Title of the Project:

Evaluation of the efficacy of a new intensive treatment model for adolescents with high-complexity eating disorders (MINERVA).

1. General Information

1.1. Study identification

Title: Evaluation of the efficacy of a new intensive treatment model for adolescents with high-complexity eating disorders.

Identification code of the protocol: MINERVA

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1.2. Identification of the promoter

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3. Summary

Introduction: Eating Disorders (EDs) are serious disorders with high rates of relapse, chronicity and mortality. It has been estimated that up to 20-30% of the adolescent patients may be resistant to treatment, whereas the disorder often persists into adulthood. A lot of the affected patients require hospitalization, frequently on a recurring basis. The transition from hospitalization to a home environment is a challenging step in the course of the illness. This transition is complex for both patients and families, which is a significant prognostic factor for the overall outcome of the patient. While support after hospitalization for ED symptoms at home is common in clinical programs, there are still relevant difficulties in generalizing dietary patterns and managing emotions within the family setting. Prior studies showed that involving the family in the treatment contributed to treatment effectiveness. **Objective:** Evaluate the efficacy, efficient, and experiences of the patient of a new family-based intervention model for adolescents with high-complexity EDs. **Method:** A single-center, longitudinal study including pre-treatment and post-treatment assessments that uses both quantitative and qualitative variables. The current study includes 60 adolescents diagnosed with EDs according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Revised (DSM-5 TR), who completed the ED-MINERVA program. The program consists of four intervention phases: Phase 0 - Hospitalization (4 weeks) for physical stabilization; Phase 1 - Treatment in Family Apartments (3 weeks) for intensive family intervention; Phase 2 - Home Treatment (9 weeks) for generalization in their regular environment; Phase 3 - Transfer to the reference center (4 weeks) for continued treatment from their ED unit. Data of the patients and their families will be assessed at the beginning of Phase 0, the end of Phase 1, the end of Phase 3 after program discharge, and at 6 and 12 months of follow-up. The evaluation will include: i) interviews - semi-structured clinical interviews and interviews about the experiences of the program; ii) questionnaires assessing the severity of eating disorder symptoms, anxiety, depression, quality of life, motivation for change, functioning, family environment, and caregiver skills; iii) biometric and analytical data monitored in each phase; iv) data from the medical history regarding the number of readmissions at 6 and 12 months after the end of the intervention, and the time spent in low-intensity devices (outpatient consultations or day hospital) after 6 and 12 months post-program discharge. A retrospective ED control group matched by age and ED severity will be used for the variables i, iii, and iv. The study about the experiences of the patients will utilize *design thinking* methodology through mixed methods, qualitative and quantitative. A representative subsample of 10 adolescents and 10 of their family members will be selected for an in-depth study of their experiences using “PREMs” (parent and patient-reported experience measures) surveys and interviews at the beginning of the intervention, the end of Phase 3, and the end of the intervention to measure reported patient and family experiences with previous interventions and MINERVA.

4. Introduction

Eating Disorders (EDs) are mental disorders characterized by disturbances in eating behavior and irrational thoughts related to weight, food, and body image (APA, 2013). EDs are serious pathologies with a high rate of relapse (Steinhausen, Grigoroiu-Serbanescu, Boyadjieva, Neumärker, & Metzke, 2009; Madden et al., 2015), chronicity (Fichter, Quadflieg, Crosby, & Koch, 2017), and mortality (Smink, Van Hoeken, Hoek, 2012). The onset of the disease usually occurs in adolescence which is a critical period in physical and psychological development. Therefore, adapting interventions during the development age and involving the family from the beginning of treatment becomes particularly relevant. The main EDs included in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Revised Edition (DSM-5 TR) are anorexia nervosa (AN), bulimia nervosa (BN), and binge-eating disorder (BED). Regarding the course of the disorder, it has been noted that almost half of AN patients fully recover (Steinhausen, 2002). BN typically has a more benign course with a cure rate of 50%, improvement in 30%, and persistence in 20% of cases (Acerate, Trabazo, & Ferri, 2013). As for BED, limited longitudinal evidence suggests a more variable course than AN or BN, with a tendency towards integrated recovery and relapse, probably in a chronic course (Hilbert, 2019). Additionally, there are other atypical or subclinical forms of EDs included as “Other Specified Feeding or Eating Disorders” in the DSM-5 TR (OSFED; e.g., atypical AN, subthreshold BED, among others). Despite the relevance, chronicity, and clinical severity of OSFED, there is a lack of research analyzing treatment outcomes. The few studies comparing treatment response between atypical/subthreshold EDs and the main EDs found similar patterns of remission and relapse but also high dropout rates. Moreover, OSFEDs exhibit a high prevalence of psychiatric comorbidities, non-suicidal self-injury, suicidal ideation, and suicide attempts, requiring intensive and complex intervention (Withnell, et al., 2022).

