Title

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Journal

Early intervention in psychiatry, 16(6)

ISSN

1751-7885

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Publication Date

2022-06-01

DOI

10.1111/eip.13208

Peer reviewed

HHS Public Access

Author manuscript

Early Interv Psychiatry. Author manuscript; available in PMC 2022 June 05.

Published in final edited form as:

Early Interv Psychiatry. 2022 June ; 16(6): 632–642. doi:10.1111/eip.13208.

Family-focused therapy for individuals at high clinical risk for psychosis: A confirmatory efficacy trial

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Abstract

Aims: Young people with attenuated psychotic symptoms (APS), brief intermittent psychosis, and/or genetic risk and functional deterioration are at high risk for developing psychotic disorders. In a prior trial, family-focused therapy for clinical high risk youth (FFT-CHR) was more effective than brief psychoeducation in reducing APS severity over 6 months. This 7-site trial will compare the efficacy of FFT-CHR to a psychoeducational and supportive intervention (enhanced care) on APS and social functioning in CHR individuals over 18 months.

Methods: Participants (N = 220, ages 13–25 years) with a CHR syndrome will be randomly assigned to FFT-CHR (18 1-h sessions of family psychoeducation and communication/problem-solving skills training) or enhanced care (3 1-h family psychoeducational sessions followed by

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5 individual support sessions), both given over 6 months. Participants will rate their weekly progress during treatment using a mobile-enhanced online platform. Family communication will be assessed in a laboratory interactional task at baseline and post-treatment. Independent evaluators will assess APS (primary outcome) and psychosocial functioning (secondary outcome) every 6 months over 18 months.

Results: We hypothesize that, compared to enhanced care, FFT-CHR will be associated with greater improvements in APS and psychosocial functioning over 18 months. Secondarily, improvements in family communication over 6 months will mediate the relationship between treatment condition and primary and secondary outcomes over 18 months. The effects of FFT-CHR are predicted to be greater in individuals with higher baseline risk for psychosis conversion.

Conclusions: Results of the trial will inform treatment guidelines for individuals at high risk for psychosis.

Keywords

expressed emotion; family therapy; prodromal symptoms; psychotic disorders; social adjustment

1 | INTRODUCTION

Adolescents and young adults who meet criteria for a clinical high risk (CHR) syndrome, with attenuated psychotic symptoms (APS), brief intermittent periods of psychosis, and/or genetic risk with functional deterioration have a 16%–30% risk of converting to a psychotic disorder within 2 years (Cannon et al., 2016; Carrión et al., 2016; Fusar-Poli et al., 2020; Yung et al., 2008). The ability to predict conversion suggests that there is a window of opportunity, typically in adolescence or early adulthood, when early intervention may prevent, delay, or minimize the severity of psychosis and the associated negative social and emotional consequences (Velthorst et al., 2018). In this article, we describe the hypotheses, design, and statistical plan for a 7-site randomized comparative efficacy trial of a preventative intervention, family-focused therapy for CHR individuals (FFT-CHR), compared to a psychoeducational and supportive therapy of equivalent duration (enhanced care, or EC).

There is considerable evidence that the courses of schizophrenia, psychosis-risk syndromes, and severe mood disorders are affected by family stress, in the form of high levels of conflict, criticism, and hostility (high expressed emotion) and/or low levels of parent/offspring constructive communication and warmth (Hooley & Miklowitz, 2018; O'Brien et al., 2009; Schlosser et al., 2010). Treatments aimed at modifying conflictual patterns of family interaction may protect against a worsening course of symptoms in high-risk individuals. Family-focused therapy, or FFT, assists family members and probands to (a) identify and intervene with worsening psychiatric symptoms and (b) adopt more constructive communication and problem-solving skills to reduce family conflict. In nine RCTs involving adult or adolescent patients with or at high risk for bipolar disorder, FFT combined with pharmacotherapy was associated with reductions in recurrence rates and improvements in psychosocial functioning over 1–2 years compared to brief psychoeducation or comparably

intensive supportive therapies with pharmacotherapy (Miklowitz & Chung, 2016; Miklowitz, Efthimiou, et al., 2021; Miklowitz, Schneck, et al., 2020; O'Donnell et al., 2017).

In a pilot randomized trial in 8 sites of the North American Prodrome Longitudinal Study (NAPLS) consortium, we compared FFT-CHR (18 sessions over 6 months) to brief (3 sessions) family psychoeducation for CHR adolescents and young adults. Participants who received FFT-CHR had greater decreases in APS severity over 6 months than those in brief psychoeducation (Miklowitz, O'Brien, et al., 2014). Moreover, probands and parents in FFT-CHR showed greater increases from baseline to 6 months in constructive communication and greater decreases in conflictual communication during family interactions than those in brief psychoeducation (O'Brien et al., 2014). Interestingly, independent of treatment, greater reductions in CHR probands' 10-point ratings of amount of criticism from parents ('Perceived Criticism'; Hooley & Teasdale, 1989) were associated with lower APS scores over 12 months (O'Brien et al., 2015).

