STUDY PROTOCOL

BODY EMOTIONAL MAP METHOD FOR THE REDUCTION OF PARENTAL STRESS RELATED TO DIABETES:

A RANDOMIZED STUDY

BEM-02

Version N° 2.1

July 26th 2023

Sponsor:

Dott. Valentino Cherubini,

Dipartimento di Diabetologia Pediatrica,
Ospedale G. Salesi,
Ancona

DECLARATION OF COMPLIANCE

The study will be conducted in accordance with the guidelines of the International Conference on Harmonisation for Good Clinical Practice (ICH E6), applicable Good Clinical Practice standards, and relevant national laws. All personnel involved in the conduct of this study have completed training on the protection of human subjects.

SIGNATURE PAGE

The signature below constitutes approval of this protocol and its attachments and provides the necessary guarantees that this study will be conducted in accordance with all provisions of the protocol, including all confidentiality statements, and in compliance with local legal and regulatory requirements and the ICH-GCP (R2) guidelines.

For the Sponsor:

Signature: Date:

Name: Dott. Valentino Cherubini

Title: Dipartimento di Diabetologia Pediatrica, Ospedale G. Salesi, Ancona

Principal Investigator:

Signature: Date:

Name:

Title:

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LIST OF ABBREVIATIONS

BEM	Body Emotional Map
B-PSQI	Brief Pittsburgh Sleep Quality Index
CGM	Continuous Glucose Monitoring
COPE	Coping Orientation to Problems Experienced
COPE-NVI	COPE, nuova versione italiana
CRA	Clinical Research Associate
CRO	Contract Research Organization
eCRF	Case Report Form elettronica
GAD-7	General Anxiety Disorder
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
HbA1c	Glycated Hemoglobin
IC	Informed Consent
ICH	International Conference on Harmonisation
IRB/IEC	Institutional Review Board/Independent Ethics Committee
ISF	Investigator's Site File
NPL	Neuro-Linguistic Programming
PHQ	Patient Health Questionnaire
PSESDM	Parental Self-Efficacy for the Management of Diabetes Mellitus
PSI-SF	Parental Stress Index Short-Form
T1DM	Type 1 Diabetes Mellitus
TAR	Time above range
TBR	Time below range
TIR	Time in range
TMF	Trial Master File

STUDY SYNOPSIS

Titolo	**BODY EMOTIONAL MAP METHOD FOR THE REDUCTION OF PARENTAL STRESS RELATED TO DIABETES: A RANDOMIZED STUDY**
Version #	2.1
Date	July 26th 2023
Project start date	2023
Project end date	2024
Project type	National multicenter randomized controlled trial.
Staff involved	Psychologists: Maria Cristina Alessandrelli (AN), Maria Cusinato (PD), Giada Boccolini (AN) Counselor: Manuela Pagnini (AN) Principal Investigator: Valentino Cherubini (AN) Doctors, dieticians and nurses of the participating teams Statisticians: Antonio Nicolucci, Giuseppe Lucisano (PE)
Background	Type 1 diabetes (T1D) in childhood and adolescence is a chronic condition characterized by significant management complexity, requiring essential therapeutic and behavioral synergy between parents and the affected child. In chronic illnesses where cure is not achievable, the therapeutic goal shifts to adaptation that allows for a good quality of life. The onset of diabetes in a child or adolescent is a critical, potentially traumatic event, also for parents, since it immediately becomes evident that they are embarking on a long journey of living with a chronic condition. A good adaptation, which in this context can be considered as the "cure" of the chronic disease, is the primary goal of therapeutic intervention. The process toward adaptation varies in duration; achieving it is not guaranteed and should be viewed as an ongoing process. During this journey, obstacles are encountered that require activating resources, which can be considered "internal" to the individual or "external," related to technology, family environment, social context, and healthcare. In the phase of good adaptation, parents experience an improved state of psycho-physical well-being, fewer worries related to diabetes, positive mental representations, increased confidence in their child's future, and a stronger sense of self-efficacy. Optimal use of technology is a key factor in this process. In a preliminary pre-post, single-arm study, the BEM (Body Emotional Maps) method demonstrated the ability to reduce parental stress measured after three months using the Parental Stress Index Short-Form (PSI-SF).
Objectives	The purpose of this study is to evaluate the impact of the BEM method on stress and well-being in parents of children/adolescents with type 1 diabetes, compared to a standard group approach focused on therapeutic education (control group).
Inclusion criteria	▪ Parents of children and adolescents under 18 years old with type 1 diabetes, with a duration of diabetes > 12 months.

