RESEARCH PROTOCOL

Protocol Title:	Using Digital Media Advertising to reduce the Duration of Untreated Psychosis
Principal Investigator:	Michael Birnbaum
Primary Contact Name:	Nicole Germano
Primary Contact Phone:	718-470-5948
Primary Contact E-mail:	ngermano1@northwell.edu
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Guidelines for Preparing a Research Protocol

Instructions:

- You do not need to complete this document if you are submitting an *Application for Exemption* or *Application for a Chart Review*.
- Do not use this template if:
  - Your study involves an FDA regulated product. In this case, use the *Clinical Trial Protocol Template.*
  - Your study has a protocol from a sponsor or cooperative group. In this case, use the *Protocol Plus*.
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  - IRB Number: Indicate the assigned IRB number, when known. At initial submission, this row will be left blank.
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1. PREVIOUS STUDY HISTORY

Has this study ever been reviewed and rejected/disapproved by another IRB prior to submission to this IRB?

☒ No ☐ Yes – if yes, please explain:

2. BRIEF SUMMARY OF RESEARCH

- *The summary should be written in **language intelligible to a moderately educated, non-scientific layperson**.*
- *It should contain a clear statement of the rationale and hypothesis of your study, a concise description of the methodology, with an emphasis on what will happen to the subjects, and a discussion of the results.*
- *This section should be ½ page*

Approximately 100,000 adolescents and young adults in the United States experience a first episode of psychosis (FEP) each year. Psychotic symptoms typically emerge during formative years of development and interfere with the establishment of healthy educational, vocational, and social foundations. Despite the severity of symptoms and significant decline in functioning, the time between symptom onset and receiving appropriate care in the U.S. is lengthy[1]. Results from the NIMH-funded Recovery After an Initial Schizophrenia Episode - Early Treatment Program (RAISE-ETP) conducted at 34 community clinics across 21 states throughout the U.S., involving 404 FEP patients, indicated a median duration of untreated psychosis (DUP) of 74 weeks[2]. Longer DUP has been shown to independently predict negative outcomes, including poorer response to treatment, worse global, vocational, social, and cognitive functioning, higher risk of relapse, greater symptom severity, and poorer quality of life[1,3,4]. As psychotic symptoms persist and disability accumulates, individuals with FEP are missing a critical period to benefit from effective early intervention services. Over the past decade, there have been increasing efforts to understand and mitigate contributing factors to increased DUP in order to inform the development of effective early intervention services, increase chances of recovery, and improve long term outcomes in individuals with psychotic disorders.

Prior successful DUP reduction initiatives[5,6] have utilized various marketing strategies including print (brochures, newspapers, pamphlets, postcards), broadcast (radio, television, cinema), and telephone contact, to educate the general public about early intervention services. These strategies, however, are expensive, inefficient, and outdated. Online outreach, supported by technological innovation, offers the prospect of reaching individuals earlier in

the course of illness development, as well as individuals who might not otherwise come into contact with traditional referral sources. In response to this challenge, Northwell Health's early psychosis research team is collaborating with Strong365, a nonprofit initiative dedicated to raising early psychosis intervention awareness, to develop and test a proactive and targeted comprehensive digital media marketing campaign designed to facilitate help-seeking and encourage treatment initiation in prospective patients with FEP and their caregivers. Our team will take advantage of search engine advertising, which allows advertisers (researchers) to select keywords/phrases and create linked advertisements appearing as a strategically placed search result. Our dedicated ads will appear in response to online search queries conducted by prospective patients and their caregivers throughout New York State (NYS) that align with the campaign's pre-selected keywords/phrases. Individuals who click on the ads will be immediately directed to our campaign landing page/website, and offered a variety of established, innovative, and interactive online engagement tools intended to instantly connect users with coordinated specialty care (CSC) staff and to facilitate earlier treatment initiation.

Campaign referrals will be centralized and individuals with FEP will be enrolled into OnTrackNY (OTNY), a network of 21 dedicated early psychosis intervention programs throughout NYS. The campaign will target individuals as well as their friends, family, and caregivers, searching for information online. We will measure the DUP of individuals enrolled into OTNY before and after campaign activation and track the impact of the campaign on the number of FEP referrals and number of patients admitted to OTNY in NYS. Furthermore, we aim to identify the campaign target audience most effective at promoting treatment initiation as well as the online tools and resources most effective at encouraging treatment initiation of identified individuals with FEP. We will additionally explore the online trajectories to care of individuals with FEP engaging with the campaign.

