STUDY PROTOCOL

Full project title: *Changes in outcomes of treatment for adolescent anorexia nervosa after implementation of Family Based Treatment in a Norwegian child and adolescent mental health service: A retrospective cohort study with prospective follow-up*

Short project title and acronym: *Akershus university hospital retrospective cohort study of family based treatment / ARCS-FBT*

Short Norwegian title for public communication: *Familiebehandling av anoreksi – effekt og erfaringer med innføring av FBT-modellen*

SUMMARY

A two-group retrospective exploratory cohort study with longitudinal follow-up comparing adolescents with anorexia nervosa treated with generic family therapy to those treated with the manualised Family Based Treatment (FBT). The primary aim is to investigate whether adoption of FBT has led to faster normalisation of weight and lower rates of eating disorder in early adulthood. Secondary aims are to investigate whether implementation of FBT has changed the time to discharge, heterogeneity of patient weight change across treatment, rates of adverse events, rates of readmission, patient experiences of the treatment, long term functional outcomes and mortality. Data are extracted from patient health records, reported by participants and extracted from public registries.

STUDY MANAGEMENT AND RESEARCH GROUP

This study will be conducted by the Department of child and adolescent mental health services at Akershus university hospital. Director of research and innovation, professor Helge Røsjø, is responsible for research at Akershus university hospital. Head of Department Morten Grøvli has the administrative responsibility for the project on behalf of the hospital.

Project manager and principal investigator:
Erling W. Rognli, PhD
Clinical psychologist, Department of child and adolescent mental health services

Project group:
Hanne C. Kaspersen, MD
Consultant, Department of child and adolescent mental health services

Marianne Aalberg, PhD
Senior researcher, Department of research and development in mental health

Victoria Frivold, MPhil
Research coordinator, Department of child and adolescent mental health services

BACKGROUND

Adolescent anorexia nervosa is a severe eating disorder related to long-lasting morbidity and premature mortality (1, 2), and recent reports from hospitals suggests the prevalence in Norway may be increasing (3). The manualised family therapy "Family Based Treatment" (FBT) is currently the treatment approach for adolescent anorexia nervosa with the largest evidence base (4). FBT is recommended as a first line treatment in multiple service contexts (5, 6).

While there has been conducted several randomised controlled trials of FBT in academic settings (7), there are few large studies examining outcomes when FBT is implemented in clinical practice. A

systematic review published in 2015 found five such dissemination studies. Of these, three were conducted in academic clinical settings with the number of patients ranging from 11 to 20, and two were retrospective studies reporting changes in service use patterns after implementation of FBT in a regular mental health service (8). Two later studies have compared the outcomes achieved in clinical trials of FBT to those of FBT provided in regular clinical care, finding these to be comparable (9, 10), but these have both been conducted in highly specialised clinical contexts. More studies with higher power are needed to confirm the effectiveness of FBT when disseminated to regular healthcare contexts.

At the Child and Adolescent Mental Health Service (CAMHS) unit Nedre Romerike BUP, adolescent anorexia nervosa has consistently been treated with family therapy for about 20 years. In 2018 the unit implemented FBT, making several changes to the form of family therapy provided. As part of treatment monitoring, patients are weighed regularly, and weight data are recorded in patient health records.

Restrictive eating and corresponding weight loss are core features of anorexia nervosa, besides distorted views of the body and rigid preoccupation with losing weight and avoiding weight gain. Normalisation of eating behaviour and weight status is hence the primary treatment goal, making the patient health records in this case contain relevant outcome data.

The long-term course of anorexia nervosa is heterogeneous, and in some patients the disorder shows a protracted course, with long term morbidity and functional impairment, as well as increased mortality (11). There are few longitudinal studies of treatment outcomes with long follow-up periods (12). As Norway has a general system of personal identification numbers, following up patients across multiple public registries is a viable way to assess long term outcomes without the patients needing to participate in reporting.