Traditionally, the treatment of Eating Disorders (EDs) is provided in two distinct clinical settings: inpatient or outpatient. Total hospitalization (TH) is the most suitable therapeutic approach for adolescents with Anorexia Nervosa (AN) who present a moderate or high risk for medical complications derived from AN or severe self-harming/suicidal behaviors (NICE, 2004;2017). TH is also the treatment of choice for patients who have not improved after receiving outpatient care (NICE, 2004; APA, 2006) because it offers an intensive and effective approach, primarily focusing on appropriate eating patterns and weight restoration if necessary. An alternative treatment modality to outpatient and traditional TH is a Partial Hospitalization (PH), where the patient attends the intervention for several hours daily or multiple days a week within a hospital setting.

It is a safe option, less costly compared to TH, providing patients with intensive treatment in a clinical environment while allowing them to stay involved in their natural environments and social network (Herpertz-Dahlmann et al., 2014).

Different studies have shown a rate between 20-30% of patients in Partial Hospitalization (PH) who have required Total Hospitalization (TH) for recovery (Herpertz-Dahlmann et al., 2014; 2016; Serrano-Troncoso et al., 2020). In both treatment modalities, patients and families encounter difficulties in transitioning from TH or PH to home, highlighting the need for additional support in managing ED symptoms at home (Herpertz-Dahlmann et al., 2014). When patients exhibit severe symptoms that require hospital care, the organization of these

facilities often predisposes to reduced family involvement in treatment during admission, often taking a step back. However, there is evidence that the family plays a central role in the recovery of individuals with EDs. Family-Based Treatment (FBT) has demonstrated its superiority in multiple studies, especially for AN (Wallin and Holmer, 2021). Clinical trials, systematic reviews, and follow-up studies of FBT for AN in adolescents have shown remission rates between 31% and 49% after 12 months post-treatment. These remission rates continue to improve after more than five years since completing the treatment (Lock, 2012). Regarding BN in adolescents, there are few randomized clinical trials. Previous studies suggest that Adapted Cognitive-Behavioral Therapy for Adolescents (CBT-A) and FBT for BN could be effective for this population. Le Grange et al. (2015) reported greater efficacy of FBT-BN compared to CBT-A in binge and purge abstinence symptoms at the end of treatment and at the 6-month follow-up. At the 12-month follow-up, there were no differences between the two treatments. Additionally, the study observed an association between lower family psychopathology and a better response to FBT-BN compared to CBT-A.

Despite these findings, FBT is not effective for a significant minority of cases where the family structure exhibits high expressed emotion, e.g. a concept related to a caregiving style with high emotional overinvolvement and criticism, leading to lower remission rates and premature treatment dropout (Eisler, 2007). Therefore, some families require longer and more supportive treatments, especially those with greater severity of EDs and higher comorbidity (Lock, 2012). Achieving therapeutic change early is particularly crucial for patients and families with the complex structures and characteristics mentioned earlier because, if not addressed early, they lead to poorer treatment outcomes. On the other hand, FBT may also be challenging to administer directly in patients with higher severity or psychopathological comorbidity.

There is a need to investigate the Family Treatment Apartment (FTA), a more intensive form of FBT. FTA involves the patient and their family living in a separate apartment owned by the healthcare system provider for a short period (two weeks), with daily interventions often following a brief hospital admission for renutrition and medical stabilization (Wallis, 2013). Improvement was found in reduced ED symptoms, increased understanding and skill development in managing EDs symptoms by parents, as well as improvement in intrafamily relationships. Therefore, it is concluded that the FTA intervention can be considered as a suitable complementary treatment that can be applied alongside FBT or before initiating it, especially in families with high complexity (Fink, et al., 2017).

The treatment in family apartments and subsequent home intervention could promote the generalization of management at home, family empowerment, therapeutic alliance, and more effective integration of the adolescent into the community. The effectiveness of a home-based program after a brief hospitalization has been evaluated in a German adolescent population with AN (Herpertz-Dahlmann et al., 2021). The results indicated that the majority of patients achieved and maintained the weight goal at the one-year follow-up. There was a significant improvement in eating disorder symptoms and overall psychopathology of the patients, as well as in caregiver skills. Family satisfaction with the treatment was also high.

The present study aims to evaluate the effectiveness, efficiency and experiences of the patients of a new intervention program for adolescents with high-complexity EDs and their families. The program will be implemented at our center in the last quarter of 2023 and includes FTA as part of the treatment. The program consists of four intervention phases, from higher to lower intensity, with the goal of stabilizing ED symptoms, restructuring family dynamics, empowering the family, generalizing the results at home, and finally, transferring the patient to their reference center.

