside the study population may be invalid.40,41 So-called pragmatic trials require that participants are similar to patients who would receive the intervention if it became usual care, which may be unknown for new interventions.40,41 Notably, the number of parents in the same household was distributed equally between the study groups (20 pairs of parents in the CSI group, 19 pairs of parents in the SC group). In addition to these 39 pairs of parents who were randomized into the same study arm, 8 pairs of parents from one

Figure 2. Evaluation of change scores between the 2 study arms from pretreatment to posttreatment (T1 to T2). We used the ratio of T2/T1 to illustrate the change. The change score represents the relative change between the pretreatment and the posttreatment value. A ratio of >0 means a symptomatic increase and a ratio <0 means a symptomatic decrease. Using the study group as the independent variable, 2-sided independent t tests showed significant between-group differences in the mean change of the (A) AC score (1.01 ± 4.2 in the CSI group vs −0.40 ± 2.6 in the SC group; difference between groups: 1.42; 95% CI, 0.30–2.54; P = .01; d_Cohen’s = 0.405; d_Corr = 0.345) and the (B) PHQ-9 score (−0.70 ± 3.1 in the CSI group vs 0.44 ± 1.9 in the SC group; difference between groups: −1.14; 95% CI, −1.98 to −0.30; P = .008; d_Cohen’s = 0.433; d_Corr = 0.419). A clinically significant change was observed between group differences in the (C) MCS score (1.19 ± 7.7 in the CSI group vs −0.70 ± 4.8 in the SC group; difference between groups: 1.89; 95% CI, −0.19 to 3.97; P = .07; d_Cohen’s = 0.292; d_Corr = 0.194). Data derive from all parents who completed the T2 assessment (CSI group: n = 77; SC group: n = 69). Error bars indicate 95% confidence intervals.

Abbreviations: AC, adaptive coping; CSI, coping support intervention; MCS, mental component summary; PHQ-9, Patient Health Questionnaire-9; SC, standard care; SF-36, 36-Item Short-Form Health Survey; T1, pretreatment; T2, posttreatment.
Table 5. Measures of Clinical Benefit

<table>
<thead>
<tr>
<th>Measure</th>
<th>SC Group n (%)</th>
<th>CSI Group n (%)</th>
<th>P Value</th>
<th>Between-Group Difference Effect Sizes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>BESD</td>
</tr>
<tr>
<td>Total</td>
<td>69</td>
<td>77</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AC score change T1–T2</td>
<td></td>
<td></td>
<td>&lt;.001</td>
<td>28%</td>
</tr>
<tr>
<td>Increase</td>
<td>18 (26)</td>
<td>42 (55)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stable/Decrease</td>
<td>51 (74)</td>
<td>35 (46)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PHQ-9 score change T1–T2</td>
<td></td>
<td></td>
<td>.006</td>
<td>22%</td>
</tr>
<tr>
<td>Decrease</td>
<td>17 (24)</td>
<td>36 (47)</td>
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</tr>
<tr>
<td>Stable/Increase</td>
<td>52 (75)</td>
<td>41 (53)</td>
<td></td>
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</tr>
<tr>
<td>PHQ-9 score ≥ 5 at T1</td>
<td></td>
<td></td>
<td>&lt;.001</td>
<td>30%</td>
</tr>
<tr>
<td>Any depression</td>
<td>18 (26)</td>
<td>43 (56)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No depression</td>
<td>51 (74)</td>
<td>34 (44)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PHQ-9 score ≥ 5 at T2</td>
<td></td>
<td></td>
<td>.12</td>
<td>13%</td>
</tr>
<tr>
<td>Any depression</td>
<td>26 (38)</td>
<td>39 (51)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No depression</td>
<td>43 (62)</td>
<td>38 (49)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PHQ-9 score impact change T1–T2</td>
<td></td>
<td></td>
<td>.05</td>
<td>23%</td>
</tr>
<tr>
<td>Any depression (score ≥ 5) at T1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased to &lt; 5</td>
<td>0</td>
<td>10 (23)</td>
<td></td>
<td>23%</td>
</tr>
<tr>
<td>Stable high</td>
<td>18 (100)</td>
<td>33 (77)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No depression (score &lt; 5) at T1</td>
<td></td>
<td></td>
<td>.81</td>
<td>–2%</td>
</tr>
<tr>
<td>Stable low</td>
<td>43 (84)</td>
<td>28 (82)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased to ≥ 5</td>
<td>8 (16)</td>
<td>6 (18)</td>
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</table>

We used the ratio of T2/T1 to illustrate the mean change. The change score represents the relative change between the pretreatment and the posttreatment value. A ratio of >1 means a symptomatic increase and a ratio <1 means a symptomatic decrease. For the PHQ-9, we also present results using a cutoff score of ≥5 indicating any depression (including minor depressive disorder up to severe major depression). Sum of percentages may slightly differ from 100 due to rounding.

Abbreviations: AC, adaptive coping; BESD, binomial effect size display; CSI, coping support intervention; SC, standard care; NNT, number needed to treat; PHQ-9, Patient Health Questionnaire-9; T1, pretreatment; T2, posttreatment.

*P values derive from chi-square test.

The BESD means the between-group difference in the success rate from pre- to posttreatment data assessment. It ranges from −100% (eg, 0% success rate in the CSI group minus 100% in the SC group) to 100% (eg, 100% success rate in the CSI group minus 0% in the SC group); positive values indicate a benefit for the CSI group and negative values indicate a benefit for the SC group. Values are rounded to the nearest whole number.

Risk difference means the between-group difference in the proportion of a specified outcome (clinically relevant depressive symptoms) at 1 measurement time. It ranges between −100% (eg, 0% with any depression in the CSI group minus 100% with any depression in the SC group) and 100% (eg, 100% with any depression in the CSI group minus 0% in the SC group). Positive values indicate a higher proportion in the CSI group and negative values indicate a higher proportion in the SC group. Values are rounded to the nearest whole number.

For dichotomous data, Cohen’s d was estimated by means of point-biserial correlations. According to the conventional standards, Cohen’s d ≥ 0.20 indicates a small effect, ≥ 0.50 indicates a moderate effect, and ≥ 0.80 indicates a strong effect.

The NNT is a measure of effect size that illustrates the number of participants who needed to be treated to achieve the desired outcome. Figures given are rounded to the nearest whole number.

The AC score change from T1 to T2 indicated a significant benefit for the CSI group (P < .001). We observed 28% more participants with increased AC in the CSI group compared with the SC group. Cohen’s d indicates a medium to strong clinical benefit. Only 4 participants needed to be treated to achieve 1 more desired outcome in the CSI group than in the SC group.

The PHQ-9 score change from T1 to T2 also indicated a significant benefit for the CSI group (P = .006). We observed 22% more participants with decreased depressive symptoms. The effect size indicates a medium to strong clinical benefit. To achieve symptom reduction in 1 participant more in the CSI group than in the SC group, 5 parents needed to be treated.

In accordance with the score-based results, at T1 we found a significantly higher percentage of parents with any depression in the CSI group (56% vs 26%; P < .001). This risk difference was reduced clearly (from 30% to 13%) through the CSI performed. As a result, at T2, the proportion of parents with any depression did not differ significantly.

In terms of impact change, 2 subgroups were analyzed. In the group of parents with any depression at T1, we found a significant benefit for the CSI group at T2. Ten parents showed a clinically relevant decrease in symptoms at T2, and in the SC group none of the parents with any depression at T1 showed a clinically relevant symptom reduction at T2. The effect size of this benefit can be estimated as being in the small to medium range. Five parents with any depression needed to be treated to achieve 1 more participant with clinically relevant symptom reduction in the CSI group than in the SC group. In the group of parents not found to be depressed initially, the number of parents with a clinically relevant increase in depressive symptoms (to a score ∼5) did not differ significantly between the CSI and SC group.

