Data analysis plan – WAYA-2

The data analysis plan is aligned with the primary and secondary outcome measures as presented in the registered project plan: https://www.isrctn.com/ISRCTN93856392

Primary outcome measure(s)	**Primary outcome measures** **1. Psychological well-being measured using the Psychological Well-being Scale (PWS) at baseline, directly after the first 8-day intervention, at 3 months, and 1 year after the first intervention** **2. Nature connectedness measured using the Nature Relatedness Scale (NRS) at baseline, directly after the first 8-day intervention, at 3 months, and 1 year after the first intervention.**
Key secondary outcome measure(s)	**Secondary outcome measures** **1. Quality of life of childhood and adolescent and young adult (AYA) cancer survivors measured using the Minneapolis Manchester Quality of Life instrument (MMQL) at baseline, directly after the first 8-day intervention, at 3 months, and 1 year after the first intervention** **2. Changes in physical activity level (moderate-to-vigorous intensity physical activity and walking steps) measured using an ActiGraph at baseline, directly after the first 8-day intervention, at 3 months and 1 year after the first intervention** **3. Changes in estimated maximal oxygen consumption (VO2max; ml/kg/min) measured using the Ekblom Bak cycle ergometer test at baseline and at 3 months after the first intervention**

	4. Blood Pressure and Heart Rate (BP/HR) measured using an electronic monitor in a seated position after a 5-min rest at baseline and at 3 months after the first intervention. **5. Body mass index (BMI) (kg/m2) will be calculated from body mass measured non-fasted and in light clothing to the nearest 0.1 kg using a digital scale and height measured to the nearest 1 mm using a stadiometer at baseline and at 3 months after the first intervention.** **6. Occurrence of (serious) adverse effects during both programs measured using the number, seriousness, intensity, and types of adverse effects that are evaluated to be certain, probable/likely, or possibly related to the study programs in study records after the first 8-day intervention, at 1, 2 and 3 months and 1 year after the first intervention.**

Detailed steps:

1. **Quality control** – run descriptive statistics on all relevant variables prior to including them in further analysis and examine distributions and outliers.
2. **Descriptive data**
    a. **Descriptive data on baseline** (Tables) for all groups (Wilderness, hotel stay, and dropout)
        i. Show means/proportion and variability.
        ii. Variables:
            1. *Preferences,*
            2. *Willingness to be randomized,*
            3. *Demographic data* (Gender, age, ethnicity, marital status, number of children, housing situation, education, employment status, economic situation
            4. *Cancer related information* (Diagnosis, treatment/treatment other, time since last treatment, medical history – including long

term/late effects, medicines (meduse), Other treatment (Counselling, self-management).

5. *Lifestyle measures* (diet, sleep, physical activity, stress, smoking, alcohol, outdoor time, caffeine, changes in: weight, physical activity, diet, alcohol, smoking, time in nature
6. *Questionnaire data (Baseline)*
    a. Psychological Well-being Scale
    b. Nature Relatedness Scale (NRS).
    c. Minneapolis Manchester Quality of Life instrument (MMQL).

b. **Descriptive data on follow up xxx2 on variables** (Tables) for the intervention group (wilderness) and control group (hotel stay)
    i. Also show means/proportion and variability.
    ii. Variables
        1. Changes: in medicines (meduse), Other treatment (Counselling, self-management).
        2. *Changes in Lifestyle measures:* diet, sleep, physical activity, stress, smoking, alcohol, outdoor time, caffeine, changes in: weight, physical activity, diet, alcohol, smoking, time in nature
        3. *Questionnaire data*
            a. Psychological Well-being Scale
            b. Nature Relatedness Scale (NRS).
            c. Minneapolis Manchester Quality of Life instrument (MMQL).
        4. *Adverse events*

c. **Descriptive data on follow up xxx3 on variables** (Tables) for the intervention group (wilderness) and control group (hotel stay)
    i. Also show means/proportion and when appropriate make tests to show if they differ from each other
    ii. Variables
        1. Changes: in medicines (meduse), Other treatment (Counselling, self-management).
        2. *Changes in Lifestyle measures:* diet, sleep, physical activity, stress, smoking, alcohol,

outdoor time, caffeine, changes in: weight, physical activity, diet, alcohol, smoking, time in nature

3. *Questionnaire data*
    a. Psychological Well-being Scale
    b. Nature Relatedness Scale (NRS).
    c. Minneapolis Manchester Quality of Life instrument (MMQL).
4. *Adverse events*

3. Inferential statistics/Comparisons differences/Sensitivity analysis

a. The primary analysis will investigate changes in the total scores of the PWS and NRS over time from baseline to the 3 and 12 months follow-up in the intervention group (Wilderness) compared to the control group (Hotel stay). The analysis of the primary outcomes will be based on a linear mixed effects model and will be fitted to test intervention effects up to 12 months. Both unadjusted and adjusted analyses will be conducted. Adjustments will be made for age, gender, age at cancer diagnoses, and country. Time, intervention arm, interaction between time and intervention arm, age, gender, age at cancer diagnoses, country are included as fixed effects, and participant is included as random effect in the model. Statistical analyses will be based on the intention-to-treat (ITT) principle (i.e., includes all participants that are randomized in the study). Missing data will be imputed by means of multiple imputation or by using full-information maximum likelihood estimation. Secondary outcomes will also be analyzed using linear (or generalized) mixed effects models.