In secondary analyses of the NAPLS trial, Worthington et al. (2021) found that CHR participants who scored higher on a baseline measure of risk of psychosis conversion—with more severe APS, recent functional deterioration, and cognitive impairment—showed greater reductions in APS in FFT-CHR than high-risk individuals in brief psychoeducation or low-risk individuals in either treatment. Individuals with higher psychosis risk may be more vulnerable to (or may provoke) higher levels of family criticism and conflict than those with lower risk, and may be more likely to benefit from treatments that aim to enhance family relationships.

1.1 | Primary aims and hypotheses

The present study, titled UPLIFT (Understanding Prodromes and Lessening Illness in Family Therapy) is being conducted at 7 NAPLS sites. In addition to seeking to confirm findings from the previous trial, it proposes a larger sample ($N = 220$), a longer follow-up (18 months), and a more intensive treatment comparator. Participants and parents will be randomly assigned to 6 months of FFT-CHR (12 weekly and 6 biweekly 1-h sessions) or 6 months of EC (3 weekly 1-h sessions of family education and 5 monthly individual support sessions). The conceptual framework for the study is outlined in Figure 1.

1.1.1 | Aim 1: Target engagement—

We expect that FFT-CHR will be associated with greater improvements in family communication (primary target) than EC, as revealed by (1a) greater increases in the proportion of calm-constructive parent/offspring and offspring/parent statements, and greater decreases in the proportion of critical-conflictual statements during family interactional assessments conducted at pre- and post-treatment (6 mos.); and (1b) greater decreases in probands' weekly mobile-enhanced online application (app) ratings of Perceived Criticism and appraisals of family interactions, both measured on 1–10 scales of frequency.

1.1.2 | Aim 2. Target validation in relation to outcome and moderation of outcome—

The primary clinical outcomes are APS scores examined over 6 months of acute treatment (proximal outcome) and over the full 18-month follow-up (distal outcome). Severity of APS over 6- and 18-months is calculated from the sum of 5 positive symptom

items assessed by the Structured Interview of Psychosis-Risk Syndromes (SIPS), each rated on 7-point severity scales (Scale of Psychosis Risk Symptoms, or SOPS; McGlashan et al., 2010). Remission of APS, estimated over 18-months, is defined as all 5 SOPS positive symptoms rated below the psychosis-risk range (≤2) for at least 1 month.

(2a) We hypothesize that, compared to EC, FFT-CHR will be associated with greater improvements in APS severity scores from baseline to end of the 6-month treatments.

(2b) FFT-CHR will be associated with lower APS scores and higher rates of APS remission over 18-months (distal outcomes, Figure 1), and better psychosocial functioning over 18 months (secondary outcome), as measured by improvements in 10-point Global Functioning-Social scores (Cornblatt et al., 2007) and Social and Occupational Functioning Assessment scores (Goldman et al., 1992).

(2c) Improvements in parent and offspring communication and Perceived Criticism scores (primary targets) from baseline to 6 months will be associated with improvements in primary and secondary outcomes over 6 and 18 months.

(2d) Improvements in treatment targets from baseline to 6 months will mediate the relationship between treatment condition and changes in primary and secondary outcomes over 18 months.

(2e) The differential effects of FFT-CHR (vs. EC) on changes in primary and secondary outcomes over 6 and 18 months will be greater in CHR individuals with higher baseline scores on a psychosis risk calculator (Cannon et al., 2016).

2 | METHODS

2.1 | Setting

UPLIFT is a single-blind, parallel group RCT with 18 months of follow-up (trial registration NCT04338152, 8 April 2020 at https://www.clinicaltrials.gov, funded by the National Institute of Mental Health grant R01-MH123575). The primary site is the University of California, Los Angeles (UCLA) Semel Institute, with subcontracts to six sites of the NAPLS consortium: University of California, San Diego, CA; University of California, San Francisco, CA; Beth Israel Deaconess Medical Center/Harvard Medical School, Boston, MA; Zucker-Hillside Hospital at Hofstra University/Northwell Health, New York, NY; Yale University School of Medicine, New Haven, CT; and University of Calgary, Calgary, Canada. Each site is expected to recruit, randomize, and treat 32 participants (16/condition), for a total of 220 participants. The study was approved by UCLA's Medical Institutional Review Board, with secondary approvals by the review boards of each study site.