AIMS

The primary aim is to assess the short and long-term effectiveness of FBT compared with non-manualised family therapy. This is operationalised as testing whether the adoption of FBT has led to patients achieving normalisation of weight faster than with the previously delivered family therapy, and whether it will lead to less treatment provided for eating disorders in adulthood. Secondary aims are to assess whether adoption of FBT have resulted in reduced time to discharge, changed the heterogeneity of weight gain across patients, whether there have been changes in the rates of adverse events and readmissions, and to assess whether the implementation of FBT has led to changes in long-term functional status and rate of mortality.

DESIGN AND METHODS

Participants and recruitment

This is a two-group retrospective exploratory cohort study with prospective longitudinal follow-up in public registries. Eligible participants are all patients initiating treatment during the years 2015-2020 with the eating disorder team at Nedre Romerike BUP with a primary ICD-10 diagnosis of F50.0 Anorexia nervosa or F50.1 Atypical anorexia nervosa. Patients will be excluded if they were treated during the years 2018-2020 and FBT was never initiated. It is estimated that the final sample size will be approximately 200.

Eligible participants will be identified through review of patient health records. Participants will be contacted by letter with information about the study, including a link to an online video explaining more about the study. Study personnel will make a follow-up telephone call approximately a week later to allow the eligible participant to ask any questions they may have before deciding on participation in the study. Participants who are interested in participating will be directed to a website

where they can sign an electronic consent form and complete a short survey about their experience of treatment. The consent form and treatment experience survey will be implemented in "Tjenester for Sensitive Data", which has appropriate security and allows for verified electronic signatures.

Participants will be contacted after they have reached age 16, and thus are able to give informed consent. They will be encouraged to discuss participation with their parents or other legal guardians.

Endpoints and data collection

Primary endpoint for the retrospective study is weight restoration, defined by patients having a weight measurement placing them at or above 95% of expected body weight (50. percentile) for age given Norwegian population norms, following established definitions of weight restoration (10).

Secondary endpoints are discharge from treatment and readmission to treatment (the latter is assumed to be right-censored).

Adverse events will be defined as debut of suicidal ideation, attempted suicide, debut of self-harming behaviour, severe self-harm where medical attention is indicated, hospitalisation for low weight or medical complications from low weight, admission to inpatient treatment for anorexia nervosa, involuntary gastric tube feeding, parental separation, and initiation of contact with child protective services.

Participant experiences and satisfaction with services will be assessed using the Generic Short Patient Experiences Questionnaire (GS-PEQ) (13).

The primary endpoint for the prospective study is continued morbidity, defined as being currently in treatment in specialist health care for any eating disorder. Secondary endpoints are mortality, level of education and employment status.

Data for the retrospective part of the study will be extracted from electronic patient health records. Weight data will be extracted directly from the electronic patient health record system (DIPS). One researcher will further go manually through all records of included patients and extract dates of treatment start, adverse events, discharge and any readmission, as well as checking the record for any weight measurements recorded but not entered into the weight database. As covariates we will also extract age, sex, gender, family structure, extent of care benefits received during treatment (pleiepenger), and comorbid disorders (ICD-10 diagnoses). Another researcher will independently extract data from a random 10% subsample for control and reliability assessment of coding.

Each participant will be assigned a random case identity number, which will be used for identification in all dataset files when data is analysed. Participant national identity numbers will be stored along with the corresponding case identity number in a separate file, the identity key file. Access to the identity key file will be restricted to the project manager and researchers performing data extraction. It will also be delivered to the agencies maintaining the relevant public registries.

When extracted, data will be entered directly into a REDCap database maintained by Akershus university hospital. Access will be restricted to researchers in the project group. Data will be stored and analysed de-identified.

Data for the prospective part of the study will be acquired from the following public registries: Norwegian Patient Registry, Norwegian Cause of Death Registry, and the databases "Attachment to employment, education and welfare benefits" and "Educational attainment of the population" collated by Statistics Norway. Data will be acquired from these databases in three waves; five, ten and twenty years after the last participant initiated treatment. All registry data will be acquired, stored and analysed de-identified.

Analysis plan

Statistical analysis will be conducted in a Bayesian framework using the Stan platform through the R (14) package brms (15).