Use of CSI AYA-Parents lowered the risk of maladaptive coping by 28% (BESD). For comparison, taking aspirin lowers the risk of a heart attack by 0.3% (BESD); in other words, 3 out of 1,000 people will be spared heart attacks if they consume aspirin on a regular basis. The NNT was 333 to prevent a myocardial infarction, meaning that 333 patients were needed in the treatment group to obtain at least 1 additional favorable outcome.

Using CSI AYA-Parents lowered the risk of depression by 23% (BESD). In other words, 23 out of 100 parents of an AYA with cancer would be spared depression if they received CSI AYA-Parents.

household were randomized into different study arms. If we had strictly focused on maximizing internal validity and ignored external validity, then recruiting and reaching the necessary sample size would have failed. Our efforts were intended to ensure transparency in study methods, provide standardized data collection for key outcomes, and use new approaches to improve data synthesis. However, with our study design presented here is the potential to replicate real-world experiences in application of our findings.
Fourth, parents of AYAs with cancer are a special population of caregivers, and CSI AYA-Parents is a caregiver-centered special consultation in the setting of standard adult oncology care. On the one hand, we can conclude that AC is an outcome of direct clinical relevance.\textsuperscript{16–21,28–34} Family caregivers have psychosocial needs that must be addressed so that they can maintain their own health and provide the best care possible to the patient.\textsuperscript{20} Caregivers are an important part of the cancer care team, and their well-being can be associated with patient-perceived quality of care.\textsuperscript{37} On the other hand, emotional support coping by the patient can be associated with higher family caregiver depression and anxiety.\textsuperscript{50} Fifth, a critical point in the terminology of AYA cancer research and an acknowledged limitation of our study is the wide age range represented by a heterogeneous real-life population of patients and caregivers.

Table 6. Sensitivity Analyses Confirmed the Robustness of the Main Intention-to-Treat Analysis

<table>
<thead>
<tr>
<th>Sensitivity Analysis</th>
<th>Statistical Method and Possible Departures</th>
<th>P Value</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Multiple imputations of measurements for T2 from measurements of T1 and the gender of the parent (mother/father)</td>
<td>(P=.020)</td>
<td>The between-group comparison confirmed a significant difference in favor of the intervention arm</td>
</tr>
<tr>
<td>2</td>
<td>Mixed model with random intercept (including taking into account the intrafamily correlation and the parents as couple)</td>
<td>(P=.016; \text{ICC}=0.348)</td>
<td>The between-group comparison confirmed a significant difference in favor of the intervention arm</td>
</tr>
<tr>
<td>3</td>
<td>Combination of sensitivity analyses 1 and 2</td>
<td>(P=.032; \text{ICC}=0.349)</td>
<td>The between-group comparison confirmed a significant difference in favor of the intervention arm</td>
</tr>
<tr>
<td>4</td>
<td>Mixed model for repeated measurements with 2 random effects: study participants as a parent couple, every study participant</td>
<td>(P=.019)</td>
<td>The between-group comparison confirmed a significant difference in favor of the intervention arm</td>
</tr>
</tbody>
</table>

All between-group comparisons confirmed significant differences in favor of the intervention arm (\(P \leq .032\)). The consideration of parent pair formation in the analyses showed hardly any influence on the overall study result (\(\text{ICC}=0.348, P=.016\)). Abbreviation: ICC, intraclass correlation coefficients.
On the one hand, significant role changes occur when parents support adult children with cancer. However, the impact of cancer on AYA patient functioning, mental health, and psychosocial outcomes should account for the developmental stage or changes at which cancer disrupts these young people’s reality. On the other hand, AYAs diagnosed with cancer often mentally regress and trust parental care again, they may experience a renewed emotional and practical dependence on their parents. At baseline, 27% of the children with cancer in our study (mean [SD] age, 29.94 [6.3] years) lived with their parents in a household. We assume that the actual age of the adult children plays less of a role than, for example, the parent–child relationship. We should not equate AYAs without cancer with AYAs with cancer in terms of psychosocial developmental dynamics; it would be fatal to not acknowledge the disruptive psychosocial changes that young adults have undergone after cancer in coping with everyday life.

**Conclusions**

This investigator-initiated trial broke new ground as the first RCT focusing on supportive care for parents of AYAs with cancer. We implemented strictly research-based methodical criteria with regard to the development and execution of the intervention, recruitment and data strategy, quality management, and primary outcome analysis. However, we were shaken by the reality of AYA families. Nearly 65 months post cancer diagnosis, 65.4% of parents of AYA patients were confronted with a wide heterogeneity of physical, emotional, and household concerns and a need for psycho-oncologic treatment.

In addition to providing research-based methodical criteria, we also applied many features of so-called pragmatic trials. Thus, patients, clinicians, clinical practices, and clinical settings were recruited as in the real world to maximize the overall transfer of the results of this trial to common practice.

Further studies with a tailored AYA research strategy are clearly warranted. Furthermore, we recommend the evaluation of a psycho-oncologic intervention program for parents of AYAs with nonhematologic malignancies. Further investigations are needed to explore intrafamily health associations and the potential pathways that link these factors. Engaging family caregivers as part of the cancer care team through ongoing psycho-oncologic risk stratification screening and personalized support interventions may improve different patient-reported outcomes in AYA cancer treatment.

**Figure 4.** Evaluation of the mean change in outcome scores between the 2 study arms from pretreatment to follow-up (T1 to T3). Using the study group as the independent variable, 2-sided independent t tests showed clinically significant but no statistically significant between-group differences in the mean change of the (A) AC score (0.47 ± 4.1 in the CSI group vs –0.45 ± 3.1 in the SC group; difference between groups: 0.91; 95% CI, –0.28 to 2.11; P=.13; dCohen’s=0.25; dCorr=0.24) and the (B) MCS score (–1.00 ± 7.5 in the CSI group vs 0.06 ± 6.1 in the SC group; difference between groups: 1.06; 95% CI, –1.22 to 3.33; P=.36; dCohen’s=0.15; dCorr=0.14). (C) The analysis of the depressive symptoms (PHQ-9 change score) from T1 to T3 showed that parents assigned to CSI AYA-Parents had significantly decreased scores compared with those assigned to SC, with an effect size in the small to medium range (–0.60 ± 2.8 in the CSI group vs 0.30 ± 2.3 in the SC group; difference between groups: –0.90; 95% CI, –1.78 to –0.04; P=.04; dCohen’s=0.35; dCorr=0.22). Data derive from all parents who completed the T3 assessment (CSI group: n=75; SC group: n=67). Error bars indicate 95% confidence intervals and standard error.

Abbreviations: AC, adaptive coping; AYA, adolescent/young adult patient; CSI, coping support intervention; MCS, mental component summary; PHQ-9, Patient Health Questionnaire-9; SC, standard care; T1, pretreatment; T3, follow-up.
be helpful in reducing the heavy psychological burden of families concerned.

Acknowledgments
Medical writing assistance was provided by John Bean, PhD, Bean Medical Writing, Halle, Belgium, and was funded by Otto-von-Guericke University, Magdeburg, Germany. We thank the parents and their children—our patients—who participated in the study, along with the staff and investigators at the participating study sites.

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**Randomized Trial of a Supportive Psychotherapy for Parents of Adolescents and Young Adults With Hematologic Malignancies**

Michael Koehler, PhD; Susanne Hoppe, MSc; Siegfried Kropf, PhD; Anke Lux, MSc; Rainer Bartsch, MSc; Bernhard Holzner, PhD; Juergen Krauter, MD; Axel Florschütz, MD; Kathleen Jentsch-Ullrich, MD; Joerg Frommer, MD; Hans-Henning Flechtner, MD; and Thomas Fischer, MD


**eAppendix 1:** Study Protocol  
**eAppendix 2:** Form AYA-PARENTS 2012 for AYA Network Partners  
**eAppendix 3:** Participant Entry Form AYA-PARENTS 2012  
**eAppendix 4:** Case Report Form AYA-PARENTS 2012  
**eAppendix 5:** Information Sheet for Participants  
**eAppendix 6:** Informed Consent Form AYA-PARENTS 2012  
**eAppendix 7:** Cooperation Contract for AYA Network Partners  
**eAppendix 8:** Positive Vote of the Ethics Committee
eAppendix 1. Study Protocol

The following protocol information* is provided solely to describe how the authors conducted the research underlying the published report associated with this article.