2.2 | Participants and recruitment

Participants will be recruited from clinical referrals and online, radio and print advertisements. They must meet the following inclusion criteria: (1) age between 13 and 25 years; (2) English speaking; (3) at least one parent or primary caregiver is available for family sessions; and (4) satisfy the Criteria of Psychosis-Risk Syndromes (McGlashan

et al., 2010). To align the study with international efforts to harmonize CHR criteria, we will accept participants who do not meet COPS if they do meet the Comprehensive Assessment of At Risk Mental States (CAARMS) criteria for CHR status (Yung et al., 2005). Correspondence between SIPS and CAARMS high- risk criteria was 86% in a UK study (Fusar-Poli et al., 2016). Participants are ineligible if they: (1) meet DSM-5 criteria for a current or lifetime psychotic disorder; (2) have impaired intellectual functioning (IQ < 70) or a past or current history of a neurological disorder; (3) have had a severe substance use disorder in the past 6 months; or (4) are currently in family therapy and unwilling to postpone this treatment.

2.3 | Assessment of eligibility

Figure 2 shows the design of the study. Participants who appear eligible from a telephone interview are invited to a baseline consenting and assessment session with family members with whom they live or are in regular contact. In our first NAPLS trial, 90.7% of CHR participants (mean age 17 years) lived with their parents (Miklowitz, Schneck, et al., 2014). At the first appointment, participants and parents will receive a full explanation of the study procedures prior to reading over and signing informed assent/consent documents. Then, a research assessor will determine diagnoses using the Structured Clinical Interview for DSM-5 (First et al., 2015) and CHR eligibility using the SIPS and items P1-P5 from the SOPS positive symptom scale (First et al., 2015). In weekly cross-site consensus calls, final eligibility of new participants will be determined by a consensus of the site PIs.

At the time of this writing, all assessment and treatment sessions were to be conducted through telehealth video, with the option of returning to live sessions once pandemic restrictions are lifted. We have not carried out a formal validation study of telehealth-based SIPS interviews. However, in the months leading up to study recruitment, neither the administration of the SIPS nor ascertainment of CHR states has been hindered by telehealth procedures at any of the sites. Moreover, the NAPLS network has historically done training of assessors via videotaped interviews, and their reliability ratings have been very comparable to the ratings of assessors conducting live SIPS interviews (Addington et al., 2020).

CHR participants will complete questionnaires concerning demographic variables, psychiatric and medical history, and premorbid social adjustment (van Mastrigt & Addington, 2002). Research staff members will administer two brief neuropsychological tests: the Hopkins Verbal Learning Test–Revised (HVLT-R; Benedict et al., 1998) and the Brief Assessment of Cognition in Schizophrenia Symbol Coding test (BACS SC; Keefe et al., 2008). A computer algorithm will be used to calculate a dimensional psychosis risk score (Cannon et al., 2016) from the following variables: (1) age at baseline, with lower age indicating higher risk; (2) sum of the SOPS items measuring unusual thought content (P1) and suspiciousness (P2); (3) sum of trials 1–3 of the HVLT-R, (4) total processing speed from the BACS SC, (5) decline in social function in the past year based on the 10-point Global Function-Social scale, and (6) history of psychotic disorders in first-degree relatives (SIPS interview). Dichotomized risk scores (high vs. low, based on a median split of risk

scores in the NAPLS- 2 study; Cannon et al., 2016) will be used to balance treatment conditions on conversion risk.

2.4 | Pharmacotherapy and random assignment to psychosocial interventions

In past NAPLS studies, psychopharmacology was relatively common among CHR participants, although only about 18% were taking antipsychotic medications (Woods et al., 2013). Probands who request a medication evaluation will be referred to psychiatrists at one of the study sites. Independent evaluators will track medication choices, starting dosages, upward titration, and clinical adjustments at each 6-month follow-up.

Following the baseline evaluation, project coordinators will enter dichotomous risk calculator scores (high vs. low) and antipsychotic status (taking vs. not-taking) into a dynamic allocation algorithm (Begg & Iglewicz, 1980). The algorithm will allocate assignments to FFT-CHR or EC within each site, so as to minimize imbalances in these variables across study arms. This method is preferred over stratified randomization when cell sizes are expected to be small. Once the treatment assignment is generated, coordinators will assign a family clinician and a 'blind' independent evaluator to the case. Independent evaluators who inadvertently become aware of a participant's treatment will be replaced by a new evaluator.

2.5 | Psychosocial treatments

The content of the 18-session FFT-CHR is identical whether conducted in person or by telehealth (Table 1). The first six sessions of psychoeducation acquaint the proband and family members with early signs of psychosis, with emphasis on the proband's subjective experiences and family members' responses to early signs. The clinician reviews risk (e.g., drug abuse) and protective factors (e.g., family support) for psychosis risk syndromes, encourages daily tracking of symptoms, and assists the proband and family with planning rewarding or pleasurable activities to improve mood and motivation (Martell et al., 2010). Methods to decrease behaviours that contribute to risk are consolidated into a 'prevention action plan' that spells out eliciting factors (e.g., severe family conflicts), early warning signs, symptom management strategies (e.g., rescue medications; mindfulness meditation) and potential obstacles (e.g., unwillingness to talk to others).