We will evaluate whether adoption of FBT has led to faster weight normalisation by fitting a parametric survival model to the number of days until weight restoration is achieved. We will also fit models with gender, age, baseline weight, comorbid disorders and family structure as covariates, and further investigate whether any of these act as moderators of FBT compared with previous treatment. Similar parametric survival models will also be used for modelling differences in time to discharge and readmission. Differences in the rate of adverse events will be modelled using Poisson regression.

We will also evaluate differences between the cohorts in treatment course by fitting multilevel spline models to weight data with knots for every 4 weeks in treatment. Weight measurements will be nested within patients, and patients nested within cohorts. Spline models will allow for modelling non-linear weight change over the course of treatment, and the multilevel structure at the patient level will allow us to evaluate changes in heterogeneity of treatment response pre and post adoption of FBT, as well as visualise trends and heterogeneity of weight change across the course of treatment.

Analysis of prospective data will use parametric survival models or logistic or ordinal regression models, depending on the level of time specificity available in the data.

We have conducted simulations to investigate statistical power, assessing the type S (sign) and type M (magnitude) error rates, given inference based on the posterior median. We made the assumption of achieving at least a sample size of 150 patients and that implementation of FBT has led to a 10% increase in the probability of an event (i. e. weight restoration or discharge). With 1000 simulations, we estimated a type S error of 0.00 and an M error of 0.89, suggesting a very low risk of estimating the sign of the effect incorrectly and a small risk of underestimating the effect size. We conclude that the study will be adequately powered to achieve its primary aim.

The analysis will employ weakly informative prior distributions, using previous studies and other external knowledge (for instance about the biological limits of weight gain per day) to construct priors that rule out impossible areas of the parameter space (17).

ETHICAL CONSIDERATIONS

This study does not involve any direct experimental manipulation, and as long as the process of extracting and analysing data from patient health records and public registries is conducted with due care, there is no risk of harm to the participants. FBT has been widely implemented in Norwegian health care based on findings from experimental studies in treatment settings quite different from regular public healthcare services. Research on the short and long-term effectiveness of FBT in a Norwegian context hence has considerable value to society and future patients receiving treatment for anorexia nervosa.

STUDY TIMELINE AND PLANS FOR DISSEMINATION

The study was approved with qualifications by the Regional Ethics Committee in 2021 with a requirement to adjust the protocol to seek informed consent from all participants or their legal guardians. Final approval was granted in July 2022. The process of identifying and contacting eligible participants will start as soon as approval is received.

Data extraction for the retrospective part of the study will start for each participant as soon as informed consent is obtained. It is expected to be finished at the latest in the fourth quarter of 2023, with reliability checking completed within 2023. Preparation of computer code for analysis will be done concurrently, and analysis will commence when data extraction is completed. Preparation of reports

for publication will be done during 2023 and early 2024. Findings will be submitted to international scientific journals specialising in eating disorders. Abbreviated reports of findings will also be prepared and submitted to the journals of relevant Norwegian professional associations.

For the prospective part of the study data will be extracted in four waves, when the participant last initiating treatment has reached the planned time for follow-up and registries are updated. An individual follow-up date will be calculated for each participant, to adjust for differences in when participants initiated treatment, and the closest relevant registry entry to that date will be extracted. The project group will consult with the agencies maintaining the registries to plan data extraction in detail. Findings from the prospective part of the study will be reported in international scientific journals as they become available.

DATA RETENTION

Documentation for the clinical study will be retained for five years after final study report/publication.

FUNDING AND CONFLICTS OF INTEREST

The study is fully funded by the Department of child and adolescent mental health services at Akershus university hospital, through time allocated for research for the researchers who are employed at the department. Dr. Kaspersen works as a clinician treating eating disorders at the Nedre Romerike CAMHS unit, but has worked there before and after implementation of FBT, and does as such not have a conflict of interest relating to the results of this study. Dr. Rognli, Dr. Aalberg and Ms. Frivold have no conflicts of interest.

DECLARATIONS AND POLICIES

Amendments to the research protocol

The research protocol may require to be amended during the conduct of a clinical study. Any amendment to the research protocol will be agreed upon between the representative for the research responsible institution and the principal investigator. The amendments will be approved by the ethics committee.