b) As sensitivity analyses, the per-protocol data set will be analyzed including only participants that have participated for at least one day in the wilderness or hotel stay. Also, complete case analysis (i.e., including those with complete outcome data) will be conducted as sensitivity analysis.

c) We will also examine the causal effect of receiving the wilderness program on primary and secondary outcomes

using complier average causal effect (CACE) analyses. Compliance will be defined a priori using three criteria reflecting different levels of engagement with the wilderness program: (1) a binary indicator of any participation (yes/no); (2) an ordinal measure reflecting attendance as the number of core components engaged with (wilderness expedition, online coaching, base camp; 0–3); and (3) a continuous measure reflecting adherence, as the total number of days/contacts across all components (0–14). For each follow-up (3 and 12 months), we will conduct instrumental-variable analyses using random assignment (Wilderness program vs. Hotel stay) as an instrument for engagement with the wilderness program. Effects will be estimated using two-stage least squares (2SLS) regression, adjusting for baseline outcome values and prespecified covariates (age, gender, age at cancer diagnosis, country, and study site). Under standard instrumental-variable assumptions (instrument relevance, exclusion restriction, and monotonicity), the binary compliance model estimates the local average treatment effect among compliers. When ordinal or continuous engagement measures are used, 2SLS estimates will be interpreted as local average dose–response effects (i.e., the causal effect per unit increase in engagement induced by assignment), under an additional assumption of linearity in the exposure–outcome relationship. Robust standard errors will be used for inference. These analyses will be considered supplementary to the primary intention-to-treat analyses.

d) In addition to reporting descriptive statistics for dropouts, attrition analysis will be conducted using logistic regression (completers vs. dropouts) with the prespecified baseline covariates and intervention arm as predictors. Dropouts are defined as participants that are randomized who leave the study preliminary (before the scheduled completion of the study), resulting in missing outcome data. Reasons for leaving the study may be withdrawal of consent, loss to follow-up, adverse events, no intervention start (non-starters). The following numbers will be reported for the

different groups: (1) Dropout-no baseline data; (2) Dropout-partial/complete baseline data; (3) Partial/full completer.

4. Safety Analyses

All safety analyses will be performed on the Safety Analysis Set (SAS), including all participants that have received at least one day of the program intervention. Safety data will be summarized by intervention arm using descriptive statistics (i.e., n, mean, SD, median, Q1, Q3, minimum and maximum for continuous variables; and n (%) for categorical variables). Safety variables include all reported adverse events as well as the adverse effects (AEs) (causally related to program-intervention). Crude (unadjusted) Relative Risk (RR) with 95% Confidence Intervals (CI) will be calculated to indicate the risk of having an AE adjusted to days of exposure in program interventions. Pearson's chi-squared test will be used to calculate differences in AE severity between the two study arms.

4.1 Exposure to the intervention

Exposure to the intervention is needed to calculate the incidence ratio (IR) of adverse events and AEs in both groups. Exposure to the intervention will be expressed as participation per program day in both groups. Exposure to the intervention is therefore equal to study program adherence, which is calculated as the total number of days/contacts across all components (0–14).

4.2 Adverse events and adverse effects

The adverse event verbatim descriptions (investigator terms from the field diaries and CRFS) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA) version 25.1. Adverse events will be coded to the preferred term (PT) and primary System Organ Class (SOC) and using MedDRA. The severity of adverse events will be graded according to the CTCAE v4.03 of the National Cancer Institute. In case of a certain, probable/likely, or possible causal relation

between the adverse event and the program intervention, it will be considered an AE.

The following variables will be analyzed and reported:

a. Frequency and IR of reported adverse events for total and per group. Frequency is calculated by dividing the total number of adverse events by the overall exposure to the program (days) and expressed in n, % and IR per day of program intervention.
b. Frequency and IR of causality with program intervention, categories: certain, probable/likely, possible, unlikely/remote, conditional/unclassified, Unassessable / unclassifiable. Expressed in n, % and IR per day of program intervention, for total and per group.
c. Frequency and IR of reported AEs (calculated as certain, probable/likely, or possible causal related) for total and per group. Values will be expressed in n, % and IR.
d. Seriousness of AE, categories non-serious and serious, for total and per group. Values will be expressed in n, % and IR.
e. Severity of AEs, categories grade 1, 2 and 3-5, for total and per group. Values will be expressed in n, % and IR.
f. Outcome of AEs, categories fatal, not recovered/not resolved, recovered/resolved, recovered/resolved with sequelae, sequelae, worsening, unknown, for total and per group. Values will be expressed in n, % and IR.

4.3 Frequency and IR of AEs per program part (wilderness versus base-camp and 8 versus 4 day holiday)

4.4 Frequency of participants with AEs and total number of AEs per age group (16-30, 31-39 years). Values will be expressed in n, % and also the IR for AEs.

4.5 Frequency and incidence of AEs per gender. Values will be expressed in n, % and IR.

4.6 Frequency and incidence of AEs per cancer survivorship (childhood cancer: Cancer diagnosis at age 0-14 years, AYA cancer: Cancer diagnosis at age 15-39 years). Values will be expressed in n, % and IR.

4.7 Five most frequent Preferred Terms per group. Preferred Terms (PT) will be described in text and codes. Frequency of the AEs per PT will be expressed in n, % and IR.

4.8 Five most frequent System Organ Class per group. System Organ Class (SOC) will be described in text and codes. Frequency of the AEs per SOC will be expressed in n, % and IR.