Results from this initiative will provide novel online strategies for achieving rapid initiation of appropriate specialty care throughout NYS. These data will also help map the online trajectories to specialty care, identify ongoing barriers and bottlenecks, and support the development of new practical, reproducible, and cost effective strategies to achieve substantial DUP reduction in the U.S.

3. INTRODUCTION/BACKGROUND MATERIAL/PRELIMINARY STUDIES AND SIGNIFICANCE

- *Describe and provide the results of previous work by yourself or others, including animal studies, laboratory studies, pilot studies, pre-clinical and/or clinical studies involving the compound or device to be studied.*

- *Include information as to why you are conducting the study and how the study differs from what has been previously researched, including what the knowledge gaps are.*
- *Describe the importance of the knowledge expected to result*

The consequences of untreated psychoses can be devastating[7]. The public health challenge of appropriate early intervention and treatment is exacerbated by the fact that the incidence of psychosis is relatively low, and that individuals who develop psychotic symptoms may not be ready to accept help, and may even be suspicious of those trying to help them. Further, there is little public awareness as to the nature of psychotic illnesses and such illnesses are still often associated with considerable discrimination. Despite international efforts to improve access to state-of-the-art FEP programs, data from the NIMH funded RAISE-ETP project support the hypothesis that such programs, in and of themselves, are not sufficient to reduce DUP. Novel, innovative, and focused strategies that act beyond traditional outreach and intake processes are necessary in order to accomplish this crucial goal.

Several initiatives in a number of countries have been implemented in order to reduce DUP with varying degrees of success[10]. Many have directed efforts towards educating family physicians and other health service providers, whereas some studies have targeted schools and the general public. Community educational programs have thus far demonstrated the most promise in reducing DUP through widespread marketing campaigns and easily accessible services. The TIPS project in Norway[5] and the EPIP project in Singapore[6] both successfully utilized mass-media to educate the general public and relevant professionals regarding the benefits of early intervention and available services. In the U.S, a similar early detection program is currently underway[9] which integrates community outreach with an online component. These strategies, however, require extensive and costly resources and organization, and focus on broadly and nonspecifically improving general public education and awareness. Limited efforts have attempted to harness available modern technological resources to more precisely and proactively target and engage prospective patients and their caregivers in order to reduce DUP.

Online outreach, supported by technological innovation, may prove critical to expediting help-seeking and facilitating specialty care treatment initiation in prospective patients with FEP and their caregivers. The Internet provides an unparalleled opportunity to diminish barriers to accessing services by reaching people earlier in the course of illness and promoting engagement with services that meet their needs, while reducing health disparities among vulnerable populations[10]. Google has been consistently ranked as the world's most popular search engine with over 660 million daily visitors, managing over three billion searches daily[11]. Reports have found that at least 80% of Internet users search online for health related information[12] including mental

health. Importantly, many individuals utilizing the Internet for mental health resources have yet to connect with psychiatric care[13].

Searching online has become the primary resource for youth seeking out mental health information[14]. This is especially true for stigmatized illnesses such as schizophrenia as the Internet provides a comfortable and anonymous setting to gather information about symptoms and treatment options[15]. We demonstrated that participants with FEP reported utilizing the Internet first, and most frequently, to gather information prior to receiving psychiatric care while psychotic symptoms were emerging[16,17]. Youth with FEP were more likely to search online for information as opposed to, or prior to, discussing with peers, family, physicians, and mental health clinicians. Moreover, the Internet has increasingly become an important source of referrals to FEP programs[18]. The Internet may represent one of the first proactive steps towards treatment initiation[16] and information gathered online appears capable of impacting mental health related help-seeking behavior[19].

There is an unexplored opportunity to harness the Internet's far reaching platform to improve early detection and intervention for psychosis. Given that adolescents and young adults in the early stages of psychotic illness, as well as their caregivers, are known to be online, searching for information, prior to receiving formal diagnoses and treatment, and throughout the DUP, we propose to capitalize on the immense power of existing and accessible online engagement tools in order to identify and meaningfully interact with patients with FEP and their caregivers, providing them with instant information and resources, designed to move them along their trajectory to care, and facilitate earlier linkage to specialty services.

4. OBJECTIVE(S)/SPECIFIC AIMS AND HYPOTHESES

- *A concise statement of the goal(s) of the current study.*
- *The rationale for and specific objectives of the study.*
- *The goals and the hypothesis to be tested should be stated.*

Aim 1: Evaluate the effectiveness of a search engine ad campaign on reducing DUP and raising rates of FEP referrals by directly comparing DUP and FEP referrals pre-campaign to DUP and FEP referrals during the campaign. Hypothesis A: Patients admitted to OTNY via campaign channels will demonstrate significantly shorter DUP than those admitted to OTNY through traditional outreach prior to campaign activation. Hypothesis B: Activating the campaign will significantly increase the number of FEP referrals and patients admitted to OTNY as compared to the number of FEP referrals and patients to OTNY admitted pre-campaign activation.