Deviations from the research protocol

The study will be performed in accordance with this research protocol. Any protocol deviations will be reviewed by the representative for the research responsible institution. All deviations will be reported to the appropriate regulatory bodies as required.

Statements of compliance

The study will be performed in accordance with the ethical requirements defined in the Declaration of Helsinki. The study will not commence until all written approvals have been obtained.

Publication policy

Upon study completion the results of this study will either be submitted for publication and/or posted in a publicly accessible database of clinical study results. The results of this study will also be submitted to the Ethics Committee according to national regulations. All personnel who have contributed significantly with the planning and performance of the study (Vancouver convention 1988) may be included in the list of authors.

REFERENCES

1. Strober M, Freeman R, Morrell W. The long-term course of severe anorexia nervosa in adolescents: Survival analysis of recovery, relapse, and outcome predictors over 10-15 years in a prospective study. Int J Eat Disord. 1997;22(4):339-60.

2. Keshaviah A, Edkins K, Hastings ER, Krishna M, Franko DL, Herzog DB, et al. Re-examining premature mortality in anorexia nervosa: a meta-analysis redux. Compr Psychiatry. 2014;55(8):1773-84.
3. Befring ÅM. Flere unge sliter med spiseforstyrrelse under koronaen2021 06.09.21. Available from: https://www.nrk.no/norge/1.15279412.
4. Gorrell S, Loeb KL, Le Grange D. Family-based Treatment of Eating Disorders: A Narrative Review. Psychiatr Clin North Am. 2019;42(2):193-204.
5. National Institute for Health and Care Excellence. Eating disorders: recognition and treatment (NG69). 2020.
6. Helsedirektoratet. Nasjonal faglig retningslinje for tidlig oppdagelse, utredning og behandling av spiseforstyrrelser. 2017.
7. Gan JKE, Wu VX, Chow G, Chan JKY, Klainin-Yobas P. Effectiveness of non-pharmacological interventions on individuals with anorexia nervosa: A systematic review and meta-analysis. Patient Educ Couns. 2021.
8. Couturier JL, Kimber MS. Dissemination and Implementation of Manualized Family-Based Treatment: A Systematic Review. Eating Disorders. 2015;23(4):281-90.
9. Accurso EC, Fitzsimmons-Craft EE, Ciao AC, Le Grange D. From efficacy to effectiveness: comparing outcomes for youth with anorexia nervosa treated in research trials versus clinical care. Behav Res Ther. 2015;65:36-41.
10. Le Grange D, Gorrell S, Hughes EK, Accurso EC, Yeo M, Pradel M, et al. Delivery of Family-Based Treatment for Adolescent Anorexia Nervosa in a Public Health Care Setting: Research Versus Non-Research Specialty Care. Front Psychiatry. 2019;10:1001.
11. Steinhausen HC. Outcome of eating disorders. Child Adolesc Psychiatr Clin N Am. 2009;18(1):225-42.
12. Andres-Pepina S, Plana MT, Flamarique I, Romero S, Borras R, Julia L, et al. Long-term outcome and psychiatric comorbidity of adolescent-onset anorexia nervosa. Clin Child Psychol Psychiatry. 2020;25(1):33-44.
13. Sjetne IS, Bjertnaes OA, Olsen RV, Iversen HH, Bukholm G. The Generic Short Patient Experiences Questionnaire (GS-PEQ): identification of core items from a survey in Norway. BMC Health Serv Res. 2011;11:88.
14. R Core Team. R: A language and environment for statistical computing. 3.6.1 ed. Vienna, Austria: R Foundation for Statistical Computing; 2019.
15. Bürkner P-C. brms: An R Package for Bayesian Multilevel Models Using Stan. Journal of Statistical Software. 2017;80(1).
16. Baldwin SA, Larson MJ. An introduction to using Bayesian linear regression with clinical data. Behav Res Ther. 2017;98:58-75.
17. Gelman A, Simpson D, Betancourt M. The prior can often only be understood in the context of the likelihood. Entropy. 2017;19(10).