I. BACKGROUND

Cancer in adolescence and young adulthood (AYA) leaves unique health and social disruptions in patients and their families for many years of survivorship even after completing successful cancer therapy [1]. In this hazardous situation parents of AYA with cancer often become key providers for several levels of care and support. At the same time parental caregivers show psychological distress similar to their child in terms of anxiety, depression and maladaptive coping strategies [2-5], which may persist over years [6,7].

In recent years, dramatic improvements in survival of hematologic malignancies were achieved by the introduction of molecular and personalized treatment approaches [8,9,10]. However, in general, AYA with cancer have not attained the same improvements in overall survival as younger children or older adults [11]. At present, the care of AYA cancer patients in standard adult oncology care is often not tailored to the specific needs of this particular patient population, tends to be incomplete, limited and does not represent integrated medical care. There is a strong need for personalized AYA treatment and prevention approaches. We are at the beginning of the development of specific AYA health services [10]. Recognition and understanding AYA patients and their parents as primary caregivers as a functional coping dyad or an intertwined ‘psychological system’ has essential clinical implications for effective cancer management and patient functioning. Although parents receive little support or any equipment to perform their essential roles, their intrinsic motivation for a successful coping with the cancer situation is always their child’s survivorship. However, this is frequently associated with feelings of guilt and personal accountability [12-14,15]. Curiously, despite the abundance of research on parenting in the pediatric cancer situation, there are little research-based data available concerning parenting for AYA with cancer [15,16].

Experiencing high levels of distress, maladaptive coping and multiple time-consuming demands may negatively affect parent’s own physical and mental health, and this in turn may negatively affect AYA patient’s health outcomes [15,17]. Parents’ subjective concepts of cancer and treatment (like the subjective theory on the causal attribution) may lead to sometimes irrational or maladaptive coping with everyday life and with their child’s cancer situation [12-14,18]. However, to the best of our knowledge, so far there is no RCT-evaluated psycho-oncologic intervention program for AYA parents.

II STUDY OBJECTIVES

A. Primary Objective

The primary objective of the study is the evaluation of a coping support intervention (CSI) compared to standard care (SC) for parental caregivers of AYA patients suffering from...
hematological malignancies. We hypothesize that parents who received caregiver-centered special consultation in the setting of standard adult oncology as compared with parents who received standard care alone care show an enhancement of adaptive coping (AC) at the post-intervention assessment.

B. Secondary objectives

The secondary objective investigates furthermore the differential effects of group assignment on depressive symptoms and mental health. We hypothesize that parents who received caregiver-centered special consultation in the setting of standard adult oncology as compared with parents who received standard care alone care show a reduction of depressive symptoms/reduction of identified cases of any depression and an improvement of mental health at the post-intervention assessment.

III. METHOD

A. Study Design

The study is planned as a prospective, nonblinded, phase III randomized, controlled trial, comparing the specific coping support intervention (CSI) to the standard care (SC) alone. The evaluation of the brief intervention will be conducted using data assessed at four measurement dates: t0 (baseline), T1 (pre-treatment), T2 (post-treatment), T3 (follow-up, max. 3 month following t0). The intervention applied with the parents randomized to the CSI group will be conducted by one trained psychologist at the university hospital Magdeburg and the respective cooperative institutions. Outcome assessors will be unaware of group assignments.

Figure 1. Treatment Plan

(continued)
eAppendix 1. Study Protocol (cont.)

B. Study Measures

1. Baseline Data

Baseline data will be assessed at t0 and include demographic information of the child (age, gender, diagnosis, time since diagnosis, ECOQ) and the parent (age, gender, own cancer history) as well as the strata variables:

1) Child’s treatment status (on active treatment vs status post treatment)
2) Family situation (1-parent family vs. 2-parent family)
3) Parental distress level (low vs. high; assessed with use of the Distress Thermometer with a score <4 indicating a low distress level and a score ≥4 indicating a high distress level)

2. Primary Outcome – Adaptive Coping

Coping strategies will be assessed with the Brief COPE Questionnaire [19]. The Brief COPE is a validated multidimensional self-assessment-questionnaire which assesses coping strategies on 14 conceptually different subscales with 2 items per scale. It is one of the most used international coping inventories, which is recommended for clinical cancer research [20,21,22]. The internal consistency and retest reliability of all scales is acceptable to good [19,23]. In addition, a good convergent and discriminant validity is confirmed [19].

The primary outcome is defined as the mean change score on the adaptive coping (AC) scale from T1 to T2 (pre- to post-intervention).

To achieve clinical validity and adequate reliability, the construction of AC scale will follow a research-based three-step evaluation strategy [24,25].

- In a first step we will check the reliability of the Brief COPE scales in terms of internal consistency (Cronbach’s alpha), inter-item correlations, and precision of Cronbach’s alpha.

- In a second step we will calculate a confirmatory factor analysis (CFA) to assess AC measurement on the basis of the a-priori defined two-factor-model differentiating between adaptive and less adaptive/maladaptive coping [24,26], and for examination the model quality (data fit) and suitable subscale formation. To evaluate the data fit we calculated three Indices: chi-square/df ratio (≤2 indicating a good, ≤3 indicating a moderate data fit), Comparative-Fit-Index (CFI≥0.97 indicating a good, ≥0.95 indicating a moderate data fit) and Root-Mean-Square-Error of Approximation (RMSEA ≤0.05 indicating a good, ≤0.08 indicating a moderate data fit).

(continued)
In a third step we will carry out the research-based extraction of the subscales [52] incl. examination of the Inter-item correlation matrix for all items. This approach has been used previously with the Brief Cope [19,27,28], is commonly used in previous research and has shown appropriate fit in other studies [25,29].

3. Secondary Outcomes – Depression and mental health

Depressive symptoms will be assessed using the Patient Health Questionnaire-9 (PHQ-9, per the criteria of the Diagnostic and Statistical Manual (fourth edition) [30,31]. Validated for clinical cancer research, total severity score ranges from 0 to 27, with a higher score indicating worse depressive symptoms. The PHQ-9 scored as a continuous measure performed well in identifying minor depressive disorder (MDD) in patients and could be considered as a valid screening instrument ((cut-off score of ≥5 in identifying MDD in cancer patients). Internal consistency is good (Cronbach's Alpha: 0.79). Test-retest reliabilities range from 0.81 to 0.96 [32]. Also, the criterion validity of the PHQ-9 is good [32,33].

Mental health will be recorded with the SF-36 (MOS-36 Item Short Form Health Survey) [31,34]. The SF-36 is a compact, reliably developed and well tested instrument with an international standardized implementation (the International Quality of Life Assessment Project: IQOLA). This 36-item instrument assesses eight dimensions, which are separated as summary scores in physical health and mental health (MCS, mental component score) with higher total scores indicating better QOL.

C. Randomization

Randomization will occur upon the anamnesis of family data and the baseline investigation (t0). Participants will be randomly assigned (randomization via software RITA by StatSol, Lübeck: http://www.statsol.de/rita_ind.html) to one of the two groups (coping support intervention (SCI) group or standard care (SC) group) in a 1:1 ratio with research-based stratification after enrolment. For this the minimization method of Pocock and Simon will be used with stratification of parental emotional distress-coping (2 stages; measured with use of the Distress Thermometer [35], cut-off ≥4), the treatment status (2 stages; present acute cancer treatment vs. no treatment) and family situation (2 stages; single parent vs. two-parent-family). After participants signed the informed consent and received the patient-information, the study administration will proceed as follows:

1) Assignment of a patient-identification number (PID) within the patient list, which will insure confidentiality. This PID will be used for data-communication and data-transfer.