	▪ Parents of children who have never been diagnosed with psychiatric or behavioral disorders. Adequate understanding of the Italian language according to the clinician's judgment. ▪ Parents willing to: - Be actively involved in group experiential activities; - Complete the required questionnaires. ▪ Signed informed consent from the participating individual. ▪ Signed informed consent for the processing of the minor's data by both parents (if applicable).
Exclusion criteria	▪ Parents: - With psychiatric conditions; - Of patients with psychiatric problems or behavioral disorders; - With any issue that, according to the clinician's judgment, precludes active participation in group experiential activities.
Experimental group: BEM	The BEM Program involves an experiential, group-based approach facilitated by 2–3 trained facilitators and a maximum of 25 parent participants. Structure of a BEM Session: each session takes place over three consecutive days and includes both plenary sessions with the entire group and smaller subgroup activities. Context: it is essential to conduct the program in a setting that is removed from participants' everyday life, ideally immersed in nature. This promotes emotional distancing from daily stressors, providing a sense of isolation and tranquility conducive to deep personal work. Setting: a reserved, welcoming, and intimate room is required to support a safe and comfortable environment. Methodology: relaxation techniques, breathing exercises, and guided visualizations NLP (Neuro-Linguistic Programming) techniques: spatial anchoring, Time Line therapy, and future pacing. Approaches based on Transactional Analysis (T.A.) and Systemic-Relational frameworks, brief interventions focused on problem-solving. Techniques for enhancing bodily and emotional awareness. Interactive group discussions.
Control group: TRADITIONAL	The control intervention will take place during a camp specifically dedicated to parents, with the same duration as the BEM program. The intervention includes educational and informational sessions on key aspects of type 1 diabetes management (management of acute complications, importance of glycemic indices, carbohydrate counting, current and emerging perspectives in type 1 diabetes care) In addition, the program includes opportunities for parents to share personal experiences and participate in recreational activities.
Study endpoint	▪ The primary endpoint is the change in the Parental Stress Index Short Form (PSI-SF) score at 3 months following participation in the group activities, compared to baseline. ▪ Secondary endpoints include: - Change in PSI-SF score at 6 months after participation, compared to baseline; - Change in the scores of the individual PSI-SF subscales (Parental Distress, Parent-Child Dysfunctional Interaction, and Difficult Child) at 3 and 6 months post-intervention, compared to baseline;

	- Change in the Patient Health Questionnaire-9 (PHQ-9) score for the assessment of depressive symptoms at 3 and 6 months post-intervention, compared to baseline; - Change in the Generalized Anxiety Disorder-7 (GAD-7) score for the assessment of anxiety symptoms at 3 and 6 months post-intervention, compared to baseline; - Change in the Brief Pittsburgh Sleep Quality Index (B-PSQI) score for the evaluation of sleep disturbances at 3 and 6 months post-intervention, compared to baseline; - Change in the Parental Self-Efficacy for the Management of Diabetes Mellitus (PSESDM) score assessing parents' perceived self-efficacy in managing diabetes at 3 and 6 months post-intervention, compared to baseline; - Change in the Coping Orientation to the Problems Experienced – New Italian Version (COPE-NVI) score for the evaluation of parental adaptation and coping strategies at 3 and 6 months post-intervention, compared to baseline; - Change in children's/adolescents' glycemic metrics (including glycemic variability, Time in Range [TIR], Time Above Range [TAR], Time Below Range [TBR], and HbA1c) at 3 and 6 months after the intervention, compared to baseline. ▪ Additionally, a qualitative analysis will be conducted to explore unmet parental needs.
Study procedure	After verification of eligibility criteria, parents will be randomly web-based randomization to either the BEM group intervention or the control group intervention. If both parents are eligible, they will be allocated to the same study arm. Randomization will be stratified by study center. Upon obtaining informed consent, parents will receive login credentials for the study's web platform, through which they will complete the required questionnaires. At enrollment, socio-demographic data of the parents and clinical data related to the child/adolescent will also be collected. Parents will then be invited to participate in either the BEM group intervention or the standard group intervention. Both group activities will be conducted under the supervision of trained healthcare personnel and will have the same duration, although their content will differ. (Non-specialized healthcare personnel will receive specific training in a two-day weekend course (8 hours per day) led by professionals experienced in the BEM methodology). Specifically, the BEM group will receive basic information on diabetes management using external resources (medical support, technology, telemedicine, carbohydrate counting techniques) and internal resources (learning effective techniques and behaviors to improve metabolic control). This will be followed by the experiential BEM-specific program. The control group will receive the same diabetes management information, combined with opportunities for parent discussion and recreational activities. Each group activity will include 25 parent participants.

	At 3 and 6 months following the group intervention, parents will be asked to complete the same questionnaires again via the web platform. Glycemic data for the children/adolescents will be retrieved from electronic medical records.
Statistical aspects	*Sample Size Estimation* - The difference between the two groups in changes in PSI-SF scores (primary endpoint) will be expressed in terms of effect size (i.e., the difference in mean scores between groups divided by the common standard deviation at baseline). An effect size of at least 0.5 is widely accepted in the literature as clinically relevant. In a previous study [13], baseline PSI-SF scores were 75.4 ± 2.5, indicating that an effect size of 0.5 corresponds to a between-group difference of 1.25. To detect an effect size of at least 0.5 with 80% statistical power ($\alpha = 0.05$), a minimum of 64 parents per group is required. Assuming a dropout rate of 15%, a total of 150 parents (75 per group) will be enrolled. *Data Analysis* - Descriptive statistics will be reported as mean and standard deviation or, in the case of non-normally distributed continuous variables, as median and interquartile range. Categorical variables will be reported as percentages. - Between-group comparisons for descriptive variables will be conducted using the Student's t-test or the Mann–Whitney U test for continuous variables, and the chi-square test for categorical variables. - Comparisons between study arms will be performed using Mixed Models for Repeated Measures (MMRM), including the baseline value of the outcome as a linear covariate and study arm as a fixed effect. MMRMs account for both within-subject and between-subject correlations using a first-order autoregressive (AR(1)) variance-covariance structure. Similarly, comparisons between study arms for secondary endpoints, including questionnaire scores and glycemic metrics (change from baseline at 3 and 6 months), will also be conducted using MMRMs. These models will include baseline values of the respective outcomes as linear covariates and the study arm as a fixed effect. Results will be reported as estimated means with corresponding 95% confidence intervals. - Subgroup analyses will also be conducted based on parental sex and child/adolescent age (<10 years vs. ≥10 years.
Participating Sites	Participation is planned for six pediatric diabetes centers. Enrollment will be competitive.
Ethics aspects	The study protocol will be submitted for approval to the Ethics Committees of the participating centers.