In communication enhancement training (sessions 7–13), participants learn to down-regulate impulsive expressions of emotions through pausing, putting difficult feelings into words, and communicating in a manner that does not trigger dysregulation in others. Aided by role-play exercises and between-session practice, clinicians teach the proband and parent(s) the five skills listed in Table 1. For example, the clinician coaches one participant to speak while another listens actively (e.g., nodding one's head, paraphrasing the speaker's content). Finally, in problem-solving (sessions 14–18, held biweekly), participants learn to break down large problems (e.g., 'we don't get along') into smaller ones ('we need to use lower tones of voice'), generate and evaluate advantages/disadvantages of various solutions, and choose solutions to implement (e.g., alert each other to escalating voice tones).

EC has been tested as a comparison treatment in several studies of bipolar disorder (Miklowitz, Efthimiou, et al., 2021). It is intended as a proxy for the type of treatment

adolescents and young adults with mood or psychosis risk syndromes receive in community health settings in the United States. The first 3 weekly 1-h telehealth sessions will involve all family members and provide a more streamlined version of the FFT-CHR psychoeducation module, including development of a prevention action plan. Then, the clinician will offer the proband monthly 1-h individual sessions for the next 5 months, for a total of 8 sessions in 6 months. The individual sessions will focus on support, validation, nondirective problem-solving, and applying prevention plans when symptoms emerge.

2.6 | FFT-CHR compared to previous versions of FFT

FFT-CHR is longer (18 sessions over 6 months) than the protocol used for youth at high risk for bipolar disorder (FFT-HR; 12 sessions over 4 months). The greater intensity of FFT-CHR reflects the higher levels of conflict and lower levels of constructive communication in families of adolescents and young adults with psychosis risk syndromes compared to families of adolescents at high-risk for bipolar disorder (Salinger et al., 2018). Specifically, there is a greater focus in FFT-CHR on communication clarity and conflict resolution than in FFT-HR. FFT-CHR is of comparable intensity to FFT-A (21 sessions in 9 months), the version of FFT used for adolescents with a diagnosis of bipolar I or II disorder. However, in the psychoeducation module, FFT-CHR places greater emphasis on the family's recognition and acceptance of attenuated positive and negative symptoms and social withdrawal, whereas FFT-A is more focused on strategies to prevent the reemergence of manic and depressive episodes (Miklowitz, O'Brien, et al., 2014).

2.7 | Modifications for telehealth

We have written previously about modifications of FFT for telehealth (Dausch et al., 2009), and previously implemented a telehealth version of FFT for youth at high risk for mood disorders (Miklowitz, Weintraub, et al., 2020). For UPLIFT, we made the following adaptations for videoconferencing: (1) families will be asked to choose a room with a good internet connection and a comfortable half-circle seating arrangement so members can look directly at each other (as well as at the therapist on-screen); (2) use of individual cell phones or tablets during the sessions will not be allowed unless they are needed for connecting to the session; (3) members will be discouraged from connecting to the session from different devices in different rooms, which tends to lead to dyadic conversations between the therapist and individual family members rather than between members.

As would occur in the clinic, participants will be told that regular and punctual attendance is an expectation of the research and treatment protocols. Treatment adherence will be measured from treatment completion, proportion of sessions attended, and length of time between sessions (relative to how frequently they should occur). When families miss sessions, the clinician will initiate telephone contacts with the parents and youth. Families who miss three consecutive sessions without an identified reason (e.g., vacations, an illness) will be withdrawn from the study.

Families can choose live sessions over telehealth, assuming pandemic restrictions do not dictate otherwise. In a prior study (Miklowitz, Weintraub, et al., 2020), the majority of families reported preferring telehealth over live sessions because of its greater convenience,

especially for those who lived a considerable distance from the clinic. We do not know, however, whether FFT-CHR will be as effective with telehealth as with live sessions. If there is variability across participants in the choice of virtual versus live sessions, we will estimate whether the effects of FFT-CHR versus EC are moderated by delivery mode.

2.8 | Clinician training and fidelity monitoring

The same clinicians will administer FFT-CHR and EC given the methodological problems inherent in nesting therapists within treatment conditions (Chambless & Hollon, 1998). In UPLIFT, site clinicians began by reading the FFT-CHR and EC treatment manuals (available at www.semel.ucla.edu/champ/downloads-clinicians). Then, in November, 2020, the principal investigator (D. J. M.) conducted a 4-h training workshop for therapists. The workshop was followed by weekly 1-h webinars, consisting of reviews of session strategies, videotaped examples, and small group role-plays.