Aim 2: Determine the efficacy of a campaign targeting caregivers in promoting treatment initiation by comparing rates of OTNY enrollment arriving through the caregiver campaign to rates of enrollment arriving through the patient campaign. Hypothesis: Engaging caregivers online will significantly increase the likelihood of promoting treatment initiation for individuals with FEP as compared to engaging prospective patients online.
Aim 3: Explore which methods of online engagement are most effective at promoting treatment initiation by comparing rates of OTNY enrollment of individuals with FEP interacting with research staff via two-way video and live chat to rates of enrollment of individuals with FEP utilizing text, email, and/or phone alone. Hypothesis: Individuals with FEP who engage via two-way video and live chat will be significantly more likely to initiate in-person contact compared to individuals with FEP who engage via text, email, and/or phone alone.

5. RESOURCES AVAILABLE TO CONDUCT THE HUMAN RESEARCH

- *Explain the feasibility of meeting recruitment goals of this project and demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period*
    - *How many potential subjects do you have access to?*
- *Describe your process to ensure that all persons assisting with the trial are adequately informed about the protocol and their trial related duties and functions*

Our campaign aims to identify and engage individuals with FEP as well as their caregivers searching for information online throughout NYS. Given that ads will appear in response to any online search query conducted by any individual in NYS that align with the campaign's keywords, we will likely interact with many individuals searching for behavioral health information online. All campaign related inquiries will be recorded centrally by research staff. Individuals experiencing FEP will be referred to OTNY.

OTNY receives on average 34 referrals weekly, of which, on average 26% are found eligible, and 8 new FEP patients are enrolled in NYS each week. Based on existing OTNY inquiry data as well as the results of our prior pilot initiatives, we anticipate approximately doubling weekly inquiries as a result of the campaign, arriving through campaign related channels over the course of the trial (30 additional referrals). Of those, we anticipate that 20% will be appropriate for OTNY (6 participants weekly) and that 4 of those individuals will be successfully enrolled each week as a result of the campaign.

The project will be led by Michael Birnbaum, MD., attending physician at The Zucker Hillside Hospital (ZHH) in New York and Program Director for Northwell Health's Early Treatment Program (ETP). Co-Investigator John

Kane, MD., together with the PI, have extensive experience with the use of search engine ads targeting individuals with early psychosis.

6. RECRUITMENT METHODS

- *Describe the source of potential subjects*
- *Describe the methods that will be used to identify potential subjects*
- *Describe any materials that will be used to recruit subjects. A copy of any advertisements (flyers, radio scripts, etc.) should be submitted along with the protocol.*
- *If monetary compensation is to be offered, this should be indicated in the protocol*

Referrals for the study will come from self-response to the search engine ads. Those individual who interact with research staff via phone, text, email, live chat, or two way video will be greeted by a member of the study team who will inform users that as part of efforts to improve services, we'll be using some of the information provided to connect them to local care. If the individual does not want their information shared they can opt out. Patients who on initial evaluation are deemed not to be capable of giving verbal informed consent will not be evaluated further for the study. Patients who are deemed capable of giving verbal informed consent will then be provided with a full and complete description of the study.
Participants who are deemed most likely to be eligible for a referral to an early intervention clinic (based on their responses to the self-screener and/or live chat with research staff) and who choose not to progress along their pathway to care and/or accept a referral to care, will be re-approached by research staff (via the provided contact information) to participate in an additional optional 10 minute qualitative interview. Verbal consent for completion of this additional interview will be obtained. The goal of the interview will be to explore barriers in the online pathways to care and ultimately improve future iterations of the campaign. Questions will be open ended and explore personal motivations for deciding against pursuing formal care at this time.

7. ELIGIBILITY CRITERIA

- *Describe the characteristics of the subject population, including their anticipated number, age, ranges, sex, ethnic background, and health status. Identify the criteria for inclusion or exclusion of any subpopulation.*
- *Explain the rationale for the involvement of special classes of subjects, such as fetuses, pregnant women, children, prisoners or other institutionalized individuals, or others who are likely to be vulnerable. You cannot include these populations in your research, unless you indicate such in the protocol*
- *Similarly, detail exclusionary criteria: age limits, special populations (minors, pregnant women, decisionally impaired), use of concomitant medications, subjects with other diseases, severity of illness, etc.*

Given that ads will appear in response to any online search query conducted by any individual in NYS that align with the campaign's keywords, we will likely interact with many individuals searching for behavioral health information online. All campaign related inquiries will be recorded centrally by research staff. Individuals experiencing FEP will be referred to OTNY.