KEY ROLES AND CONTACTS

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1. INTRODUCTION: SCIENTIFIC RATIONALE

Type 1 diabetes (T1D) in pediatric and adolescent populations represents a chronic condition characterized by significant management complexity, requiring essential therapeutic and behavioral synergy between parents and the affected child (1).
The parent's need to possess awareness and management skills regarding their child's illness is fundamental to ensuring that the child achieves optimal glycemic and metabolic control and to preventing or appropriately managing potential disease-related complications (2,3). In particular, the daily requirement of insulin therapy entails passive acceptance of the inherent risks associated with the treatment, notably the potential occurrence of hypoglycemic episodes (4–6).
From the moment of diagnosis, parents must be adequately trained on the necessity of promptly initiating interventions to resolve hypoglycemic crises, should they occur in their severe form, to prevent serious complications that could lead to adverse outcomes (7).
Another serious complication of T1D is diabetic ketoacidosis (DKA) (4,8). In this context, parents must be knowledgeable about this complication and its possible manifestations to recognize it promptly and to implement the necessary therapeutic procedures (9).
All these factors contribute to a high level of distress among parents, which can further impair the management of their child's disease (10,11).
Despite the objective consensus that the most traumatic moment for parents is the diagnosis of their child's T1D, it is certainly plausible that the adaptation process to the child's condition is highly subjective and can vary in duration over time (12). In chronic illness, where cure is not achievable, the primary goal of therapeutic intervention becomes adaptation, enabling the attainment and maintenance of a good quality of life. However, achieving adaptation is not guaranteed. Throughout the process aimed at reaching it, obstacles and resources are encountered that significantly influence the possibility of adaptation. Obstacles and resources can, in turn, be considered either "internal" to the individual or "external," related to the family, social, and healthcare environment. During the phase of successful adaptation, parents experience a greater sense of psychological and physical well-being, fewer concerns related to diabetes, positive mental representations, increased confidence in their child's future, and a stronger sense of self-efficacy. In the field of diabetology, but not only, educational approaches aimed at learning and reinforcing knowledge related to the management of this chronic disease have been implemented and improved over time. Among these, the so-called "summer camps" are certainly noteworthy; these are designed for children and adolescents with T1D who participate either alone or accompanied by their parents. Obstacles and resources can, in turn, be considered either "internal" to the individual or "external," related to the family, social, and healthcare environment. During the phase of successful adaptation, parents experience a greater sense of psychological and physical well-being, fewer concerns related to diabetes, positive mental representations, increased confidence in their child's future, and a stronger sense of self-efficacy. In the field of diabetology, but not only, educational approaches aimed at learning and reinforcing knowledge related to the management of this chronic disease have been implemented and improved over time. Among these, the so-called "summer camps" are certainly noteworthy; these are designed for children and adolescents with T1D who participate either alone or accompanied by their parents.
The areas addressed during these interventions primarily concern clinical aspects related to the management of situations in which the child or adolescent is the main actor. The parents' perspective regarding their feelings about their child's illness and the potential impact on their quality of life is sometimes considered marginal. The experiential group process for parents can more specifically target these areas, helping to

improve adaptation to the child's particular condition. The BEM (Body Emotional Maps) program involves an experiential, group-based approach with the participation of 2-3 facilitators and the parents of children affected by chronic illness. It includes techniques such as relaxation, breathing exercises, guided visualizations; NLP (Neuro-Linguistic Programming) techniques like spatial anchoring, timeline work, future pacing; brief problem-solving interventions; body and emotional awareness techniques; and interactive discussions (13).
By applying the BEM methodology, it is expected that parents will improve their adaptation to their child's illness, process the trauma associated with the diagnosis, and enhance their quality of life by reducing distress and fear related to hypoglycemia.

In a preliminary pre-post, single-arm study, the BEM method demonstrated the ability to reduce parental stress, as measured by the Parental Stress Index Short-Form (PSI-SF), after three months (13).

2. STUDY OBJECTIVES

2.1 Objectives of the study

The aim of this study is to evaluate the impact of the BEM method on stress and well-being in parents of children/adolescents with type 1 diabetes, in comparison to a standard group approach focused on therapeutic education (control group).