5. Hypotheses/objectives

General hypothesis:
The program ED-MINERVA will be an effective and efficient model for the pediatric population with high-complexity disorders. Furthermore, the patient/family experience will be positive. The program will be more effective and efficient than previous interventions in maintaining clinical improvement and overall functioning.

Main specific hypotheses:

Related to effectiveness:

H1. Patients included in the ED-MINERVA program will improve in the BMI percentile between the start and the end of the MINERVA intervention. Weight improvement will be at least equal to that achieved by the retrospective control group. This is a non-inferiority hypothesis.

H2. Patients included in the ED-MINERVA program will show improvement in their eating habits between the beginning and the end of the intervention, measured by specific questionnaires.

H3. Patients included in the ED-MINERVA program will improve in functionality between the beginning and the end of the intervention, and this improvement will be maintained at 6 and 12 months after completing the MINERVA program.

H4. In comparison with the retrospective control group, the ED-MINERVA program will achieve a higher recovery rate at the 6 months follow-up after completing the program: a higher percentage of patients with the absence of binge-eating episodes and compensatory behaviors (self-induced vomiting and/or use of laxatives/diuretics) among those who exhibited these behaviors, a higher percentage of patients in weight recovery (return to their pre-disorder BMI percentile) in the underweight group, and a higher percentage of patients who do not meet diagnostic criteria for an ED anymore.

*For the ED-MINERVA program to be considered effective, H1 and H2 must be fulfilled. It is anticipated that the ED-MINERVA program will meet at least one of the other two hypotheses (H3 and/or H4), and thereby concluding that it is effective at clinical and functional levels, and/or more effective than previous programs.

Related to efficiency

H5. At the 6 month follow-up after discharge from the ED-MINERVA program, more than 60% of the patients will be able to continue treatment through low-intensity outpatient services (including day hospitals and specific external consultations) in ED units.

H6. In comparison with the retrospective control group, the ED-MINERVA program will lead to a lower number of readmissions at 6 months and 12 months after completing the program.

*The program will be considered as efficient if it fulfills H5 and even more efficient than previous programs if it fulfills both H5 and H6.

Related to experiences of the patient

H7. The patients and the families will perceive a high level of satisfaction with the received intervention and adhere to the program, including a low dropout rate (less than 20%).

Secondary specific hypotheses:

H8. Family variables (mental illness in parents, knowledge and baseline skills in managing ED) and clinical variables (age, age of onset of the disorder, severity, time without treatment for the ED, total duration of the ED) will be related to a worse outcome (maintenance of ED symptoms, which is a reduction of symptoms less than 40%, or comorbidity) and will be associated with hospital readmission.

H9. Patients included in the ED-MINERVA program will show a significant reduction of symptoms of anxiety and depression, as well as an improvement in motivation for change from admission to discharge from the program.

H10. The families in the ED-MINERVA program will significantly increase caregiver skills from admission to discharge from the program.

H11. The ED-MINERVA program will improve the quality of life for both patients and their families from the beginning to the end of the program.

Objectives:

General objective:

Investigate the effectiveness, efficiency, and the patient/family experience of the treatment program for adolescents with high-complexity ED. The study will also assess the effectiveness and efficiency of the program in comparison to previous programs at discharge and at 6 months and 12 months after completing the intervention.

ED-MINERVA is already an approved program and is set to commence at a clinical level. The current research study involved evaluating the ED-MINERVA program.

Main specific objectives:

Related to effectiveness:

O1. Evaluate the change in BMI percentile between the start and the end of the intervention in patients included in the program. Assess these changes in comparison with the retrospective control group.

O2. Evaluate the change in ED symptoms in patients included in the ED-MINERVA program between the start and the end of the program.

O3. Evaluate functionality between the start and the end of the intervention in patients included in the ED-MINERVA program, and at 6 and 12 months after completing the intervention.

O4. Examine recovery percentages at 6 month follow-up: percentage of patients with the absence of binge-eating episodes and compensatory behaviors (self-induced vomiting or use of laxatives/diuretics), percentage of patients in weight recovery (return to their pre-disorder BMI percentile) in the underweight group, percentage of patients not meeting diagnostic criteria for a primary ED, and compare them with a retrospective control group with ED.

Related to efficiency:

O5. Study the percentage of patients in low-intensity outpatient services (including day hospitals and specific external consultations) at 6 months after completing the intervention.

O6. Study the percentage of the number of readmissions at 6 and 12 months follow-up and compare it with a retrospective control group with ED.

Related to experiences of the patient:

O7. Evaluate the degree of satisfaction with the received intervention, adherence, and dropout rates of the patients and families.

Secondary specific objectives:

O8. Study the relationship between family variables (mental illness in parents, knowledge and baseline skills in managing ED) and clinical variables (age, age of onset of the disorder, severity, time without treatment for the ED, total duration of the ED) with the intensity of the outpatient services after discharge, the number of hospital readmissions during the 6 month follow-up, and clinical severity of the ED (symptom reduction, readmissions).