(continued)
eAppendix 1. Study Protocol (cont.)

2) Before the randomization starts, it needs to be assessed if all data of the baseline investigation (t0) are documented.

3) The study administration will conduct the randomization with the software RITA by STatSol Lübeck.

4) After randomization the study administration will inform the participants about the assignment to one of the treatment arms and the following study procedure.

D. Interventions

1. Standard Care (SC)
AYA parents randomly assigned to SC will not be invited to a special counselling unless a standard of care consultation was requested by the AYA patient, the parent, or the oncologist. If needed, amount of counselling will be documented. After completing the follow-up measurement parents will be provided with information about contact points for potential psycho-oncological support needs.

2. Coping Support Intervention (CSI)
Successful coping strategies develop not only based on objective, but also subjective evaluation mechanisms. Coping with illness is generally modulated by patients’ subjective theories of illness (STOI [12-15,18]. STOI are defined as the cognitive constructions ill people make regarding (1) the nature of their disease, (2) its source, and (3) its treatment [18]. We assumed that maladaptive coping results from maladaptive STOI.

Clinical Case Study:
For example, excessive strain on the daughter (28 years old, Hodgkin lymphoma) as an integral part of the mother’s STOI regarding subjective source of the daughter’s cancer. As a result, the mother behaves overprotectively. The overprotective mother demonstrates ‘love’ with anxiety and fails to honor the daughter’s boundaries (physical, emotional, social and psychological boundaries). Thus, she provokes further conflicts with the young adult daughter striving for autonomy as well as further problems in her cancer survivorship [12-18].

The AYA parents who will be assigned to CSI will be invited to special caregiver-centered consultation integrated in a standard of care adult oncology setting.

The 5-session intervention represents a special consultation according to concepts from psychoeducation and psycho-oncologic supportive psychotherapy [36-40], that has been developed and clinically tested with AYA parents since 2009 [41]. The central
elements are the support of psycho-oncological information processing, the reflection and the modification of the subjective theory of illness and the individual coping strategies as well as the reflection and the verbalization of role changes within the family system and changes in the relation to the ill child. The perspective from which the single elements are applied is always based on an empathic therapeutic stance and acknowledges the subjectivity of each participant to enable an adaptive modification of the intervention.

The primary therapeutic focus of the intervention was the parental self-support. CSI AYA-Parents consisted of following elements:

- Communication of objective information relevant to cancer and cancer treatment using information from recognized cancer counselling services. By using verified information, we achieve standardization of the basic information.
- Verbalization of subjective illness concepts to the nature of the illness, nature of the treatment, subjective attribution of causes and prognosis estimation, cognitive-affective evaluation and modification.
- Development of individual, especially functional aspects of coping with illness and clarification of approaches for the development of problem-oriented strategies.
- Reflecting on the effects of the current illness situation on the parent-patient relationship from the point of view of the developmental psychological situation of the AYA patients and pointing out change options taking into account the emotional coping with the illness. The fifth treatment session was carried out together with the mothers or fathers and their AYA patients in order to be able to deeply assess changed relationship aspects and their effects on subjective regulation based on the cancer diagnosis.

CSI AYA-Parents has been developed and clinically tested with AYA parents within the study group. The 5 session were offered once weekly. One psychotherapist (SH) was trained and supervised by three experienced psycho-oncologists and psychodynamic psychotherapists (MK, JF, HHF). In order to assure treatment integrity, psychotherapist presented each participant at two time points in individual supervision (after first session with MK, before fourth session with JF/HHF).

AYA parents randomly assigned to the SC group were not invited to a special counseling unless a standard of care consultation was requested by the AYA patient, parent, or oncologist (‘as usual’). However, this situation was never encountered in our

(continued)
clinical trial. All SC parent-child-dyads continued to receive routine oncologic care throughout the study period.

E. Treatment Integrity
To ensure treatment integrity, following quality management elements from studies regarding psychotherapy are used in accordance with guidelines of the Deutsche Krebshilfe as well as international advices [42]:
1) Training of therapist.
2) Supervision. The study-oriented supervision schema includes 100 supervisions and 400 hours of treatment and is based on rules of the state training for the profession of psychological psychotherapists.
3) Description of therapeutic approach by means of the manual.
4) Psychometric scales will be used to examine the realization of the therapy concept. Therefore, the Helping Alliance Questionnaire [43,44] will be applied at three times during the study as a self-assessment version for participants and an external version for therapists. Two relevant dimensions (contentment with relations and contentment with success) will be measured by two types of helping alliance underlying the questionnaire: subjective experienced support by the therapist and subjective experienced alliance with the therapist concerning the treatment aim.

F. Study Population
1. Inclusion Criteria

Diagnosis
Only parents of patients with systemic hematological malignancies (leukemia, lymphoma, myeloproliferative neoplasm) will be included.

Sex
None. Including mothers and fathers. If both parents will participate, the second parental caregiver will not be included until the study is completed with the first. The order will be set by the parents themselves.

Age of patients
According to the National Cancer Institute’s Adolescent and Young Adult Oncology Progress Review Group [45,46] patients between the 18th and 40th years of age will be included (with initial manifestation between the 15th and 40th year of age).

(continued)
However, there were two main reasons for us to here focus on age 18 - 40 years:

a) Originally, we wanted to carry out this study in cooperation with our colleagues at the children's clinic. However, unfortunately, this cooperation could not be realized.

b) Occasionally, patients under the age of 18 are referred to our department. Thus, initially, we wanted to keep the study open for these families.

Treatment status
We will include parents of patients with acute care or follow-up care after cancer treatment with curative intent. To control for differences in effects on the primary outcome the treatment status will be used as a strata variable.

Performance status
For patients an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2 is required. 0 indicates that the patient is asymptomatic, 1 that the patient is symptomatic but fully ambulatory, and 2 that the patient is ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours.

Communicative skills
Parents and patients have to possess sufficient German language skills and cognitive capabilities to comprehend, read and respond to questions.

2. Exclusion Criteria
Restrictions related to the course of disease. Participants will be excluded from data assessment in case of the death of the child, the transition towards a palliative treatment, the occurrence of a brain organic syndrome or a strongly sedating medication. Every case of dropout or withdrawal for other reasons will be documented.

G. Study Procedures

1. Terms of Participation
AYA patients were approached when their parents were or were not with them in the clinic. When parents were not with them, AYA patients were asked to approach their parents in order to get in contact with the investigators. After a detailed informational discussion based on a standardized fact sheet for participants, each AYA-patient and
eAppendix 1. Study Protocol (cont.)

their parents have to sign an informed consent prior to study inclusion and to data assessment.

2. Recruitment

Successful initialization and management of rare cancer populations such as (parents of) AYA with cancer pose specific problems. The unique developmental needs of AYA with cancer along with changes that AYA cancer families specifically experience can compound the challenges to recruitment and retention in a clinical trial. Thus, strategies and pragmatic solutions to enable some level of evidence-based health care for AYA cancer families were elaborated in pragmatic clinical trials.

Here, we present a 4-point AYA-Parents recruitment and data strategy concerning communication with AYA families and AYA study centers. In the communication with the AYA-families we have to pay specific attention to:

1) Developmental tasks and needs usually resolved during AYA’s and their parents’ stage of life,

2) Perspectives and contrary needs of AYA and their parents,

3) Characteristics and needs of cancer treatment (acute/aftercare) which can be contrary to developmental tasks and needs usually resolved during AYA’s stage of life (e.g., establishing independence and autonomy from parents or powerful others like oncologists/nurses, development of romantic relationships and sexuality), and

4) Rarity of AYA cancer families in health care and clinical trials.

Our research strategy included as key principle the maximization of the usefulness of the data gathered in the trial (e.g. to prevent any missing data).