2.2 Study Endpoint

2.2.1 Primary

The primary endpoint is represented by the difference in PSI-SF (Parental Stress Index Short-Form) scores after 3 months of participation in the group activities compared to baseline**.**

2.2.2 Secondary

- Difference in PSI-SF (Parental Stress Index Short-Form) scores after 6 months of participation in the group activities compared to baseline;
- Difference in the scores of the individual components of the PSI-SF questionnaire (Parental Distress, Parent-Child Dysfunctional Interaction, Difficult Child) after 3 and 6 months of participation in the group activities compared to baseline;
- Difference in the scores of the Patient Health Questionnaire (PHQ-9) for the assessment of depression and depressive symptoms after 3 and 6 months of participation in the group activities compared to baseline;
- Difference in the scores of the General Anxiety Disorder (GAD-7) questionnaire for the assessment of anxiety and anxious symptoms after 3 and 6 months of participation in the group activities

compared to baseline;

- Difference in the scores of the Brief Pittsburgh Sleep Quality Index (B-PSQI) for the assessment of sleep disturbances after 3 and 6 months of participation in the group activities compared to baseline;
- Difference in the scores of the Parental Self-Efficacy for the Management of Diabetes Mellitus (PSESDM) questionnaire for the evaluation of self-efficacy perception in managing their child's diabetes after 3 and 6 months of participation in the group activities compared to baseline;
- Difference in the scores of the Coping Orientation to the Problems Experienced - Italian Version (COPE-NVI) questionnaire for assessing parental adaptation and coping strategies after 3 and 6 months of participation in the group activities compared to baseline;
- Difference in glucometric data of children/adolescents (variability, Time In Range [TIR], Time Above Range [TAR], Time Below Range [TBR], HbA1c) after 3 and 6 months of participation in the group activities compared to baseline;
- Additionally, a qualitative analysis will be conducted to further explore parents' experiences regarding their perception of their child (e.g., "How do I see my child's life now?").

3 STUDY DESIGN

A randomized, controlled, two-arm, open-label trial. Following verification of eligibility criteria, parents will be assigned via centralized web-based randomization to participate in either the BEM group activity or the control group. In cases where both parents are eligible, they will be allocated to the same study arm.

3.1 Study duration and participating clinical sites

The study includes a 6-month follow-up after participation in the group activity.
Six pediatric diabetology sites will participate in the study.

4 STUDY POPULATION

4.1 Inclusion criteria

- Parents of children and adolescents under 18 years of age with type 1 diabetes duration exceeding 12 months
- Parents of children who have never been diagnosed with psychiatric or behavioral disorders
- Adequate understanding of the Italian language, as assessed by the clinician
- Parents willing to:
    - Actively participate in group experiential activities
    - Complete the required questionnaires
    - Signed informed consent from the participating individual
    - Signed informed consent for data processing of the minor by both parents (if applicable)

4.2 Exclusion criteria

- Parents:
  - with psychiatric conditions
  - of patients with psychiatric issues or behavioral disorders
  - with any problem that, according to the clinician's judgment, would prevent active participation in group experiential activities

4.3 Procedures for assigning interventions in the study

4.3.1 Randomization procedure

After verification of the eligibility criteria, the parents will be assigned via centralized web-based randomization to participate in either the BEM group activity or the control group (1:1 randomization). In cases where both parents are eligible, they will be allocated to the same study arm. The randomization will be stratified by center.

4.3.2 Masking procedure

The study will be conducted in an open-label design.

5 STUDY INTERVENTION

Both study groups (BEM method and control) will participate in activities conducted over three consecutive days at an off-hospital location, in contact with nature. Both group activities will be carried out under the supervision of specially trained healthcare personnel and will have equal duration, although the content will differ.
The non-specialist staff supervising the school camps will undergo appropriate training during a weekend course lasting two days (8 hours per day). The course will be conducted by experienced professionals in the BEM method.

5.1 Description of the BEM method

In the BEM group, participants will receive basic information on diabetes management through external resources (medical support, technology, telemedicine, carbohydrate counting techniques) and internal resources (learning effective techniques and behaviors to improve metabolic control). Subsequently, the specific experiential BEM program will be initiated. The BEM method involves an intervention with the parents of children with diabetes, conducted in group settings, aimed at facilitating parents' adaptation to their child's "diabetes condition" (13). The intervention is organized into three sessions.
The first session consists of an introduction and group formation.
The second session involves sharing the onset of diabetes, identifying the most critical daily challenges, and the primary change the participants wish to implement.

The third session features the BEM pathway, which includes guided visualization and the creation of a map with spatial anchors. This final session is conducted partly in a plenary setting and partly in small groups, allowing each participant the necessary time to connect with their deeper parts and express themselves. A description of the operational phases of the BEM method is included in Appendix 1 of this study protocol.

5.2 Description of the control method

In the control group, basic information on diabetes management will be provided through external resources (medical support, technology, telemedicine, carbohydrate counting techniques) and internal resources (learning effective techniques and behaviors to improve metabolic control).
The control group will receive the same diabetes management information, accompanied by parent discussion sessions and recreational activities guided by the diabetes team staff. As with the BEM group, activities will take place over three days in an off-hospital location, in contact with nature. Each group activity will involve 25 parents.