OTNY Inclusion criteria include: 1) DSM-V diagnosis of schizophrenia, schizophreniform, schizoaffective disorder, brief psychotic disorder, delusional disorder, unspecified schizophrenia spectrum disorder, assessed via clinical interview; 2) psychotic symptom onset within the past two years; 3) ages 16 to 30 years; 4) NYS resident

OTNY Exclusion criteria include: 1) diagnosis of substance-induced psychotic disorder, a psychotic disorder due to a general medical condition, or mood disorder with psychotic features; 2) Intellectual disability (IQ < 70) or autistic spectrum disorder assessed by clinical interview.

All individuals who meet OTNY inclusion criteria will be offered care regardless of insurance status or ability to pay. All ineligible OTNY referrals will be referred to appropriate local services.

8. NUMBER OF SUBJECTS

- *Indicate the total number of subjects to be accrued locally. If applicable, distinguish between the number of subjects who are expected to be pre-screened, enrolled (consent obtained), randomized and complete the research procedures.*
- *If your study includes different cohorts, include the total number of subjects in each cohort.*
- *If this is multisite study, include total number of subjects across all sites.*

OTNY receives on average 34 referrals weekly, of which, on average 26% are found eligible, and 8 new FEP patients are enrolled in NYS each week. Based on existing OTNY inquiry data as well as the results of our prior pilot initiatives, we anticipate approximately doubling weekly inquiries as a result of the campaign, arriving through campaign related channels over the course of the trial (30 additional referrals). Of those, we anticipate that 20% will be appropriate for OTNY (6 participants weekly) and that 4 of those individuals will be successfully enrolled each week as a result of the campaign.

9. STUDY TIMELINES

- *Describe the duration of an individuals participation in the study*
- *Describe the duration anticipated to enroll all study subjects*
- *The estimated date of study completion*

Phase 1 (6 Months): Development and optimization of campaign ads and landing page, begin collecting baseline OTNY referral and DUP data. **Phase 2** (18 Months): Campaign deployment and data gathering. **Phase 3** (6 Months): Data cleaning, analysis, and manuscript preparation. Participation will end once an individual accepts or refuses an outpatient referral.

10. ENDPOINTS

- *Describe the primary and secondary study endpoints*
- *Describe any primary or secondary safety endpoints*

N/A

11. RESEARCH PROCEDURES

- *Include a detailed description of all procedures to be performed on the research subject and the schedule for each procedure.*
- *Include any screening procedures for eligibility and/or baseline diagnostic tests*
- *Include procedures being performed to monitor subjects for safety or minimize risks*
- *Include information about drug washout periods*
- *If drugs or biologics are being administered provide information on dosing and route of administration*
- *Clearly indicate which procedures are only being conducted for research purposes.*
- *If any specimens will be used for this research, explain whether they are being collected specifically for research purposes.*
- *Describe any source records that will be used to collect data about subjects*
- *Indicate the data to be collected, including long term follow-up*

We will develop and test two comprehensive digital media campaigns running in parallel. The first campaign will target prospective patients searching online for information. The second will target caregivers. Each campaign will run simultaneously and will each be comprised of their own search engine ads/ results and dedicated landing page both geared specifically towards their respective target audience. The ads and their associated landing page/website will be selected and displayed automatically based on the keywords/search terms entered by an individual user online as well as the age of individual searching. The campaign will be accessible both via desktop and mobile.

For each campaign, a landing page will be developed with the primary goal of facilitating treatment initiation for individuals with FEP and their caregivers searching for information online in NYS. In order to optimize website visibility, the landing page will focus on core messages derived from our initial evaluations that were found to be most relevant to information seeking individuals. These include accurately identifying and understanding early signs and symptoms of psychosis and finding local support. The landing page content will be driven by ETP staff along with input from Strong365's development team. Additional input will be obtained from existing ETP participants with lived FEP experience.

The campaign website page will offer:

1) **Education.** The website will be designed to be an interactive educational experience encouraging visitors to effortlessly communicate directly with research staff online via live chat, over the phone, text, or email. The landing page will include information regarding signs and symptoms of psychosis as well as available local service options. The information will be displayed in a simple yet informative, youth friendly, and engaging manner utilizing text, images, videos, and animations.