During the trial, clinicians will receive weekly group supervision from the PI and designated FFT-CHR or EC supervisors. Supervisors will make fidelity ratings of at least three videotaped sessions from each FFT-CHR case and at least one session from each EC case using the 16-item Therapist Competence and Adherence Scales, Rev. (TCAS-R; Marvin et al., 2016). The TCAS-R includes items that are specific to FFT-CHR (e.g., quality of communication training) as well as nonspecific factors (e.g., rapport-building). Interrater reliability for TCAS-R items in the prior NAPLS trial ranged from 0.74 to 0.98. If clinicians fall below established fidelity thresholds, supervisors will provide additional consultation.

2.9 | Remote monitoring with MyCoachConnect application

During the 6-month treatment period, weekly remote monitoring will provide higher density data on the temporal relationships between changes in targets and outcomes. We expect greater reductions in FFT-CHR compared to EC in probands' weekly 1–10 ratings of perceived criticism, and stronger associations in FFT-CHR between changes in perceived criticism and self- and clinician-rated symptoms over 6 and 18 months.

In both treatment conditions, CHR participants and at least one parent will be given login information and instructions for weekly use of the 'MyCoachConnect' mobile-enhanced online app (Arevian et al., 2020; Miklowitz, Weintraub, et al., 2020). The app will send weekly push notifications asking probands to make ratings of positive and negative symptoms, mood, anxiety, family functioning, and social interactions; and Perceived Criticism from other members of the family. In the FFT-CHR condition, the mobile app has additional purposes: to provide reviews of session content and remind probands and family members to practice skills learned in sessions. Participants will be asked to record, on a weekly basis, their attempts to use the various FFT skills (e.g., communication skills like active listening) and the degree to which their attempts had satisfactory outcomes.

2.10 | Family interactional assessment task

The primary treatment target, family communication behaviour, will be assessed using the family interactional assessment task (FIAT), a 10-min observer-rated, problem-oriented family discussion. The FIAT, administered by the assigned clinician, will be conducted

after the first or second FFT-CHR or EC session and again at the last session with the proband, parents, and other relatives involved in treatment. The clinician will choose a topic that the proband and family members agree has caused substantial distress for the family (e.g., arguments about the proband's irritability or withdrawal), and instruct the family to 'discuss this topic and attempt to reach a resolution'. The participants discuss the topic among themselves for 10 min, with the clinician observing but off-camera. Discussions will be videotaped and transcribed.

Mary O'Brien, PhD, who developed the FIAT coding system (O'Brien et al., 2009), trained a cohort of raters to acceptable levels of reliability prior to UPLIFT. Two trained raters will review the transcripts and make tally marks for every speaking turn in which a proband or family member expresses a calm or constructive statement (e.g., praise for another member) or a critical-conflictual statement (e.g., criticizes another or cuts them off). Sums of the speech turns classified as calm-constructive or critical-conflictual will be divided by the total number of speaking turns to create percentage scores for each participant. Withdrawal (disengagement) is indicated by the raw number of speaking turns taken by each participant. The system also includes a rating for the degree of problem resolution reached in the discussion.

In the first NAPLS study, interrater reliabilities were 0.89 for calm-constructive behaviours and 0.79 for critical-conflictual behaviours (O'Brien et al., 2014). Reliabilities will be reassessed throughout the present study.

2.11 | Symptom and social functioning assessments

At baseline and every 6 months over 18 months, independent evaluators will interview probands and rate the onset and severity of 5 SOPS positive symptoms. They will assess negative symptoms with the Negative Symptom Inventory–Psychosis Risk (Strauss, Pelletier-Baldelli, Visser, Walker, & Mittal, 2020). This inventory consists of 11 items, each rated on 0–6 scales of severity and covering diminished motivation/pleasure and diminished expressiveness. Current mood and anxiety symptoms will be assessed via participants' self-report using the Calgary Depression Scale (Addington et al., 2012) and the Generalized Anxiety Disorder-7 scale (Spitzer et al., 2006). Although not the focus of primary hypotheses, negative symptoms and depression are important exploratory outcomes given that FFT was associated with reductions in depressive symptoms among youth at high risk for bipolar disorder (Miklowitz et al., 2013; Miklowitz, Schneck, et al., 2020).

At baseline and every 6 months, the evaluator will rate current functioning with the Global Functioning-Social and Role scales and the Social and Occupational Functioning Assessment. Participants will also be rated on the Alcohol and Drug Use Scales (Drake et al., 1996) and the Medication and Psychotherapy Use logs (Addington et al., 2015). Independent evaluators will undergo a rigorous protocol for training in these measures, with annual reliability checks (Addington et al., 2015). Initial cross-site reliabilities, obtained in January 2021, averaged 0.91 for SOPS APS ratings and 0.78 for the Calgary Depression Scale.