STUDY PROCEDURES

5.3 Procedures

All parents of participating children will be offered the opportunity to participate in the study and will be asked to sign an informed consent form during a routine visit of their child. After verifying eligibility criteria and obtaining informed consent, parents will be randomly assigned via a centralized web-based randomization process to either participate in the BEM group activity or to the control group. If both parents are eligible, they will be allocated to the same study arm.
Once consent to participate has been obtained, parents will receive login credentials for the study's web platform, through which they will be able to complete the required questionnaires. Socio-demographic information of the parents and clinical data related to the child/adolescent will also be collected at enrollment.
Parents will then be invited to participate in either the BEM group activity or the standard activity. At 3 and 6 months after the group activity, parents will be asked to complete the questionnaires again via access to the portal. The glycemic data of the children/adolescents will be derived from continuous glucose monitoring (CGM) measurements and extracted from the electronic medical records provided by the participating diabetes centers.

5.4 Questionnaires

All participants will be asked to complete the following questionnaires on a web platform, both at enrollment and at three and six months after the completion of group activities.

Parenting Stress Index Short form (PSI-SF)

The Parenting Stress Index is designed for the early identification of characteristics that, at the level of parents or the family as a whole, may compromise the normal development and functioning of the child. It aims to identify children with emotional and behavioral disorders as well as parents who may experience their parental role in a dysfunctional manner. The instrument is based on the premise that the stress

experienced by a parent result from a combination of specific characteristics of the child, the parent themselves, and a series of situational factors closely related to the parental role. The Italian validation pertains only to the short form of the test (PSI-SF), which is directly derived from the extended version. The short form is highly practical, easy to administer and interpret, making it particularly useful in clinical settings [14]. The PSI-SF investigates three main domains of stress-related factors, which are attributable to the child's characteristics, the parent's traits, and situational-demographic events. The short form consists of 36 items divided into three subscales: 1) Parental Distress (12 items), which assesses the level of distress a parent is experiencing in their parental role, understood as stemming from personal factors directly related to that role; 2) Dysfunctional Parent-Child Interaction (12 items), focusing on the parent's perception that the child does not meet their expectations and that interactions with the child do not reinforce their parental role; 3) Difficult Child (12 items), centered on key characteristics of the child that make them easy or difficult to manage, often originating from temperament, including behavioral patterns of defiance, disobedience, and demanding behaviors. Additionally, it is possible to calculate a response style score, which evaluates the extent to which the respondent answers the questionnaire with a tendency to present a more favorable image of themselves, thereby minimizing indications of problems or stress in the parent-child relationship.

Patient Health Questionnaire (PHQ9)

The PHQ-9 is a 9-item questionnaire developed as a depression screening tool for use in primary care settings [15]. Each of the nine items corresponds to one of the symptoms listed in Criterion A of the DSM-IV for Major Depressive Disorder [16]. Participants are asked how often they have been bothered by each depressive symptom over the past two weeks. Response options include "not at all," "several days," "more than half the days," and "nearly every day," with corresponding scores of 0, 1, 2, and 3. The PHQ-9 scores range from 0 to 27, with cut-off points of ≥5, ≥10, and ≥15 indicating mild, moderate, and severe levels of depression severity, respectively [17]. The psychometric properties of the PHQ-9 are well established [18]. An Italian version of the questionnaire is available.

General Anxiety Disorder (GAD-7)

The GAD-7 is a self-reported questionnaire assessing generalized anxiety, consisting of seven items. The instrument is designed to evaluate the individual’s mental health status over the previous two weeks [19]. The items investigate the extent to which the individual has been bothered by feeling nervous, anxious, or on edge; being unable to stop or control worrying; worrying too much about different things; having trouble relaxing; being so restless that it is hard to sit still; becoming easily annoyed or irritable; and feeling afraid as if something awful might happen. Responses are scored 0, 1, 2, or 3 for experiencing these symptoms "not at all," "several days," "more than half the days," and "nearly every day," respectively. The scores are then summed to yield a total ranging from 0 to 21. Cut-off scores of 5, 10, and 15 represent thresholds for mild, moderate, and severe anxiety, respectively. When screening for an anxiety disorder, a recommended threshold for referral for further evaluation is a score of 10 or greater.
The questionnaire has been validated for use both as a screening tool and as a measure of symptom severity [19,20], including in primary care settings [21] and the general population [22]. An Italian version of the questionnaire is available.

Brief Pittsburgh Sleep Quality Index (B-PSQI)

The B-PSQI is the brief version (13 items) of the Pittsburgh Sleep Quality Index (PSQI) [23]. This questionnaire assesses the presence of sleep-related problems over the past month across five domains: sleep duration and efficiency, sleep latency, sleep disturbances, nighttime awakenings, and daytime dysfunction. Each domain is scored on a scale from 0 (best outcome) to 3 (worst outcome). A global score is then calculated by

summing the scores of the individual domains, resulting in a total score ranging from 0 to 15. A total score greater than 4 is indicative of poor sleep quality. An Italian version of the PSQI is available, of which the B-PSQI includes a subset of the original items.