2) **Needs assessment**. An online survey will be designed to obtain demographic information regarding the individuals visiting the campaign landing page, the motivations supporting their search, as well as their desired outcome. Responses are encouraged though not required in order to proceed. The survey will consist of 7 multiple choice questions with additional open ended response options.

3) **Quick clinical connection.** The landing page will offer easy and efficient access to research staff including a licensed mental health counselor through dedicated campaign email and phone number for calling and texting. Users may leave their own personal contact details if they prefer that someone from the team contact them directly. Staff will be available 12 hours daily during the week and 6 hours daily on weekends. Staffing availability will be flexible and dependent on peak website traffic as well as the needs and requests of users.

4) **Live chat.** The landing page will offer an opportunity to chat live with a licensed mental health clinician using an online pop up chat option. Staff will be available 12 hours daily throughout the week and 6 hours daily during the weekend. Hours will fluctuate depending on identified peak online activity when users are most active. Users will also be offered the opportunity to schedule a virtual video chat with a clinician via two-way video, providing an opportunity for face to face interaction.

5) **The Prodromal Questionnaire-Brief (PQ-B)**. The PQ-B is a 21 item evidence-based screening tool used to assess psychosis risk[34]. During our pilot project, Fifteen percent (n=671) of visitors completed the PQ-B and 453 (67.5%) scored positive suggesting the presence of psychotic experiences. The caregiver campaign will offer the unpublished parent PQ-B designed to obtain caregivers' perspectives of emerging experiences in a loved one. Users who complete the questionnaire will be offered the opportunity to download a copy of their results and all will be encouraged to instantly discuss scores with research staff online.

Clinical research material will be obtained through a variety of mechanisms. Participants may choose to complete our online demographic survey/needs assessment as well as the psychosis screener (PQ-B). Participants who choose to leave contact information will be contacted via their preferred method including email, phone, and text. Participants may also choose to interact with research staff directly via live chat and two way video available on our campaign website. All information gained from theses interactions will be recorded by research staff and kept confidential. Any notes and test results obtained as part of the engagement and referral process will be treated with the same stringent confidentiality as treatment as usual. Investigators will collect the results of the referral and eligibility assessment. Qualitative interviews and assessments done with participants and collateral sources will be collected and kept confidential. Online activity including engagement with campaign advertisements and website will be tracked by Google analytics and sent to research staff on a weekly basis.

12. STATISTICAL ANALYSIS

- *Describe how your data will be used to test the hypotheses.*
- *State clearly what variables will be tested and what statistical tests will be used.*
- *Include sample size calculations.*
- *If this is a pilot study, state which variables will be examined for hypothesis generation in later studies.*

A stepped-wedge cluster randomization (CR) design will be implemented. After a baseline period of six months, two clusters (grouped clinics) will be randomly assigned in month 7 and by month 18, all of NYS will be running the campaign. This strategy allows each region to serve as its own control[37]. The treatment effect can be modeled as a random effect at the cluster level which will accommodate treatment heterogeneity across the clinics. We grouped the 21 OTNY sites into 6 clusters based on geolocation as well as the total number of FEP referrals at each clinic between 10/01/2017 to 09/30/2018. We combined some regions to ensure that each cluster will be able to successfully meet recruitment criteria. The six clusters are; 1) Bronx, 2) Manhattan, 3) Queens, 4) Brooklyn, 5) Hudson River/Central NY, 6) Staten

Island/Long-Island/Western NY. There will be a total of four 6-month time periods, including the baseline period where all 6 clusters receive the control treatment. All analyses for Aim 1 (hypotheses A and B) will be conducted within the Generalized Linear Mixed Models (GLMM) framework with an identity link for continuous outcomes and logit link for binary outcomes. Analyses for Aim 2 will be done using asymptotic z-tests for proportions after accounting for the variance inflation factors (VIF). Aim 3 is exploratory, and hence only 95% confidence intervals, accounting for VIFs, will be calculated for the rates.

Aim 1: Evaluate the effectiveness of a search engine ad campaign on reducing DUP and raising rates of FEP referrals by directly comparing DUP and FEP referrals pre and post campaign activation. *Hypothesis A:* Patients admitted to OTNY via campaign channels will demonstrate a significantly shorter DUP than those admitted to OTNY through traditional outreach prior to campaign activation.