<p>| Table 1. Limitations of vs. strategies for clinical AYA studies modified according to Burke et al. 2007 |</p>
<table>
<thead>
<tr>
<th>Limitations of clinical AYA studies</th>
<th>Strategies for clinical AYA studies and tools of improvement</th>
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<tr>
<td>• Separation of pediatric versus adult oncology and lack of AYA research networks</td>
<td>• High-frequency cooperation and committed communication between participating clinics in the study group AYA network</td>
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<tr>
<td>• Special age limits and challenging development needs of AYA patients</td>
<td>• Advocate and support clinical trials for an underserved patient population</td>
</tr>
<tr>
<td>• Low incidence of cancer / hardly any prospect of sufficient study case numbers</td>
<td>• Development / initiation of AYA-specific studies</td>
</tr>
<tr>
<td>• Very few clinical trial initiations</td>
<td>• Advanced training for medical professionals on AYA-specific characteristics and support needs</td>
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<tr>
<td>• Hardly any funding for AYA-specific studies</td>
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(continued)
Based on the evaluation of treatment cases per year at the university hospital Magdeburg, there are 90 AYA-patients on average in ambulant or inpatient treatment per year. To ensure a sufficient recruitment for the given time of study, co-operation partners of the AYA-network of the university hospital Magdeburg will be successively included. Recruitment will be performed ad-hoc by medical staff of the respective treatment center accompanied by consecutive systematic register data base queries. All recruitment activities and contacts to possible participants will be documented according to standards of quality and data management.

IV Data Collection

Baseline data and strata variables will be assessed by means of a brief interview following the informed consent discussion and will be computerized by a research assistant in preparation of the randomization.

The self-assessment-questionnaires, which represent the outcome data will be assessed computer-based at four measurement dates: t0 (baseline), T1 (pre-treatment), T2 (post-treatment), T3 (follow-up, maximal 3 months following t0). The items will be presented on tablet computers with touch screen. The core benefits are the simple data import by means of statistic programs, the optimization of data security by saving the data on a central server, as well as the avoidance of any missing data. We assume that the use of a tablet computer will increase the willingness to participate and acceptance of the survey. We will use the software Computer-based Health Evaluation System (CHES), which is a common method in different clinics for clinical routines but also for scientific projects for several years [47-49]. The items were presented on tablet computers with touch screen (Panasonic CF-H1 with docking station). To ensure valid data collection of participants and an unobstructed data transfer from portable tablet computers to data servers for the institute for biometry and medical informatics (medical faculty of Otto-von-Guericke-University Magdeburg) EDP-trials and content-related controls of plausibility will be conducted regularly during the preparation and the assessment phase.

V Data Analysis

A. Sample Size Considerations

We estimate the required sample size on the basis of results from a previous meta-analysis [15], which showed an overall effect size of $g=0.47$ regarding changes in coping efforts during the first 3 months after an intervention. To provide a power of 80% at a one-tailed alpha level of 0.025 we planned to include at least 146 participants. With a reserve of approximately 10% drop-out, there is a final sample size of 160 participants (80 participants per intervention group and control group). Taking into consideration
the possible treatment mortality of AYA-patients [50] and rejection rate of relatives, the recruitment will be completed in approximately four years.

B. Statistical Methodology

All primary and secondary analyses will be conducted on an “intent-to-treat” basis. Participants will be included in the analyses as randomized, if T2 data assessment will be completed disregarding intervention related protocol deviations (less than five sessions) in the CSI group. If necessary, imputation strategies for handling missing data will be chosen due to the character of the problem. Additionally per-protocol analyses as statistical method of pragmatic trials will be made and considered for the discussion in case of deviating results.

Baseline differences between the groups concerning demographic and strata variables will be examined with Pearson’s chi-squared tests for categorical data or two-tailed independent t-tests for time data. If any between group differences in the baseline variables occur, we will investigate their respective specific interactions with the group assignment by means of univariate analysis of variance (ANOVA) with the group assignment as an effect on the outcome scores. Further subgroup analyses might be required at the expense of statistical power.

Concerning the outcome data we define the intervention effect as the difference of mean change from pre- to post-treatment between the SC and the CSI group. For score-based data of the primary (adaptive coping) and secondary (depressive symptoms, mental health) outcome we will conduct two-tailed independent t-test to examine the significance of this between group differences.

We used the ratio of T2/T1 to illustrate the change of outcome values. The change score represents the relative change between the pre-treatment and the post-treatment value. A ratio of > 0 means a symptomatic increase and a ratio < 0 means a symptomatic decrease.

To evaluate the clinical significance of group differences, we calculated the effect sizes $d$ (e.g. $d_{corr}$ as corrected effect size by Klauer considering baseline mean differences as well as differences in standard deviation, representing a more conservative method compared to Cohen’s $d$). According to conventional standards, effect sizes of $d$ equal to 0.20, 0.50, and 0.80 were considered small, medium, and strong, respectively [51]. As additional measures of clinical benefit we calculated 1) the number needed to treat (NNT) as a measure of an effect size which illustrates the number of participants who need to be treated to achieve the desired outcome; 2) the risk difference as a measure of an effect size which represents the actual difference in observed risks in the
eAppendix 1. Study Protocol (cont.)

proportion of a specified treatment outcome (e.g. clinically relevant depressive symptoms) between two groups, and 3) the binomial effect size display (BESD) as a measure of an effect size which demonstrates the increase of success through the treatment.

For the PHQ-9 we use a cut-off score of ≥ 5 indicating any depression (including minor depressive disorder up to severe major depression). This will enable on one hand enable between group comparisons (using Pearson’s chi square test) of the “prevalence” (proportion of parents with any depression with a PHQ-9 score≥5). As effect sizes we will calculate the risk difference, which represents the between-group difference in the proportion of a specified outcome (clinically relevant depressive symptoms) at one measurement time. It ranges between -100% (e.g. 0% with any depression in the CSI group minus 100% with any depression in the SC group) and 100% (e.g. 100% with any depression in the CSI group minus 0% in the SC group). Positive values indicate a higher proportion in the CSI group, negative values higher proportion in the SC group. On the other hand by means of identifying cases of any depression we can investigate the development of initially depressed parents and initially not depressed parents separately from each other. For the group of initially depressed parents we define success as the decrease of depressive symptoms below the cut-off (from PHQ9 score ≥5 at T1 to a PHQ9 score <5 at T2) whereas for the group of initially undepressed parents success means that the PHQ9 score remains below the cut-off (<5 at T1 and T2). For each subgroup we will test the significance of the difference between SC and CSI group using Pearson’s chi square test. To estimate the effect size we will use the binominal effect size display (BESD, see above).

With 146 participants, we estimated the study would have 80% power at a one-tailed alpha level of 0.025 to detect a significant between-group difference in the change in the AC score from baseline to post-treatment with a medium effect size of $g = 0.47$ [15].

All statistical tests were done two-sided at a significance level of 0.05 and at a marginally significance level of 0.10. All data analyses were conducted with the software packages IBM SPSS statistics, version 24 and SAS 9.4.
eAppendix 1. Study Protocol (cont.)

VII Study Limitations

However, we also acknowledge the limitations of this trial. First, this RCT will be carried out by a specialized psychotherapist working in cooperation with a specialized group of hematologists. This particular setting may limit generalization of the results to other care settings or parents of AYA with other types of cancer. Second, participants will be aware of their randomized intervention assignment. This awareness may initiate biases in the treatment courses and trial results. Third, parents of AYA with cancer are a special population of caregivers and CSI AYA-Parents is a caregiver-centered special consultation in the setting of standard adult oncology care.

Additionally according to the international AYA literature the recruitment phase can be seen as a sensitive stage in surveys with AYA-patients and their relatives. Therefore, potential limitations (e.g. missing perception of the disease, insufficient regard for age-specific themes related to the clinical study design) are already considered and attempted to improve with the help of solution approaches [45,46] during the planning phase. Due to the age-specific format and the drop-out implications for the sample size, the project duration amounts four years to realize the scientific aim of the study.

VIII Ethical Considerations

The original study protocol underwent a standardized review process with regard to the adherence to ethical guidelines and received a positive ethics committee vote.