Parental Self-Efficacy for the Management of Diabetes Mellitus (PSESDM)

The PSESDM was developed to assess parental self-efficacy in performing diabetes-related tasks for their young children [24]. This questionnaire, designed for parents of children with diabetes, consists of eight items, each rated on a 5-point Likert scale. Responses range from 1 = "Strongly disagree" to 5 = "Strongly agree." Items 1, 2, 6, and 7 are reverse-scored. The total score ranges from 8 to 40, with higher scores indicating greater parental confidence in managing their child's diabetes.
The Italian version of the instrument will be validated using data from the present study.

Coping Orientation to Problems Experienced (COPE)

The COPE inventory will be used to assess parental adjustment and the adoption of different coping styles. The study will utilize the new Italian version of the instrument (COPE-NVI) [25]. The questionnaire consists of 60 items covering five domains: social support (12 items), avoidance strategies (16 items), positive attitude (12 items), problem-focused coping (12 items), and transcendence orientation (8 items). Participants are asked to indicate how frequently they engage in a given coping strategy when faced with difficult or stressful situations. Responses are rated on a 4-point scale ranging from 1 (I usually don't do this at all) to 4 (I do this a lot). Scores for individual items are summed separately for each of the five domains.

It should be noted that the instruments used in this study are intended for epidemiological and screening purposes and are not to be considered diagnostic tools. Furthermore, the questionnaires are anonymous, as they are completed directly through a dedicated online platform accessed via personal login credentials. Therefore, the researchers will not have access to individual scores. However, if pathological scores are identified, the participant will be informed and, if necessary, referred to specialized services.

6 EVALUATION OF EFFICACY

6.1 Efficacy parameters

The effectiveness of the BEM method compared to a standard educational approach will be assessed by comparing the differences in scores from baseline between the two groups, based on self-administered questionnaires (PSI-SF, PHQ-9, GAD-7, B-PSQI, PSESDM, COPE). Additionally, differences in glycemic indices in children/adolescents (variability, TIR, TAR, TBR) and HbA1c values relative to baseline will be evaluated. The definitions of the glycemic indices and the recommended targets are provided in the table below [26].

Glucose Index	**Blood glucose range**	**Recommended target (% of readings and daily duration)**
Variability	Coefficient of variation (%)	≤36%
Time in Range (TIR)	70-180 mg/dl	>70%; >16 hours and 48 min
Time below range (TBR) livello 1	<70 mg/dl	<4%; <1 hour

Time below range (TBR) livello 2	<54 mg/dl	<1%; <15 min
Time above range (TAR) livello 1	>180 mg/dl	<25%; <6 hours
Time below range (TAR) livello 2	>250 mg/dl	<5%; <1 hour

6.2 Frequency of endpoint assessment

Study questionnaires will be completed at baseline (randomization) and at 3 and 6 months following participation in group activities. The primary endpoint will be the comparison between study arms of the difference in PSI-SF questionnaire scores at 3 months post-participation relative to baseline. Clinical parameters (glycemic indices) will be recorded with the same frequency (baseline, 3 and 6 months), and the values considered will be those from the two weeks preceding baseline and follow-up at 3 and 6 months.

7 STATISTICAL CONSIDERATIONS

7.1 Sample Size Calculation

The primary endpoint is the PSI-SF questionnaire score at 3 months after the completion of group activities. The primary efficacy assessment will therefore involve comparing the differences in PSI-SF scores at 3 months relative to baseline between the study arms.
The difference between the two groups in changes of PSI-SF scores will be expressed in terms of effect size (the difference in scores between the two groups divided by the common standard deviation at baseline). It is widely accepted in the literature that an effect size of at least 0.5 can be considered clinically relevant [27]. From the previous study [13], baseline PSI-SF values were 75.4 ± 2.5; therefore, an effect size of 0.5 would correspond to a difference of 1.25 between groups.
To detect an effect size of at least 0.5 with a statistical power of 80% (α=0.05), at least 64 parents per group need to be evaluated. Assuming a dropout rate of 15%, a total of 150 parents will be enrolled (75 per group)

7.2 Statistical Analysis

All subjects enrolled in the study will be included in the analysis.
Descriptive data will be expressed as means and standard deviations or as medians and interquartile ranges for continuous variables, and as percentages for categorical variables.
Group comparisons for descriptive variables will be performed using Student's t-test or the Mann-Whitney U test for continuous variables, and the chi-square test for categorical variables.
Regarding the primary endpoint (difference in PSI-SF scores at 3 months compared to baseline), the comparison between study arms will be conducted using mixed-effects models for repeated measures (MMRM), which will include the baseline outcome value as a linear covariate and the study arm as a fixed effect. MMRM accounts for within- and between-subject correlations through a variance-covariance matrix with an autoregressive order 1 structure.
Similarly, comparisons between study arms for secondary endpoints related to questionnaire scores and glucometric measures (differences at 3 and 6 months compared to baseline) will be performed using MMRM.

These models will include the baseline value of the respective outcomes as a linear covariate and the study arm as a fixed effect. Results will be expressed as estimated means with 95% confidence intervals.
In addition to the analysis of the entire sample, subgroup analyses will be conducted separately based on parent sex and children/adolescents' age (<10 years and ≥10 years).

8 QUALITY ASSURANCE

The study will be conducted in accordance with Good Clinical Practice (GCP) guidelines to ensure the ethics and data integrity of the study. The study documents and data will be stored in the Trial Master File (TMF) and the Investigator Study File (ISF), to be completed and archived in compliance with current regulations.