O9. Evaluate changes in symptoms of anxiety, depression, motivation for change, functionality, and quality of life from admission to discharge in patients included in the program.

O10. Evaluate changes in caregiver skills from admission to discharge in families of patients included in the program.

O11. Evaluate changes in the quality of life of patients and their families included in the program from admission to discharge.

6. Methods:

6.1. Study design

The current study is a single-center, longitudinal, pre-post treatment study using both quantitative and qualitative variables, including a retrospective control group for selected quantitative variables. The study evaluates a new intervention model that will be implemented in the Integrated Functional Unit (UFI) for Eating Disorders at the Hospital Sant Joan de Déu Barcelona, starting in the last quarter of 2023. This unit will provide all patients with high-complexity ED in Catalonia. Therefore, it has been considered that obtaining a good control group to be evaluated in parallel is not feasible. For the variables that can be collected from medical records, a retrospective control group of patients will be obtained. This eventually leads to a mixed prospective and retrospective design. For the rest of the variables, there will be no control group in the longitudinal evaluation, and patients will serve as their own control, taking the baseline assessment into account (prospective design).

The methodology for evaluating experiences of the patient will consist of mixed methods, both qualitative and quantitative. For the qualitative part, a representative sample of 10 adolescents and 10 of their family members will be selected from the 60 included patients to conduct an in-depth study of their lived experience. For the current study, *design thinking* techniques (Smiechowski et al., 2021) will be used to obtain valuable information about possible improvements in the treatment.

The qualitative analysis of the patient and family experience will be divided into four interviews, coinciding with each of the phases of the program, from the initial treatment phase to the phase of transferring the patients to the specialized reference center.

- Phase 0 - Total Hospitalization (4 weeks)
  - Individual interview with the patient during the last week of the phase.
  - Interview with parents, caregivers, or legal guardians during the last week of the phase.
- Phase 1 - Treatment in Family Apartment (3 weeks)
  - Individual interview with the patient during the last week of the phase.
  - Interview with parents, caregivers, or legal guardians during the last week of the phase.
- Phase 2 - Home Treatment (9 weeks)
  - Individual interview with the patient during the last week of the phase.
  - Interview with parents, caregivers, or legal guardians during the last week of the phase.
- Phase 3 - Transfer to the Reference Treatment Center (4 weeks)
  - Individual interview with the patients after 4 weeks from the start of this phase.
  - Interview with parents, caregivers, or legal guardians after 4 weeks from the start of this phase.

Regarding the patient/family experience, interviews will be conducted and the ¨PREMs¨ survey (Parent and Patient-Reported Experience Measures) will be distributed at the beginning of the intervention, at the end of phase 3, and at the end of the intervention. This serves as a manner to measure the experiences that were reported by the patient and

families, both in relation to their experiences before the program and during the different phases of the program. This evaluation will be carried out with a subsample of *N*=10 patients and their families. It includes both quantitative and qualitative variables and aims to represent the experience of the total participants by analyzing the results obtained in both the quantitative and qualitative phases. For the qualitative research, semi-structured interviews will be used, based on a set of open-ended questions and topics exploring the patients´ experience within the MINERVA program. There will be no predetermined order of presenting the question, and new questions may be incorporated in case they are relevant or appropriate for the research. The interviews will cover socio-cultural, domestic, and emotional aspects to identify different patient and family profiles. Furthermore, perceptions and expectations regarding the received treatment will be obtained. The analysis of this information will enable informed *decision-making* on how to better adapt the treatment to the requirements and needs of those receiving it.

6.2 Participants

A total of 60 patients aged between 12 and 18 years with a diagnosis of ED (according to DSM-5 TR criteria, APA, 2022) will be evaluated. These patients will be referred to the ED-MINERVA program at the Eating Disorder Unit (UFI) between October 2023 and December 2024.

Inclusion criteria for the ED-MINERVA Program:

To enter the program, the patient must present a ¨turbulent evolution¨, receiving specialized treatment in an Eating Disorder Unit in Catalonia. ¨Turbulent evolution¨ is considered to be present in two different situations for this study: Firstly, having undergone more than a year of specialized treatment, including partial and total hospitalization, without achieving stabilization of ED symptoms (clinical improvement of at least 50 on the CGAS functioning scale - see section 2.3 - implying moderate to correct functioning with difficulties present in specific vital areas). Secondly, having undergone more than three total hospitalizations without achieving stabilization of ED symptoms upon discharge. Exclusion criteria are limited to patients with acute ED or biological decompensation that require urgent pediatric attention.