DUP will be defined as per Compton[36]. DUP onset will be defined as the first full threshold delusion or hallucination, lasting throughout the day for several days or several times a week, not limited to a few brief moments. The endpoint will be defined as treatment with an antipsychotic (DUP 1). Given that our aim is to connect patients with specialty care, we will also define the DUP endpoint (DUP II) as enrollment in OTNY.

OTNY programs currently assess DUP at each site locally as part of the intake process. The mean DUP (n=1222) from symptom onset to OTNY enrollment is reported to be 7.6 months (median 5.5 months). For the duration of the award, all de-identified DUP data routinely uploaded to OTNY central (as part of standard quality improvement) will be provided to research staff for analyses. We will compare DUP from each site prior to activing the campaign, to DUP during the active phase of the campaign, arriving both through the campaign as well as through traditional channels.

Power Analysis: Sample size calculations were done using Hemming and Taljaard's second strategy[38] for stepped wedge CR design, where a fixed number of clusters (6) and number of steps (3) was specified based on feasibility, and the required number of participants per site per period was determined as the positive solution of a quadratic equation. In addition, intra-cluster correlation (ICC) for the sites was also required. Mean DUP reported from the RAISE-ETP study[3] was 179 weeks (SD = 249), and the ICC used for the original power analysis for the RAISE study was 0.1. Prior marketing campaigns have reduced DUP substantially[5,6]. Assuming a 50% reduction with our new intervention, the sample size required at 80% power and α = 0.05, is 32 participants per 6-month period per cluster, leading to (32 x 4 x 6=) 768 participants for Aim 1. Based on existing OTNY enrollment data, the Bronx will receive approximately 30 new intakes per 6-month period. In order to compensate, we will be collecting DUP data from 40 participants per 6-months period in the Manhattan and Brooklyn clusters. Power analysis was done only for the primary outcome (hypothesis A).

Hypothesis B: Activating the campaign will significantly increase the number of FEP referrals and patients admitted to OTNY as compared to number of FEP referrals and patients admitted pre-campaign. All OTNY referral data are thoroughly recorded as part of treatment as usual and stored in a centralized database within OTNY central. Extracted information includes the name and contact details of the individual making the inquiry, reason for the inquiry, presenting symptoms, duration of symptoms, age of the prospective patient, and outcome of the referral including OTNY intake/acceptance or screen out. For the duration of the award, all de-identified referral data routinely uploaded to OTNY central will be provided to research staff for analyses. We will extract OTNY referral data from each site prior to activing the campaign to serve as baseline, and will continue to extract all OTNY inquiry data during the active campaign. Additional referrals arriving through dedicated campaign channels (email, phone calls, text, live chat, and two way video) will be recorded centrally by research staff. All FEP referrals will be provided an appointment for an evaluation at the nearest OTNY program and admission to the program will be recorded. All ineligible referrals will be referred to appropriate local services. Based on existing OTNY inquiry data as well as the results of our prior pilot initiatives, we anticipate approximately doubling weekly inquiries as a result of the campaign, arriving through campaign related channels over the course of the trial (30 additional referrals). Of those, we anticipate that 20% will be appropriate for OTNY (6 participants weekly) and that 4 of those individuals will be successfully enrolled each week as a result of the campaign. We will compare baseline rates of inquiries, number of FEP referrals, and number of patients admitted to OTNY in NYS prior to campaign activation, to rate of inquiries, number of FEP referrals, and number of patients admitted to OTNY in NYS while the campaign is active both arriving through the campaign, and traditional referral channels.

Aim 2: Determine the efficacy of a campaign targeting caregivers in promoting treatment initiation by comparing rates of OTNY enrollment arriving through the caregiver campaign to rates of enrollment arriving through the patient campaign. *Hypothesis:* Engaging caregivers online will significantly increase the likelihood of promoting treatment initiation of individuals with FEP as compared to engaging prospective patients alone.

Throughout the campaign, one dedicated landing page for each unique target audience (prospective patients and caregivers), will be promoted online, presenting each audience with a unique and identifiable campaign phone line, email, text line, and live chat options. We will compare rates of inquiries, number of FEP referrals, and number of patients admitted to OTNY throughout NYS arriving through the caregiver campaign to rates of inquiries, number of FEP referrals, and number of patients admitted to OTNY arriving through the participant campaign. Both campaigns will run in parallel and