The protocol, including the statistical analysis plan was approved by the ethics committee of the Otto-von-Guericke University, Magdeburg in September 2012, and written informed consent was obtained from all participants (Universal Trial Number, UTN: U1111-1132-8011). All authors guarantee for the completeness and accuracy of the data and attest to the fidelity of the trial with the protocol.

IX References


(continued)

(continued)
45. Adolescent and Young Adult Oncology Progress Review Group. Closing the gap: Research and care imperatives for adolescents and young adults with cancer. Bethesda, MD: Department of Health and Human Services, National Institutes of Health, National Cancer Institute, and the LiveStrong Young Adult Alliance, 2006. (NIH publication no. 06-6067) (http://planning.cancer.gov/disease/AYAO_PRG_Report_2006_FINAL.pdf)
eAppendix 1. Study Protocol (cont.)


eAppendix 2. Form AYA-PARENTS 2012 for AYA Network Partners

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<th>Vermittlungsformular AYA-PARENTS 2012</th>
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<tr>
<td>Für Partner im AYA-Netzwerk des Universitätsklinikums Magdeburg</td>
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Bei Vermittlung eines AYA-Patienten und Angehörigen bitte per FAX an Studiensekretariat
Fax-Nr.: 0391-67-290353

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<tr>
<th>Klinik:</th>
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| Angehörige / Angehöriger wünscht Studenteilnahme | □ ja □ nein |

Klinische Einschlusskriterien AYA-Patient / AYA-Patientin:

a) Akute / chronische hämatologisch maligne Erkrankung (ICD-10-C-Diagnosen) □ ja □ nein

UND / ODER

b) ambulante / stationäre Behandlungssituation □ ja □ nein
c) ECOG Performance Status ≤ 2 □ ja □ nein
d) Patienten 18. – 40. Lebensjahr □ ja □ nein
e) ausreichendes Beherrschen der deutschen Sprache □ ja □ nein
f) ausreichend kognitive Fähigkeiten zum Verständnis von Diagnose und Behandlung □ ja □ nein

Klinische Ausschlusskriterien AYA-Patient / AYA-Patientin:

g) Behandlungsmortalität □ ja □ nein
h) Einnahme von stark sedierenden oder stark psychotrop wirkenden Medikamenten □ ja □ nein
i) hinorganisches Psychosyndrom □ ja □ nein

<table>
<thead>
<tr>
<th>Datum:</th>
<th>Name:</th>
<th>Unterschrift:</th>
</tr>
</thead>
</table>
### Aufnahmebogen AYA-PARENTS 2012

Bei Aufnahme eines AYA-Patienten und Angehörigen bitte ausfüllen.

Im Anschluss: Vergabe der Patienten-Identifikationsnummer und Randomisation.

<table>
<thead>
<tr>
<th>Klinik:</th>
<th>Aktuelle Behandlungssituation:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>☐ Akut-Behandlung ☐ keine Akut-Behandlung</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Angaben zum Patienten:</th>
<th>PID:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name:</td>
<td>Geschlecht: ☐ männlich ☐ weiblich</td>
</tr>
<tr>
<td>Vorname:</td>
<td>Geburtsdatum:</td>
</tr>
<tr>
<td>Tel.-Nr.:</td>
<td>Diagnose:</td>
</tr>
</tbody>
</table>

**Angehörige / Angehöriger wünscht Studienteilnahme** ☐ ja ☐ nein

### Klinische Einschlusskriterien:

<table>
<thead>
<tr>
<th>j) Akute / chronische hämatologisch maligne Erkrankungssituation (ICD-10-C-Diagnosen)</th>
<th>☐ ja ☐ nein</th>
</tr>
</thead>
<tbody>
<tr>
<td>UND / ODER</td>
<td></td>
</tr>
<tr>
<td>k) ambulante / stationäre Behandlungssituation</td>
<td>☐ ja ☐ nein</td>
</tr>
<tr>
<td>l) ECOG Performance Status ≤ 2</td>
<td>☐ ja ☐ nein</td>
</tr>
<tr>
<td>m) Patienten 18. – 40. Lebensjahr</td>
<td>☐ ja ☐ nein</td>
</tr>
<tr>
<td>n) ausreichendes Beherrschen der deutschen Sprache</td>
<td>☐ ja ☐ nein</td>
</tr>
<tr>
<td>o) ausreichend kognitive Fähigkeiten zum Verständnis von Diagnose und Behandlung</td>
<td>☐ ja ☐ nein</td>
</tr>
</tbody>
</table>

### Klinische Ausschlusskriterien:

| p) Behandlungsmortalität | ☐ ja ☐ nein |
| q) Einnahme von stark sedierenden oder stark psychotrop wirkenden Medikamenten | ☐ ja ☐ nein |
| r) hemorganisches Psychosyndrom | ☐ ja ☐ nein |

Studienaufklärung AYA-PARENTS 2012 mit Angehöriger(m) und AYA-Patienten durchgeführt ☐ ja ☐ nein

Informed Consent AYA-PARENTS 2012 bei Angehöriger(m) und AYA-Patienten eingeholt ☐ ja ☐ nein

| Datum: | Name: | Unterschrift: |
### Case Report Form (CRF) AYA-PARENTS 2012 bei Nichtteilnahme / Drop-out

Bei Nichtteilnahme/ Drop-out eines AYA-Patienten und Angehörigen

den CRF bitte im Studienordner (PI-Ordner) hinterlegen

<table>
<thead>
<tr>
<th>Klinik:</th>
<th>Datum:</th>
</tr>
</thead>
</table>

### Angaben zum Patienten:

Patienten-Identifikationsnummer (PID):

#### Was ist der hauptsächliche Grund für die Nicht-Teilnahme oder Drop-Out?

<p>| |</p>
<table>
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<th></th>
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</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>

### Liste der möglichen Gründe:

a) Angehörige(r) / AYA-Patient(in) möchte nicht mehr teilnehmen ohne Angabe von Gründen  
   
   1

b) Angehörige(r) / AYA-Patient(in) fühlt sich seelisch zu belastet aufgrund der Studie  
   
   2

c) Untersucher(in) schätzt Angehörige(n) / AYA-Patient(in) als seelisch zu belastet ein aufgrund der Studie  
   
   3

d) Unangenehm, die ganze Studie kostet zu viel Zeit  
   
   4

e) In der Privatsphäre verletzt fühlen  
   
   5

f) Organisatorische Schwierigkeiten  
   
   6

g) Unbekannt  
   
   7

h) Schwere Krankheit / Tod  
   
   8

i) Andere Gründe, bitte kurz benennen:  
   
   9
Sehr geehrte Angehörige, sehr geehrter Angehöriger,

wir freuen uns, dass wir Ihnen derzeit eine neue Behandlung anbieten können, die erstmals die seelischen Belastungen von nahen Angehörigen unserer jungen Patienten verbessern möchte. Um herauszufinden, ob diese Behandlung tatsächlich wirksam ist, führen wir parallel eine wissenschaftliche Untersuchung durch, bei der wir Ihre Art der Krankheitsbewältigung und Ihre Lebensqualität messen werden. Dieses Projekt wird unterstützt von der Deutschen Krebshilfe e.V.

Wir bitten Sie herzlich, an dieser Untersuchung teilzunehmen. Mit der Teilnahme an unserer Studie werden Sie keine Medikamente einnehmen müssen. Sie werden ebenfalls Ihrem Alltag und Ihren alltäglichen Aufgaben weiterhin vollständig nachgeben können. Wir beschreiben Ihnen auf den folgenden Seiten, was das Studienziel ist und was wir im Einzelnen machen wollen. Natürlich stehen wir Ihnen für Fragen jederzeit gerne zur Verfügung, vor allem auch dann, wenn Sie etwas nicht verstehen.