Inclusion/exclusion criteria for the prospective study:

Inclusion criteria:

- Patient with a diagnosis of ED who has been included in the MINERVA program.
- Age between 12 and 18 years.
- The patient and parents must accept participation in the study and sign the informed consent for participation.

Exclusion criteria:

There are no exclusion criteria, except for refusal to participate in the study.

Selection of the subsample for the qualitative study regarding patient experience:

For the study evaluating the experience of patients and families, in the first phase of the qualitative research, a group of participants will be selected from the entire sample of 60 patients, considering the following characteristics:

- 9 females and 1 male will be chosen (taking into account the representation of sexes in AN : 90% females, 10% males).
- 2 patients with single-parent families and 8 with nuclear and/or composite families will be selected.
- 5 patients with one or more siblings and 5 only children will be chosen.
- Finally, 2 prepubertal patients (12-13 years old), 5 patients aged between 14 and 15 years, and 3 patients aged between 16 and 18 years will be selected (following the approximate age distribution representation of the sample).

Inclusion/exclusion criteria for the retrospective study:

Patients will be consecutively chosen in pairs by sex, age, and diagnosis of ED with the patients included in the prospective study. The temporal reference point will be the first day of admission to acute total hospitalization, and the weight percentile on this day will also be taken into account for the matching subjects. Additionally, these subjects must meet the same ¨turbulent evolution¨ criteria required to be included in the ED-MINERVA program, to ensure comparability in severity.

Inclusion criteria:

- Patients aged between 12-18 years treated in our center between the years 2000 and 2015 for an ED.
- Patients with a turbulent evolution: undergoing more than a year of treatment including partial and total hospitalization, without achieving stabilization of ED symptoms, or having undergone more than three total hospitalizations without achieving stabilization of ED symptoms upon discharge.
- Must have at least one total hospitalization admission in our center.

Exclusion criteria:

- Those who do not have at least 80% of the required data will not be selected.

6.3 Instruments:

- **Eating Disorders Inventory 3 (EDI-3) (Garner, 2004):** Evaluates clinically relevant psychological traits and constructs in individuals with ED aged 12 and older. Consists of 91 items and is divided into 12 main scales: three specific to ED and nine more general psychological scales. Responses are provided on a Likert scale (0-4). Excellent test-retest stability coefficients were obtained in adolescent and adult clinical populations (r= 0.98 for the eating disorders risk index). Additionally, the scales show adequate consistency coefficients (between α=.63 and α=.97). There is also evidence of construct

and criterion validity (Elosua et al., 2010).

- **Beck Depression Inventory (BDI) (Beck et al., 1996):** Assesses the severity of depressive symptoms in individuals aged 13 and older, with a cutoff point of 13 or higher indicating the presence of depressive symptoms. Consists of 21 items on a Likert scale. It demonstrates high reliability in terms of internal consistency (Cronbach's alpha coefficient = 0.83) and temporal stability, with test-retest scores ranging between 0.6 and 0.72 (Sanz and Vázquez, 1998). The version for children and adolescents allows for the assessment of symptoms between the ages of 7 and 18 (https://www.pearsonclinical.es/).

- **State Trait Anxiety Inventory (STAI) (Spielberger, 1970):** Divided into two parts, each with 20 Likert-format items, and applied to adolescents from the age of 16 and adults. One part assesses state anxiety, and the other assesses trait anxiety. In terms of reliability analysis, Cronbach's alpha of 0.90 was obtained for trait anxiety, and 0.94 for state anxiety. These results support that the questionnaire maintains appropriate psychometric properties and is sensitive to the increase in environmental stimuli produced by stress (Guillén and Buela, 2011). In its forms for children/adolescents (STAI-C), it allows for assessment in individuals between 9 and 15 years old (https://web.teaediciones.com/).

- **Kidscreen-27 Quality of Life Inventory (Bullinger et al., 2006):** Assesses the quality of life in children, defined as the subjective well-being of healthy children and adolescents, as well as those with chronic illnesses, over the past week. Consists of 27 Likert-format items (1-5), divided into 5 scales allowing interpretation of physical well-being, psychological well-being, autonomy and relationship with parents, emotional support, and school environment. The current study uses a shortened version of the Kidscreen-52 and it demonstrates very good psychometric quality. According to Spanish population norms, the factorial analysis explains 56% of the variance, and the reliability of each dimension has a Cronbach's alpha > 0.7. According to the authors, the construct validity of the instrument is satisfactory (Ravens-Sieberer et al., 2007).

- **The Anorexia Nervosa Stages of Change Questionnaire (ANSOCQ) (Prochaska and DiClemente, 1982):** Comprises 20 items with Likert scores (1-5) that assess motivation for recovery from anorexia nervosa in the adolescent population. The questionnaire's structure is derived from Prochaska and DiClemente's Stages of Change model, with each item corresponding to one of the stages: Precontemplation, Contemplation, Preparation, Action, and Maintenance. The internal consistency of the Spanish adaptation, measured with Cronbach's alpha, is 0.94, and the test-retest reliability is 0.90 (Serrano et al., 2004).