2.12 | Data analysis and statistical power

Our primary analytical techniques will be generalized linear mixed models (GLMMs) and survival analyses, run on an intent-to-treat basis. For power calculations, we assumed randomization of 220 subjects (16/arm at each site) and 20% attrition over 18 months (the average rate in prior FFT trials; Miklowitz & Chung, 2016), leaving 176 subjects (88/group) with full follow-up. We assumed a standard medium correlation of 0.50 between repeated measurements within subjects and a two-sided significance level of $\alpha = .01$, allowing for up to 5 primary/secondary measures within each study aim.

The GLMM and survival models described below will be fit initially without covariates, following standard practices (Kraemer, 2015). We will use logistic regression to identify factors associated with attrition and data loss and control for them in sensitivity analyses. We will protect against multiple comparisons by focusing on a limited set of a priori primary outcomes and contrasts and by reporting results within each hypothesis using false discovery rate procedures (Hochberg & Benjamini, 1990). The power calculations cited below are conservative because (a) the mixed and survival models use observed time-points from participants with only partial data, and (b) the estimates were computed using Bonferroni adjustments, which is conservative compared to the false discovery rate procedure to be used in the final analyses.

For aim 1a (target engagement), we will fit GLMMs over the treatment interval (0–6 months) to determine whether, compared to EC, FFT-CHR is associated with greater improvements in proportions of calm-constructive and critical-conflictual speech turns among probands and parents during the pre- and post-treatment FIATs. Secondarily, we will examine treatment-related changes in degree of problem resolution (for each individual and the family as a whole) and degree of engagement/disengagement over the 6-month period.

Assuming two measurement points and 20% attrition, we will have 80% power to detect a group by time interaction on family communication measures of $f^2 = 0.011$, corresponding to a change from no difference at baseline to a difference of 0.52 (Cohen's d) at 6 months ($p < .01$). For Aim 1b, treatment effects on weekly app-based Perceived Criticism ratings, we have 80% power for an effect size of $f^2 = .0025$ (equivalent to a change from no difference to $d = 0.25$ at 27 weeks, assuming a linear pattern of effects). For mobile app ratings, we should have a sufficient number of weekly time-points to identify quadratic or cyclical trends for Perceived Criticism scores using participant-level random effects.

For aim 2, the effects of treatment on primary APS outcomes, we will use GLMMs with treatment as the between-subjects factor; APS at 0, 6, 12, and 18 months as repeated measures; a group by time interaction; and subject level random effects to account for individual variation in response trajectories. The contrasts of interest are the group by time interactions in SOPS scores over the 6-month treatment period (aim 2a) and over the 18-month study window (aim 2b). The power for the differential treatment effect on proximal APS scores is the same as for the Aim 1a measures. For aim 2b, distal APS outcomes, the minimum detectable effect size for a treatment group by time interaction is Cohen's $f^2 = 0.008$ (equivalent to a change from no difference at baseline to $d = 0.50$ at 18 months,

assuming a linear pattern of effects). The power is identical when examining differential treatment effects on social functioning measures over 18 months (secondary outcomes).

Symptom remission (aim 2b), in which all five SOPS items are rated ≤2 for at least one month, is estimated to occur in 30% of CHR cases in a 2-year interval (Addington et al., 2019). We will use survival analytic models to evaluate treatment differences in time to remission and, if there is sufficient occurrence over 18 months (i.e., >20%), time to conversion to psychosis (a rating of 6 on any of the 5 SOPSs items, with symptom frequency of ≥4 times per week over ≥ 1 month; Cannon et al., 2016). Outcomes will be computed as time from randomization to the beginning of the remission or conversion period. We will obtain Kaplan–Meier estimates of the group survival curves and log-rank tests to compare rates and times to remission/conversion, and Cox proportional hazards models when adjusting for potential confounding or moderator variables. With 220 participants and 20% attrition, the design is powered (80%) to detect a group difference in remission with hazard ratio of 1.70, similar to the 2-year hazard ratio observed for FFT versus EC on new mood episodes in youth at high risk for bipolar disorder (Miklowitz, Schneck, et al., 2020).

For aims 2c and 2d (target validation), we will add the 0–6 month change scores in family communication variables and their interactions with treatment group and time to the GLMMs and survival models for 18-month outcomes. For aim 2e, we will add dimensional risk calculator scores and their interactions with treatment and time to the primary GLMMs and survival models described above. If there is evidence of treatment by baseline risk interactions, post-hoc contrasts will be used to identify the subset of subjects for whom the interventions are most effective.