9 STUDY MONITORING

The investigator/institution will permit monitoring, audits, IRB/IEC review, and regulatory inspections where required, providing direct access to all collected data and original documents.
The monitor (CRA) from the Contract Research Organization (CRO) and any potential auditor will have access to all electronic Case Report Forms (eCRFs) and informed consents collected for source data verification. Paper or electronic medical records are considered source documents that provide evidence of the patient's existence and confirm the integrity of the collected data. Source documents are stored at the investigative site.
A monitoring plan will be developed, and monitoring reports will be prepared during various monitoring visits (site initiation visit, remote monitoring, and close-out visit), conducted either remotely or onsite at the investigative centers.

10 ETHICAL ASPECTS

10.1 Ethical Standards

This study will be conducted in accordance with the Declaration of Helsinki concerning medical research involving human subjects (Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects - 64th WMA General Assembly, Fortaleza, Brazil, October 2013), in compliance with the protocol, Good Clinical Practice (GCP), the General Data Protection Regulation (GDPR), and applicable Italian regulations.
The investigator, by signing the protocol, affirms adherence to the instructions and procedures described therein and also declares compliance with GCP principles.
Prior to the initiation of the study, the protocol, the informed consent form, and the information provided to children and their parents must be approved by the local Independent Ethics Committee (IEC). Any amendments to the protocol, except for administrative changes, must also be approved by the local IEC.

10.2 Informed Consent

Before participating in the study, informed consent (IC) must be obtained, signed by each parent, and drafted in accordance with GCP guidelines and national regulatory and legal requirements. The paper IC

must be personally signed and dated by both the parent and the investigator. Any documents related to the parent will be retained by the investigator as part of the study documentation. Each parent will be provided with a signed copy of the informed consent and the clinical trial information sheet. Along with the IC, parents will also sign a authorization for the processing of their personal data and their child's data with DT1.

11 DATA COLLECTION

The medical history and data of children with T1D, who are the offspring of study participants, will be extracted from their medical records and recorded on a pseudonymized eCRF.
At study entry, the following information regarding the child will be collected: sex, age, level of education, ethnicity, body weight, height, duration of diabetes, diabetes treatment, presence of diabetes-related complications, last HbA1c value, glucometric data from continuous glucose monitoring (TIR, TAR, TBR), presence of other chronic conditions, hospitalizations in the past year due to severe hypoglycemia, diabetic ketoacidosis, or other reasons, participation in school camps, and engagement in physical activity. The medical records will serve as source documents for these data.

The data required by the protocol will be entered into an electronic case report form (eCRF). The quality and completeness of the data will be verified during and after data collection.

Regarding the parents, the collected data will include age, education level, employment status, marital status (married or cohabiting, separated, divorced, widowed, single/celibate), number of children, household size, and presence of other family members with diabetes. These details will be directly recorded by the parents through personalized access to the dedicated web platform used for the study, which will also facilitate questionnaire completion.

Throughout and at the end of the study, a database review will be performed to monitor data quality and completeness. Any modifications will be tracked using audit trail systems. Once all queries are resolved, the database will be frozen. The database will then be archived and subjected to backup and storage policies in accordance with GCP guidelines, and made available for subsequent audits if required. Raw data will be stored in a database for statistical analysis, which will be conducted after database lock. The impact of missing data on the primary endpoint will be assessed, and the need for imputation techniques will be considered.

An anonymized database will be managed and analyzed at the Center for Outcomes Research and Clinical Epidemiology (CORESEARCH s.r.l.) in Pescara.

12 Publication Policy

All analysis results will be produced solely and exclusively in aggregated form and in a manner that is not attributable, either directly or indirectly, to any individual patient.
The researcher and the sponsor commit to making the results of this study publicly available within one year of its completion, regardless of the outcome. The authorship, acknowledgments, and review procedures for scientific publications will be established prior to the end of the study and before any publication plan is developed.