- **Caregiver Skills (CASK) (Hibbs et al., 2015):** Evaluates caregivers' skills on a scale of 0 to 100. Confirmatory factor analysis of the Spanish version confirms strong factorial validity of the 6 factors of the original questionnaire (flexibility to change (p=.141), self-care (p=.447), impulse control (p=.998), understanding and acceptance (p=.627), emotional intelligence (p=.724), and frustration tolerance (p=.695)). Internal consistency falls within a moderate range (Vintró et al., 2018).

- **Children's Global Assessment Scale (CGAS) (Shaffer et al., 1983):** Developed to assess the level of functional impairment in children/adolescents at the time of examination. CGAS is scored on a range of 1 (maximum impairment) to 100 (normal functioning). Scores above 70 reflect normal functioning. Psychometric properties of the adaptation for the Spanish population have been studied with satisfactory results in terms of reliability (over time and between evaluators) and validity (differentiating between groups of children with and without pathology and those with a different number of disorders) (Ezpeleta, Granero, and de la Osa, 1999).

- **PREMs Survey:** Implemented as a systematic online survey, the PREMs survey aims to assess and personally describe the patients´ experience of healthcare services. It allows for continuous monitoring over time through the voluntary collaboration of patients and families. The survey helps identify opportunities for improving service quality and promotes ongoing enhancement of the provided services. It consists of closed-ended questions with Likert scale ratings and open-ended questions to gather narrative information that enriches quantitative data with greater detail and context. The survey includes a brief explanation of the initiative, objectives, and data protection policy, providing information about the anonymity of the survey.

The following table summarizes at what time the questionnaires will be administered in the current study:

Questionnaires	Beginning of MINERVA		End of MINERVA	6 month follow-up	12 month follow-up
EDI-3	X		X		
BDI	X		X		
STAI	X		X		
KIDSCREEN-27	X		X		
ANSOCQ	X		X		
CASK	X		X		
CGAS	X		X	X	X
PREMs	X	X (end of phase 3)	X		
BMI	X		X		
Assessment of recovery percentages	X			X	
Evaluation of treatment intensity				X	

Evaluation of readmissions				X	X
Clinical interview	X		X		

6.4. Description of the clinical program

ED-MINERVA Program aims to improve the eating disorder symptoms and associated problems of the affected individuals and provide tools to enhance the family's management (nutritionally, emotionally, and behaviorally) in their natural environment. The treatment consists of four phases with a gradually decreasing therapeutic intensity, ranging from total hospitalization to home-based treatment and subsequent linkage with specialized local facilities.

Below are the main objectives for each treatment phase:

- P0: Total hospitalization
- Maintenance of physical stabilization
- Ensuring adequate food intake while preventing compensatory behaviors
- Addressing ED-related problems
- Improving nutritional administration
- Enhancing awareness of the disorder and motivating the patient to change

- P1: Family Treatment Apartment (FTA)
- Intensifying the intervention to the needs of the patient and family
- Intervening from a systemic perspective
- Involving other family members in the treatment
- Collaborating with the family in developing skills to cope with the disorder
- Working on more autonomy and improved ED decision-making
- Facilitating a good transition from hospitalization to home

- P2: Home Treatment (HoT)
- Facilitating a good transition from hospitalization and family treatment apartments to home
- Assisting in the progress that began in the hospital environment
- Providing treatment in a more family and social context
- Empowering families in their natural setting
- Promoting integration of the patient into their family, social, and school environments

- P3: Transferring to their specialized reference center
- Gradually reducing the intervention promoting autonomy and emotional management within their family and school environment
- Ensuring continued care with their ED hospital unit
- Monitoring the implemented intervention

The entire care process aims at empowering the family, promoting autonomy in the care of the affected individual, and facilitating their social, familial, and school integration.

Depending on the patient's or family's characteristics, it is possible to initiate treatment at a more advanced intervention phase (for example, starting treatment at Phase 1) or skip a phase considering it as completed or contraindicated (for example, moving from Phase 0 to Phase 2 without going through treatment in family apartments). This will not be a reason to exclude participants from the study, but it will be taken into account when conducting the study analyses.

6.5. Study Procedure

Patients diagnosed with EDs who meet the inclusion criteria for the study will be individually assessed during the first three days of admission (P0). Parents and patients over 12 years old who agree to participate in the study will complete and sign the informed consent and assent forms, respectively. Subsequently, children/adolescents will respond to the EDI-3, BDI-2, STAI, KIDSCREEN-27, ANSOCQ scales, and parents will complete the CASK scales. These questionnaires will be filled out at the beginning, at the end of the intervention, and at 6 and 12 months after the intervention ends. At the end of Phase 3, selected patients and families will complete the PREMS questionnaire and participate in the interview about the experience of patients/families. The referring clinician will complete the CGAS at the beginning of the treatment (P0), at the end of the intervention (P3), and at 6 and 12 months after this completion.