We will fit exploratory mixed effect models comparing treatment groups crossed with baseline risk calculator scores on negative symptom and depression ratings. If there are sufficient subjects that meet CAARMS but not SIPS criteria for psychosis-risk syndromes, post-hoc analyses of this subset of participants will be conducted. Additionally, we will examine whether there are between-group differences at any time-point in the likelihood of taking any psychiatric medication. If such differences emerge, we will adjust all GLMM and survival models using medication regimen as a time-varying covariate (Lavori et al., 1994). Finally, if pandemic restrictions are lifted and subgroup sample sizes are adequate, we will examine whether CHR persons who received FFT or EC via telehealth have different attendance rates, attrition, or primary/secondary outcomes than those who were treated in the clinic.

3 | DISCUSSION

The results of UPLIFT are likely to inform treatment guidelines for individuals at high risk for psychosis. The study will examine whether FFT-CHR can improve the targets of family communication and conflict, as found in our first trial; whether these changes in family functioning are associated with improved outcomes; and whether treatment effects remain beyond the 6-month treatment period. Additionally, we will explore which subpopulations of CHR individuals defined by conversion risk respond best to family treatment and which do equally well with less intensive psychoeducation and support. Relatively intensive

treatments such as FFT-CHR may need to be reserved for individuals who are at higher risk for conversion to psychosis.

A possible outcome of UPLIFT is that FFT-CHR will be associated with improvements in symptoms or social functioning, but not by the mechanism of family communication. For example, CHR persons who benefit from FFT-CHR may learn to use communication skills with peers or employers but not with parents. This outcome would suggest that group approaches to skill training may be equally or more cost-effective than FFT-CHR.

The comparison EC condition includes several components of FFT-CHR: family involvement, personalized attention from a caring professional, psychoeducation, development of a prevention plan, and duration (6 months). The fact that FFT-CHR and EC are not matched on number of sessions (18 vs. 8) raises the possibility that differences in outcome may be attributable to differences in the frequency of therapeutic contact. We would argue that EC is similar to the brief, supportive case management protocols often given in community mental health settings. The inclusion of an attention-matched nonspecific therapy in this study would have significantly increased treatment and supervision costs and would not necessarily be acceptable to probands (Chambless & Hollon, 2012). Choosing other evidence-based treatments for CHR individuals as attention-matched controls, such as cognitive-behavioural therapy (e.g., Ising et al., 2016; Morrison et al., 2004; Stain et al., 2016), would generate the problem of how to interpret null outcome differences between two equally intensive treatments, which usually requires a no-psychotherapy reference group (Charney et al., 2002). Demonstrating that FFT-CHR has clear preventative benefits compared to brief psychoeducation and support is, in our estimation, a reasonable, scalable, and economical comparison.

Future directions include how best to disseminate FFT-CHR in community care settings. It appears that clinicians have a relatively easy time learning FFT: in a randomized comparison of clinician training methods, community providers administered FFT with high levels of fidelity following an online training seminar and supervision every 3 weeks (Miklowitz, Weintraub, et al., 2021). However, clarifying treatment mechanisms will be critical to determining what components of FFT-CHR should be emphasized in training of new clinicians. If we are correct that family communication should be a target of preventative interventions for individuals at high psychosis risk, the next stage would be to examine lower-cost and more efficient methods of training in communication and problem-solving skills, such as cognitive remediation or digital mental health tools.

ACKNOWLEDGEMENTS

D. J. M. has received research support from the National Institute for Mental Health (NIMH), Danny Alberts Foundation, Attias Family Foundation, Carl and Roberta Deutsch Foundation, Kayne Family Foundation, AIM for Youth Mental Health, Jewish Community Foundation of Los Angeles, and the Max Gray Fund; and book royalties from Guilford Press and John Wiley and Sons. M. J. W. reports research support from NIMH, AIM for Youth Mental Health, the Shear Family Foundation, and the Friends of the UCLA Semel Institute. D. H. M. has served as a consultant for Boehringer Ingelheim, Cadent Therapeutics, Syndesi, and Recognify. B. A. C. receives research support from AIM for Youth Mental Health. S. W. W. reports receiving research funding from Boehringer-Ingelheim, Amarex, and SyneuRx. He has consulted to Boehringer-Ingelheim, New England Research Institute, and Takeda. He has been granted US patent no. 8492418 B2 for a method of treating prodromal schizophrenia with glycine agonists, and has received royalties from Oxford University Press. C. S. has received grants from the National Institutes of Health. The other authors report no conflicts of interest.

Funding information

National Institute for Mental Health, Grant/Award number R01-MH123575-02 (UCLA: David J. Miklowitz and Carrie E. Bearden, PIs).