Die Teilnahme an der Studie ist freiwillig, d.h. Sie sind selbstverständlich frei in Ihrer Entscheidung, daran teilzunehmen. Sie können Ihr Einverständnis jederzeit zurückziehen, ohne dass Ihnen daraus Nachteile entstehen. Insbesondere hat die Teilnahme an der Studie keinen Einfluss auf die onkologische Betreuung Ihres Kindes. Natürlich können Sie auch während der Studie zu jeder Zeit und ohne Angabe von Gründen Ihr Einverständnis widerrufen und die Studie abbrechen. Auch in diesem Fall werden weder für Sie noch für Ihr Kind Nachteile entstehen.

(continued)
**WAS WIR BEREITS WISSEN:**


Aus diesen Gründen haben wir eine aus fünf Behandlungsstunden bestehende psychoonkologische Kurzintervention (KI) für nächste Angehörige von jungen Krebspatienten mit hämatologischen Krebserkrankungen entwickelt.

(continued)
**WAS WIR MIT IHRER HILFE GEMEINSAMER MÖCHTEN:**

Das Ziel unserer Behandlung ist eine Verbesserung ihrer persönlichen Krankheitsbewältigung. Dazu müssen wir messen, wie wirksam die neue Behandlung gegenüber bisherigen Unterstützungsangeboten für nahe Angehörige von jungen Krebspatienten ist.


Für Sie besteht zunächst die Aufgabe darin, zum Zeitpunkt t0 eine einzige Frage zu beantworten. Falls Sie nicht in der Universitätsklinik für Hämatologie und Onkologie Magdeburg behandelt werden, hinterlassen Sie bitte Ihre Telefonnummer und einige persönliche Angaben bei Ihrer behandelnden Ärztin oder behandelnden Arzt, auf dass wir mit Ihnen Kontakt aufnehmen können. Nach unserer gegebenen Studienaufklärung und Ihrem schriftlichen Einverständnis werden wir Ihnen sagen, ob Sie die fünfstündige Behandlung erhalten werden oder ein Beratungsgespräch. Die Entscheidung darüber wird per Zufall gefällt (gelbes R). Das heißt, niemand kann diese Entscheidung beeinflussen. Ganz gleich jedoch, ob Sie die neue Behandlung erhalten werden oder nicht, möchten wir Sie bitten, insgesamt vier Mal (t0, t1, t2, t3) unsere Fragen zu beantworten. Ihre Antworten sind für uns die einzige Möglichkeit herauszufinden, ob die Behandlung wirksam ist.

Abbildung A: Übersicht zum Ablauf der Studie
eAppendix 5. Information Sheet for Participants (From Original Study Protocol pp. 79–83) (cont.)

Damit das auch für die Angehörigen, welche zwar an der Studie teilnehmen werden, aber keine fünfmalige Behandlung bekommen werden immer noch mit einem möglichst geringen Aufwand verbunden sein wird, würden wir Sie sogar zu Hause oder in Ihrem Ort besuchen, um Ihnen den Fahrweg zu ersparen. Die Angehörigen, welche die fünfmalige Behandlung in Magdeburg erhalten werden, sind durch unsere Wege-Unfall-Versicherung abgesichert. Die Versicherung wurde bei:
ECCLESIA mildenberger HOSPITAL GmbH

abgeschlossen mit der Versicherungsnummer: Nr. 50 039 737/282.


Mit der Teilnahme an dieser Studie gehen Sie keinerlei gesundheitliches Risiko ein und auch Ihr zeitlicher Aufwand ist begrenzt. Demgegenüber kann es für Sie Vorteile haben, wenn Sie uns mit Ihrer Teilnahme an unserer Studie darin unterstützen, die Wirksamkeit dieser fünf Behandlungsstunden zu überprüfen: Sie erhalten unentgeltlich und ohne sich selbst darum kümmern zu müssen diese deutschlandweit erstmalig zur Verfügung stehende spezialisierte Angehörigenunterstützung. Zudem helfen Sie eventuell mit, zukünftig Angehörige von jungen Krebspatienten mit einer gegebenenfalls als zuverlässig geprüften Methoden wirksam zu unterstützen.


(continued)

PROJEKTLIEITUNG UND ANSPRECHPARTNER FÜR RÜCKFRAGEN:

Prof. Dr. Thomas Fischer
Dipl.-Psych. Michael Köhler
Universitätsklinik für Hämatologie und Onkologie
Universitätsklinikum Magdeburg A,ö.R.
Leipziger Str. 44
39120 Magdeburg
Kontakt: Tel.: 0391 67 13266
Fax: 0391 67 13267
E-Mail: thomas.fischer@med.ovgu.de
       michael.koehler@med.ovgu.de
eAppendix 6. Informed Consent Form AYA-PARENTS 2012 (From Original Study Protocol pp. 84–87)

Universitätsklinikum Magdeburg AöR.
Zentrum für Innere Medizin
Klinik für Hämatologie/Onkologie
Direktor: Prof. Dr. med. Thomas Fischer
Universitätsklinikum Magdeburg - AöR. | Leipziger Straße 44 | 39120 Magdeburg

Psychonkologische Kurzintervention für Eltern Adoleszenter und junger Erwachsener mit malignen hämatologischen Erkrankungen

- Angehörigenerklärung AYA-PARENTS 2012

Name, Vorname: .................................................................

Geburtsdatum: .................................................................

der Studienteilnehmerin bzw. des Studienteilnehmers.


Ich bin bereit, die erhobenen Behandlungsdaten pseudonymisiert* zur Verfügung zu stellen. Weiterhin bin ich damit einverstanden, dass im Rahmen dieser Behandlung erhobene Daten, insbesondere Angaben über meine Gesundheit wissenschaftlich ausgewertet werden.

*Unter dem Begriff pseudonymisieren von Daten versteht man die Umwandlung oder Verschlüsselung des Namens eines Betroffenen in ein Pseudonym, z.B. einen Code.

Datenschutzerklärung


(continued)
Einwilligung zum Datenschutz
Ich erkläre mich damit einverstanden, dass im Rahmen dieser Behandlung erhobene Daten, insbesondere Angaben über meine Gesundheit, in Papierform und auf elektronischen Datenträgern in der mich behandelnden Klinik aufgezeichnet und wissenschaftlich ausgewertet werden. Soweit erforderlich, dürfen die erhobenen Daten pseudonymisiert (verschlüsselt) weitergegeben werden.

Einverständniserklärung AYA-PARENTS 2012

Mit der Erhebung und Auswertung meiner Daten bin ich

O einverstanden
O nicht einverstanden (Zutreffendes bitte ankreuzen).

Ich habe eine Kopie der Einverständniserklärung AYA-PARENTS 2012 erhalten.
Weiterhin wurde ich über folgende Fragen aufgeklärt, die ich in diesem Zusammenhang hatte:

........................................................................................................................................................................

........................................................................................................................................................................

O Studienteilnehmerin/ Studienteilnehmer hatte keine weiteren Fragen

........................................................................................................................................................................

Ort, Datum Unterschrift der Studienteilnehmerin / des Studienteilnehmers

........................................................................................................................................................................

Ort, Datum Unterschrift auflärende Untersucherin / auflärender Untersucher

(continued)
Psychoonkologische Kurzintervention für Eltern Adoleszenter und junger Erwachsener mit malignen hämatologischen Erkrankungen

- Patientenerklärung AYA-PARENTS 2012

Name, Vorname: ..............................................................

Geburtsdatum: ..............................................................

der Patientin bzw. des Patienten.


Ich bin bereit, die erhobenen Behandlungsdaten pseudonymisiert* zur Verfügung zu stellen. Weiterhin bin ich damit einverstanden, dass im Rahmen dieser Behandlung erhobene Daten, insbesondere Angaben über meine Gesundheit wissenschaftlich ausgewertet werden. Ich entbinde meine behandelnde Einrichtung von der Schweigepflicht gegenüber meinen Eltern.

*Unter dem Begriff pseudonymisieren von Daten versteht man die Umwandlung oder Verschlüsselung des Namens eines Betroffenen in ein Pseudonym, z.B. einen Code.