6.6. Statistical Analysis

6.6.1. Sample Size

The sample size has been demonstrated to be 60 causes per group. This size is obtained by accepting an alpha risk of 0.05, a beta risk below 0.10 in a two-sided test for a significant difference between re-admission at 6 months were 4.7% in the FTA group and 32% in the conventional intervention group. A follow-up loss of 13% is estimated.

6.6.2. Statistical Analysis

For quantitative variables:

The data will be analyzed using SPSS v.22. Firstly, descriptive statistics of the variables will be performed, and their normality will be assessed.

i. Longitudinal design, with the patient as their own control.
    a. Repeated measures ANOVA for continuous variables
    b. McNemar's test for repeated measures for percentage variables
i. Longitudinal design, with a retrospective control group.
    a. Repeated measures ANOVA for continuous variables, with the group factor
    b. McNemar's test for repeated measures for percentage variables

For the qualitative variables:

Qualitative analysis is a dynamic and creative process primarily fueled by the researchers' direct experience in the studied scenarios and consists of different phases:

i. Data synthesis, focused on the selection and condensation of data collected through the creation of summaries, codifications, theme relationships, classifications, etc., generating profiles of patients and families with specific needs.
ii. Presentation and visualization of data, aimed at facilitating the reflective view of the researcher through condensed presentations, such as structured summaries, synopses, sketches, diagrams, etc.
iii. Elaboration and verification of conclusions, where various tactics are used to extract meanings from the data, including comparison/contrast, identification of patterns and themes, triangulation, searching for negative cases, etc.

The analysis will be conducted using the ATLAS.ti. software.

7. Study Schedule

A period of one year is estimated for the recruitment of 60 patients with EDs for the ED-MINERVA program. The project's initiation is planned for October 2023, with an expected recruitment pace of approximately 2 patients per month for entry into the program (P0).

Considering the average duration of treatment for each phase:

- Phase 0: Total hospitalization - 4 weeks
- Phase 1: Hospitalization in family apartments - 3 weeks
- Phase 2: Home-based treatment - 9 weeks
- Phase 3: Transfer for the reference ED unit - 4 weeks
- Total weeks of the ED-MINERVA program: 20 weeks.

Based on this projection, the last patient would enter during July 2024, concluding the study 5 months after completing Phase 3 of the ED-MINERVA Program to assess retesting during this timeframe. Therefore, the study would conclude in December 2025. Data analysis and communication of results to the scientific community will take place in the following months, from December to March 2026.

The study will commence upon approval from research committees and the ethics committee of our institution, and the schedule will be adjusted accordingly if required.

8. Limitations and benefits

The main limitation of the study on the effectiveness of the ED-MINERVA Program for adolescents with high-complexity ED is the absence of a parallel control group to compare the effectiveness to another similar treatment with the same patient profile. As there is no

similar intervention model in operation simultaneously, a retrospective control group will be used to study the selected quantitative variables (patients with a similar psychopathological and family profile who attended another treatment center in the same area previously).

Patients will not receive a specific benefit from participating in the study, but they may contribute to a better understanding of the potential contributions of a program addressing high-complexity EDs with the mentioned characteristics.

9. Data Management

9.1. Data source

The researcher must ensure data confidentiality and the protection of patients' identities from unauthorized third parties. In the Data Collection Logbook (DCL) or other documents sent to the sponsor, patients will be identified not by their names but by an identification code. The researcher must ensure the confidentiality of the collected information.

For prospectively collected data: participation in the study will be proposed to all patients and families entering the ED-MINERVA Program. After their acceptance and signing of the informed consent and assent, a code will be assigned to each participant. The code will use letters referring to the study's name and a number for each patient, which will not be linked to the subject's personal data. An Excel file will identify the correspondence between the patient's code, their name, surname, and data of birth. This document will be stored within a share folder on the internal computer network of the Hospital Sant Joan de Déu. Only the researchers Eduardo Serrano and Esther Via will have access to this document. All other study data, excluding personal information, will be entered by the research team into an online electronic DCL using a platform accepted for clinical data management, with the necessary security and traceability guarantees for this use (RECAp, Research Electronic Data Capture, Vanderbilt University, USA). The obtained (coded) information will be transferred to Excel and/or SPSS, which will also be stored in local folders when required. All study researchers will have access to this data.