13 REFERENCES

1. Sullivan-Bolyai S, Bova C, Johnson K, Cullen K, Jaffarian C, Quinn D, Aroke EN, Crawford S, Lee MM, Gupta O. Engaging Teens and Parents in Collaborative Practice: Perspectives on Diabetes Self-Management. Diabetes Educ 2014 Jan 27.
2. Lewandowski A, Drotar D. The relationship between parent-reported social support and adherence to medical treatment in families of adolescents with type 1 diabetes. J Pediatr Psychol 2007;32(4):427-36.
3. Berg CA, King PS, Butler JM, Pham P, Palmer D, Wiebe DJ. Parental involvement and adolescents' diabetes management: the mediating role of self-efficacy and externalizing and internalizing behaviors. J Pediatr Psychol 2011;36(3):329-39.
4. Cherubini V, Pintaudi B, Rossi MC, Lucisano G, Pellegrini F, Chiumello G, Frongia AP, Monciotti C, Patera IP, Toni S, Zucchini S, Nicolucci A; the SHIP-D Study Group. Severe hypoglycemia and ketoacidosis over one year in Italian pediatric population with type 1 diabetes mellitus: A multicenter retrospective observational study. Nutr Metab Cardiovasc Dis 2013 Dec 3.
5. Wagner VM, Grabert M, Holl RW. Severe hypoglycaemia, metabolic control and diabetes management in children with type 1 diabetes in the decade after the Diabetes Control and Complications Trial - a large-scale multicentre study. Eur J Pediatr 2005;164:73-79.
6. Cryer PE. Hypoglycemia: still the limiting factor in the glycemic management of diabetes. Endocr Pract 2008;14:750-756.
7. Edge JA, Ford-Adams ME, Dunger DB. Causes of death in children with insulin dependent diabetes 1990–96. Arch Dis Child 1999;81:318–396.
8. Realsen J, Goettle H, Chase HP. Morbidity and Mortality of Diabetic Ketoacidosis With and Without Insulin Pump Care. Diabetes Technol Ther 2012;14:1149-1154.
9. Couch R, Jetha M, Dryden DM, Hooton N, Liang Y, Durec T, Sumamo E, Spooner C, Milne A, O'Gorman K, Klassen TP. Diabetes Education for Children With Type 1 Diabetes Mellitus and Their Families. Evidence Report/Technology Assessment No. 166. (Prepared by the University of Alberta/Capital Health Evidence-based Practice Center under Contract No. 290-02-0023.) AHRQ Publication No. 08-E011. Rockville, MD: Agency for Healthcare Research and Quality. April 2008.
10. Patton SR, Dolan LM, Smith LB, Thomas IH, Powers SW. Pediatric parenting stress and its relation to depressive symptoms and fear of hypoglycemia in parents of young children with type 1 diabetes mellitus. J Clin Psychol Med Settings 2011;18(4):345-52.
11. Streisand R, Swift E, Wickmark T, Chen R, Holmes CS. Pediatric parenting stress among parents of children with type 1 diabetes: the role of self-efficacy, responsibility, and fear. J Pediatr Psychol 2005;30(6):513-21.
12. Smaldone A, Ritholz MD. Perceptions of parenting children with type 1 diabetes diagnosed in early childhood. J Pediatr Health Care 2011;25(2):87-95.
13. Ferrito L, Predieri B, Pjetraj D, Alessandrelli MC, Pagnini M, Iannilli A, Marino M, Tombolini S, Pintaudi B, Lucisano G, Zani F, Iughetti L, Nicolucci A, Cherubini V. Weekend-Based Parent-Group Intervention to Reduce Stress in Parents of Children and Adolescents with Type 1 Diabetes: A Pilot Study. J Diabetes Res. 2019 Nov 29;2019:7935945.

14. Esposito M, Marotta R, Roccella M, Gallai B, Parisi L, Lavano SM, Carotenuto M. Pediatric neurofibromatosis 1 and parental stress: a multicenter study. Neuropsychiatr Dis Treat 2014;10:141-6.

15. Lowe B, Kroenke K, Herzog W, et al. Measuring depression outcome with a brief self-report instrument: sensitivity to change of the Patient Health Questionnaire (PHQ-9). J Affect Disord 2004;81:61–6.

16. APA. Diagnostic and Statistical Manual of Mental Disorders DSM-IV-TR. 4th ed.Washington DC: American Psychiatric Press; 2000.

17. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med 2001;16:606–13.

18. Kroenke K, Spitzer RL, Williams JB, et al. The Patient Health Questionnaire Somatic, Anxiety, and Depressive Symptom Scales: a systematic review. Gen Hosp Psychiatry 2010;32:345–59.

19. Spitzer RL, Kroenke K, Williams JB et al. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med 2006;166:1092–1097.

20. Swinson RP. The GAD-7 scale was accurate for diagnosing generalised anxiety disorder. Evid Based Med 2006;11:184.

21. Ruiz MA, Zamorano E, Garcia-Campayo J et al. Validity of the GAD-7 scale as an outcome measure of disability in patients with generalized anxiety disorders in primary care. J Affect Disord 2011;128:277–286.

22. Lowe B, Decker O, Muller S et al. Validation and standardization of the Generalized Anxiety Disorder Screener (GAD-7) in the General Population. Med Care 2008;46:266–274.

23. Famodu OA, Barr ML, Holásková I, Zhou W, Morrell JS, Colby SE, Olfert MD. Shortening of the Pittsburgh Sleep Quality Index Survey Using Factor Analysis. Sleep Disord. 2018 Apr 12;2018:9643937.

24. Marchante AN, Pulgaron ER, Daigre A, et al**.** Measurement of Parental Self-Efficacy for Diabetes Management in Young Children**.** Children's Health Care, 2014;43:110-119.

25. Sica C, Magni C, Ghisi M, Altoè G, Sighinolfi C, Chiri LR, Franceschini S. Coping Orientation to Problems Experienced - Nuova Versione Italiana (COPE-NVI): uno strumento per la misura degli stili di coping. Psicoterapia Cognitiva e Comportamentale – 2008; Vol. 14 - n. 1:27-53.

26. Battelino T, Danne T, Bergenstal RM, et al. Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations From the International Consensus on Time in Range. Diabetes Care. 2019;42(8):1593-1603.

27. Cohen J. A power primer. Psychol Bull. 1992;112(1):155-9.