Datenschutzerklärung

Einwilligung zum Datenschutz

Ich erkläre mich damit einverstanden, dass im Rahmen dieser Behandlung erhobene Daten insbesondere Angaben über meine Gesundheit, in Papierform und auf elektronische Datenträgern in der mich behandelnden Klinik aufgezeichnet und wissenschaftlich ausgewertet werden. Soweit erforderlich, dürfen die erhobenen Daten pseudonymisiert (verschlüsselt) weitergegeben werden.

Einverständniserklärung AYA-PARENTS 2012

Mit der Erhebung und Auswertung meiner Daten bin ich

O einverstanden
O nicht einverstanden (Zutreffendes bitte ankreuzen).


Ich habe eine Kopie der Einverständniserklärung AYA-PARENTS 2012 erhalten. Weiterhin wurde ich über folgende Fragen aufgeklärt, die ich in diesem Zusammenhang hatte:

Patientin/ Patient hatte keine weiteren Fragen

Ort, Datum  Unterschrift der Patientin / des Patienten

Ort, Datum  Unterschrift aufklärende Untersucherin / aufklärender Untersucher
Universitätsklinikum Magdeburg A.ö.R.
Zentrum für Innere Medizin
Klinik für Hämatologie/Onkologie
Direktor: Prof. Dr. med. Thomas Fischer
T: 0391-67 1264, F: 0391 67 1265

Kooperationsvereinbarung

Zwischen dem:

Zentrum für Innere Medizin
Klinik für Hämatologie und Onkologie
Universitätsklinikum Magdeburg A.ö.R.
Leipziger Str. 44
39120 Magdeburg

Und der

... ... ...
... ... ...
... ... ...
... ... ...
... ... ...


Die o.g. Einrichtung behandelt jährlich ca. _______ Patientinnen und Patienten mit einer malignen hämatologischen Erkrankung im Alter von 18 bis 40 Jahren.
eAppendix 7. Cooperation Contract for AYA Network Partners (cont.)

Die Projektleitung des Forschungsprojektes „Psychoonkologische Kurzintervention für Eltern Adoleszenter und junger Erwachsener mit malignen hämatologischen Erkrankungen“ wird bei wissenschaftlichen Präsentationen die Mitarbeit der …………………………………………………………………………………… angemessen darstellen und über die Studienergebnisse informieren.

Die Unterzeichner bestätigen hiermit an dieser Stelle, dass sie eine Studienzusammenarbeit eingehen sowie ihre Verantwortlichkeit und Kompetenz in die Studie einbringen werden.

<table>
<thead>
<tr>
<th>Projektleitung</th>
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<tbody>
<tr>
<td>Datum</td>
<td>Unterschrift</td>
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<tr>
<th>Projektleitung</th>
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<tr>
<td>Datum</td>
<td>Unterschrift</td>
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<tr>
<th>Co-Investigator</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Datum</td>
<td>Unterschrift</td>
</tr>
</tbody>
</table>
eAppendix 8. Positive Vote of the Ethics Committee

OTTO-VON-GUERICKE-UNIVERSITÄT MAGDEBURG
Ethik-Kommission
der Otto-von-Guericke-Universität an der Medizinischen Fakultät
und am Universitätsklinikum Magdeburg A.ö.R.
Vorsitzender: Univ.-Prof. Dr. med. C. Huth

Universitätsklinikum Leipziger Straße 44 D-39120 Magdeburg

Herrn Prof. Dr. med. Th. Fischer, Dipl-Psych. Köhler
Universitätsklinik für Hämatologie und Onkologie
Universitätsklinikum Magdeburg A.O.R.
Leipziger Ditr. 44
39120 Magdeburg

Tel. (0391) 6714214 Fax (0391) 6714344 eMail norbert.basov@med.ovgu.de


Unser Zeichen: 143/12
Psychoonkologische Kurzinterventionen für Eltern Adoleszenter und junger Erwachsener mit
malignen hämatologischen Erkrankungen
AYA-PARENTS 2012

Sehr geehrter Herr Prof. Fischer, sehr geehrter Herr Dipl.Psych. Köhler,
die Ethik-Kommission der Otto-von-Guericke-Universität an der Medizinischen Fakultät und
am Universitätsklinikum Magdeburg hat die übergebenen Unterlagen zur o.g. Studie
überprüft, in der letzten Kommissionssitzung eingehend erörtert und ist zu der Auffassung
gekommen, dass gegen die Durchführung keine ethischen Bedenken bestehen.
Diese zustimmende Bewertung ergeht unter dem Vorbehalt gleichbleibender
Gegebenheiten.

Die Verantwortlichkeit des jeweiligen Prüfwissenschaftlers / behandelnden Prüfärztes bleibt
in vollem Umfang erhalten und wird durch diese Entscheidung nicht beeinträchtigt. Alle zivil-
or haftungsrechtlichen Folgen, die sich ergeben könnten, verbleiben uneingeschränkt beim
Projektleiter und seinen Mitarbeitern.

Beim Monitoring sind die Bestimmungen des Bundes- und Landesdatenschutzgesetzes
sowie die sich aus der ärztlichen Schweigepflicht ergebenden Einschränkungen zu
beachten, was eine Aushändigungkomplett Patientenakten zum Monitoring ausschließt.
Ein Monitoring personen- und studienbezogener Daten wird dadurch nicht beeinträchtigt.

Um die Übersendung von studienbezogenen Jahresberichten / Abschlussberichten /
Publikationen wird unter Nennung unserer Registraturnummer gebeten.

Mit freundlichen Grüßen

j. Dr. med. Norbert Basov, Geschäftsleiter
Prof. Dr. med. C. Huth
Vorsitzender der Ethik-Kommission

Ethik-Kommission
der Otto-von-Guericke-Universität an der Medizinischen Fakultät
Universitätsklinikum Magdeburg A.Ö.R.
Vorsitzender: Univ.-Prof. Dr. med. C. Huth

(continued)
eAppendix 8. Positive Vote of the Ethics Committee (cont.)

Anlage zum Votum der Studie 143/12 vom 20.09.2012

Zum Zeitpunkt der Bewertung der vorstehenden Studie waren folgende Damen und Herren Mitglied der Ethik-Kommission der Otto-von-Guericke-Universität an der Medizinischen Fakultät und am Universitätsklinikum Magdeburg:

Herr
Prof. Dr. med. Norbert Bannert Medizinische Fakultät / Universitätsklinikum, Pädiater
Frau
Prof. Dr. phil. Eva Brinkschulte Medizinische Fakultät / Universitätsklinikum, Bereich Geschichte, Ethik und Theorie der Medizin
Herr
Prof. Dr.-Ing. Rolf Findeisen Fakultät für Elektrotechnik und Informations-technik, Institut für Automatisierungstechnik
Herr
Prof. Dr. med. Thomas Fischer Medizinische Fakultät / Universitätsklinikum, Universitätsklinik für Hämatologie und Onkologie
Herr
Prof. Dr. med. Christof Huth Medizinische Fakultät / Universitätsklinikum, Universitätsklinik für Herz- und Thoraxchirurgie
Frau
Assessorin Ute Klanten Medizinische Fakultät / Universitätsklinikum, Stabstelle Recht
Herr
OA Dr. med. Werner Kuchheuser Medizinische Fakultät / Universitätsklinikum, Institut für Rechtsmedizin
Herr
Prof. Dr. rer. nat. Jürgen Läuter Medizinische Fakultät / Universitätsklinikum, Mathematiker, Biometriker
Herr
Prof. Dr. phil. Georg Lohmann Fakultät Geistes-, Sozial- und Erziehungswissenschaften, Institut für Philosophie
Herr
Prof. Dr. med. Frank Peter Meyer Medizinische Fakultät / Universitätsklinikum, Klinischer Pharmakologe

Mitglieder der Ethik-Kommission, die in eine Studie eingebunden sind, haben für die Vollziehung der betreffenden Studie kein Stimmrecht.


Dr. med. Norbert Bock
Geschäftsführer der Ethik-Kommission