For retrospective data: An external personal, not directly involved in the research study but from the hospital environment (with permission to access health data), will be assigned to conduct a review of medical records. They will extract the variables of interest in a coded form, performing pseudonymization. This person will create a coded database with this information and send it to the research team. The years evaluated will be between 2000 and 2015, starting with the most recent years and progressively moving backward until reaching the required sample size (*N*). Cases with less than 80% of the required information will not be considered.

Patients will be selected consecutively, matched by sex, age, and ED diagnosis, with those included in the prospective study. They must meet the same criteria for "high-complexity" as required for inclusion in the ED-MINERVA Program (described above). In this case, since it is not possible to obtain consent from these patients who are no longer followed in our center, an exemption from consent is requested. This database will also be stored in local

computer network folders, protected, as in the previous cases, with restricted access based on user level and password, and antivirus protection.

The information collected from the interviews of the patients will be stored in a paper format, along with the informed consent and assent forms. All these documents will be kept in a folder in a cabinet of the study's Principal Investigator (IP) office, secured with a key. The IP will be responsible for safeguarding this study database.

The databases will be stored in folders on the local computer network of the Hospital Sant Joan de Déu, protected, as in the previous cases, by restricted access based on user level and password, and antivirus protection. The computer equipment of the sponsoring center will be located at all times in premises secured with keys and alarms, and in buildings guarded by security personnel. Complete identification data and written consent will be stored in the investigator's file in accordance with Constitutional Law 3/2018, of December 5, on Personal Data Protection and guarantee of digital rights. According to this law, the personal data required from the subjects are necessary to fulfill the study's objectives. The participating subject has the right to access their personal data and to request their rectification or cancellation.

10. Ethics and legal aspects

The study will be conducted in compliance with the Declaration of Helsinki (current version; currently Fortaleza, Brasil, October 2013). The study will be carried out according to the protocol and legal requirement relevant to Law 14/2007 of July 3, on Biomedical Research. Regarding the use of health data in research, the study will comply with Constitutional Law 3/2018, of December 5, on Personal Data Protection and guarantee of digital rights.

All participants will receive the informed consent where they can confirm their participation in the study and receive information regarding research purpose, procedures to follow, and the confidentiality of their data. Patients (12 years or older) will also receive information, and if they agree to participate, they must sign the assent. Patients who turn 18 during their participation in the study must reaffirm their participation by signing the informed consent once they reach this age.

11. Data confidentiality

The processing, communication, and transfer of personal data of all participants will comply with the provisions of EU Regulation 2016/679 of the European Parliament and the Council of April 27, 2016 regarding the protection of individuals concerning the processing of data and the free movement of such data. This regulation became mandatory from May 25, 2018, and also with Constitutional Law 3/2018, of December 5, on Personal Data Protection and guarantee of digital rights. The legal basis justifying the data processing is the consent signed by the patient, as established in Article 9 of EU Regulation 2016/679.

The data collected for these studies will be identified only by a code, so no information allowing the identification of participants will be included. Only the doctor/psychologist

conducting the study and their collaborators with the right to access source data (medical history) will be able to link the data collected in the study to the patient's medical history.

The identity of the participants will not be accessible to anyone else except in the case of a medical emergency or legal requirement.

They may have access to personally identifiable information, health authorities, the Research Ethics Committee, and personnel authorized by the study promoter, when necessary to verify data and study procedures, but always maintaining confidentiality in accordance with current legislation. Only coded data, which will in no case contain information that can directly identify the participant (such as name and surname, initials, address, social security number, etc.) will be disclosed to third parties and other countries. In the event of such disclosure, it will be for the same purpose as described in the study and ensuring confidentiality. If there is a transfer of coded data outside the EU, whether to entities related to the hospital where the patient participates, services providers, or collaborating researchers, participants' data will be protected by safeguards such as contracts or other mechanisms established by data protection authorities. As project promoters, we commit to processing the data in accordance with EU Regulation 2016/679 and, therefore, to maintaining a record of the processing activities we carry out and assessing the risks of the treatments we perform to determine what measures we need to apply and how to do so. In addition to the rights already provided by previous legislation (access, modification, opposition, and cancellation of data, which is now deletion in the new Regulation), participants can now also limit the processing of data collected for the project that is incorrect, request a copy, or have it transferred to a third party (portability). To exercise these rights, they should contact the principal investigator of the study or the Data Protection Delegate of the Hospital Sant Joan de Déu at dpd@sjdhospitalbarcelona.org. They also have the right to contact the Data Protection Agency if they are not satisfied.

The Investigator and the Promoter will retain the data collected for the study for a least 5 years after its completion. Subsequently, personal information will only be retained by the center for health care purposes and by the promoter for other scientific research purposes if the patient has given consent for it, and it is allowed by law and applicable ethical requirements.

12. Funding and Insurance

This research is not funded by any public and/or private entity

13. Publication Policy

The researchers involved in the study commit to the dissemination of the results, whether they turn out to be negative or positive.

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