each will target a dedicated audience based on demographics (age) and online search query. For example, “I am hearing voices” will generate the participant ad/campaign, while “my daughter is acting strange” will generate an entirely different set of ads geared towards caregivers. Power Analysis: Current OTNY referral data suggest that caregivers including parents are 5 times more likely to initiate a referral inquiry as compared to prospective participants themselves. We therefore anticipate that at least 2/3 (66.7%) of campaign referrals (approximately 20 weekly) will be generated by the parent campaign. Based on OTNY referral data, we anticipate that 20% will be appropriate and all will be enrolled into OTNY. Sample size necessary to detect a prevalence of 66.7% for the caregiver campaign compared to the null hypothesis of equal rates for the two campaigns is 68, which has to be multiplied by the design effect (variance inflation factor), $[1 + (n-1)\rho]$, to get required sample size. As ICC (ρ) ranges from 0.01 to 0.06, the design effect will range from 1.67 to 5.02 and the sample size required will vary from 114 to 342. Although there are 24 six-month time periods from all clusters (4 per cluster and 6 clusters, 4 x 6 = 24) based on the stepped wedge design for Aim 1, only 12 of them will have the campaign. Based on recent OTNY referral data, the number of enrolled subjects per cluster in a 6-month period varied from 26 to 34, with an average of approximately 30. Thus, we expect to have (30 x 12) 360 subjects enrolled from the campaign part of the stepped wedge design. This sample size will be sufficient to detect the hypothesized difference in rates (66.7% vs. 33.3%) at 80% power and $\alpha = 0.05$, with an ICC as high as 0.06.

Aim 3: Explore which methods of online engagement are most effective at promoting treatment initiation by comparing rates of OTNY enrollment of individuals interacting with research staff via live chat or two-way video to rates of enrollment of individuals utilizing text, email, and/or phone alone. *Hypothesis:* individuals with FEP who engage via two-way video or live chat will be significantly more likely to initiate in-person contact compared to individuals with FEP who engage via text, email, and/or phone alone.

The campaign will encourage all website visitors to interact with research staff via phone, email, text, live chat, or two way video. During these interactions, research staff will obtain information regarding the eligibility of each user and facilitate treatment initiation if indicated as would be done for any other traditional OTNY referral. Research staff will record as much data as the user is willing to provide at the time. This includes the name and contact details of the individual, presenting concerns, presenting symptoms, duration of symptoms, age of the prospective patient, and outcome of the discussion including OTNY intake or screen out. As early help seeking is likely an ongoing process for many, users will be offered the opportunity to repeatedly return to our landing page as many times as they wish for ongoing online support. Each interaction will be recorded. Individuals with FEP will be referred to a local OTNY program for assessment. Based on rates of live chat

utilization in prior marketing initiatives[32], we anticipate that at least 30% of campaign website visitors will engage live chat/two way video at least once. Based on OTNY referral data, we anticipate that 20% will be eligible for OTNY. We will compare the rates of treatment initiation of individuals with FEP who engage in online two-way video or live chat support to rates of treatment initiation of individuals with FEP who interact with the campaign through phone, email, or text alone. Analysis for Aim 3 will be exploratory in nature, and hence a power analysis was not done.

In order to analyze qualitative interviews conducted throughout the trial, the study team would like to send the interview data to a Northwell approved transcription service (Perry Johnson & Associates). We will try to obtain verbal consent from all participants prior to sharing their data. If any participant refuses to provide consent, their data will not be sent for transcription.

13. SPECIMEN BANKING

- *If specimens will be banked for future research, describe where the specimens will be stored, how long they will be stored, how they will be accessed and who will have access to the specimens*
- *List the information that will be stored with each specimen, including how specimens are labeled/coded*
- *Describe the procedures to release the specimens, including: the process to request release, approvals required for release, who can obtain the specimens, and the information to be provided with the specimens.*

N/A

14. DATA MANAGEMENT AND CONFIDENTIALITY

- *Describe the data and specimens to be sent out or received. As applicable, describe:*
  - *What information will be included in that data or associated with the specimens?*
  - *Where and how data and specimens will be stored?*
  - *How long the data will be stored?*
  - *Who will have access to the data?*
  - *Who is responsible for receipt or transmission of data and specimens?*
- *Describe the steps that will be taken to secure the data during storage, use and transmission.*

Clinical research material will be obtained through a variety of mechanisms. Participants may choose to complete our online demographic survey/needs assessment as well as the psychosis screener (PQ-B). Participants who choose to leave contact information will be contacted via their preferred method including email, phone, and text. Participants may also choose to interact with research staff directly via live chat and two way video available on our campaign website. All information gained from theses interactions will be recorded by research staff and kept confidential through Northwell REDcap. Any data collected in excel files will be stored on protected Northwell servers. Any notes and test results obtained as part of the engagement and referral process will be treated with the same stringent confidentiality as treatment as usual. Investigators will collect the results of the referral and eligibility assessment. Online activity including engagement with campaign advertisements and website will be tracked by Google analytics and sent to research staff on a weekly basis. Study records that identify patients will be kept private. They will not be identified in study records or publications disclosed outside of the Northwell Health System, except as detailed below. The information that is collected for research will be analyzed for many years and it is not possible to know how long this analysis and follow-up will take.