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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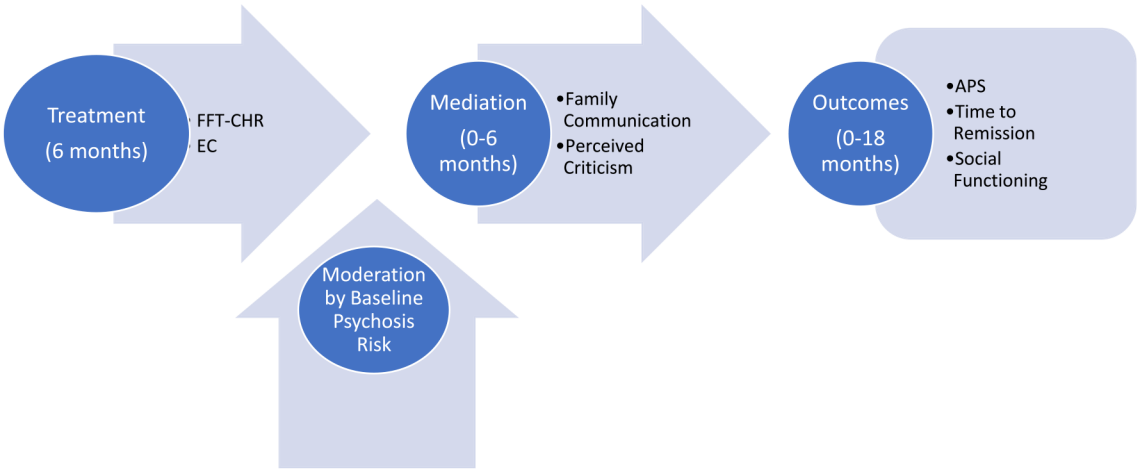

FIGURE 1.

Study framework. APS, attenuated positive symptoms; EC, enhanced care; FFT-CHR, family-focused treatment for clinical high risk persons. The effects of psychosocial treatment on mediating and outcome variables are hypothesized to be moderated by baseline levels of risk for conversion to psychosis

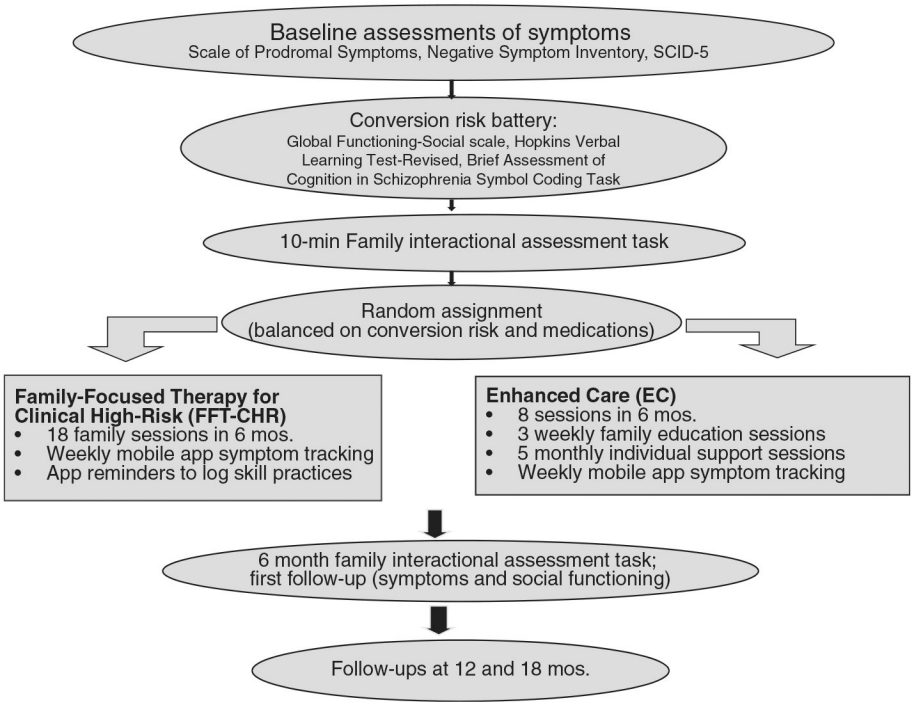

FIGURE 2.

Study flow diagram. SCID-5, Structured Clinical Interview for DSM-5. App refers to a mobile-enhanced online application

TABLE 1

Structure and topical outline of FFT-CHR

Psychoeducation (6 sessions)

The symptoms and course of clinical high-risk conditions

- Signs and symptoms of positive and negative symptoms, depression, anxiety, and mood instability
- Mood and thinking chart

Self-management

- Risk and protective factors
- Stress and coping strategies
- Medications and psychosocial interventions
- Behavioural activation plan
- How the family can help
- Prevention action plan

Communication enhancement training (7–10 sessions)

- Expressing positive feelings
- Active listening
- Making positive requests for change
- Communication clarity
- Expressing negative feelings

Problem-solving skills training (4–5 sessions)

- Define problems
- Generate possible solutions
- Evaluate advantages-disadvantages of each solution
- Choose one or a combination of solutions
- Develop an implementation plan
- Review the problem’s status