Data from this research may be used in medical publications or presentations. The information will be de-identified so that individual participants cannot be recognized and the information will no longer be considered Protected Health Information (PHI).

All study documents that contain PHI (e.g. contact information forms) will be stored together in a locked cabinet that will be accessible only by study personnel who require access to the information. The subject name-identification number link will also be kept in this locked cabinet. All study documents will be de-identified of HIPAA data and will be stored in a separate locked file cabinet by unique ID number. Again, the study documents will only be accessible by study personnel who require access to the information. Final data entry will be completed on the study coordinators computer, which will be password protected and will be set up using ID numbers and will not contain any PHI. Subjects' identities will be kept confidential and will not be revealed in any descriptions or publications related to the research.

15. DATA AND SAFETY MONITORING PLAN

A specific data and safety monitoring plan is only required for greater than minimal risk research. For guidance on creating this plan, please see the Guidance Document *on the HRPP website.*

Part I – this part should be completed for all studies that require a DSMP.
Part II – This part should be completed when your study needs a Data and Safety Monitoring Board or Committee (DSMB/C) as part of your Data and Safety Monitoring Plan.

Part I: Elements of the Data and Safety Monitoring Plan

- *Indicate who will perform the data and safety monitoring for this study.*
- *Justify your choice of monitor, in terms of assessed risk to the research subject's health and well being. In studies where the monitor is independent of the study staff, indicate the individual's credentials, relationship to the PI, and rationale for selection*
- *List the specific items that will be monitored for safety (e.g. adverse events, protocol compliance, etc)*
- *Indicate the frequency at which accumulated safety and data information (items listed in # above) will be reviewed by the monitor (s) or the DSMB/C.*
- *Where applicable, describe rules which will guide interruption or alteration of the study design.*
- *Where applicable, indicate dose selection procedures that will be used to minimize toxicity.*
- *Should a temporary or permanent suspension of your study occur, in addition to the IRB, indicate to whom will you report the occurrence.*

The principal investigator, Michael Birnbaum, MD., and co-investigator, John Kane, MD., will be responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews.

Data and safety reporting will follow the requirements of the Northwell IRB as well as the requirements of the DSMB.

The study intervention is targeted online advertisements and educational material intended to link individuals searching online for information to specialty care staff and treatment. The material is not anticipated to cause any associated harm to the individual.

Adverse events will be monitored for each subject participating in the study.

The PI will determine whether the adverse event meets the criteria for SAE.

The PI will report the following types of adverse events to the IRB: Any unexpected and related serious adverse events. The PI will keep an SAE log to note any events for every subject.

The PI will review all adverse events and report events deemed significant.

Part II: Data and Safety Monitoring Board or Committee

- *When appropriate, attach a description of the DSMB.*
- *Provide the number of members and area of professional expertise.*
- *Provide confirmation that the members of the board are all independent of the study.*

16. WITHDRAWAL OF SUBJECTS

- *Describe anticipated circumstances under which subjects will be withdrawn from the research without their consent*
- *Describe procedures for orderly termination*
- *Describe procedures that will be followed when subjects withdraw from the research, including partial withdrawal from procedures with continued data collection.*

Participant's online activity will remain anonymous unless they chose to provide contact information to research staff. In such cases, individuals will be screened for FEP as per standard clinical screening procedures. During the screening process research staff will inform participants that information provided to research staff will be recorded and that they may opt out verbally if they wish.

17. RISKS TO SUBJECTS

- *Describe any potential risks and discomforts to the subject (physical, psychological, social, legal, or other) and assess their likelihood and seriousness and whether side effects are reversible. Where appropriate, describe alternative treatments and procedures that might be advantageous to the subjects.*
- *Include risks to others , like sexual partners (if appropriate)*
- *Discuss why the risks to subjects are reasonable in relation to the anticipated benefits and in relation to the importance of the knowledge that may reasonably be expected to result.*
- *Describe the procedures for protecting against or minimizing any potential risks, including risks to confidentiality, and assess their likely effectiveness.*

The proposed study involves no more than minimal risk. The risks associated with the participation in an online digital media campaign are the possible discomfort in answering personal questions, feeling fatigued, bored or anxious, and learning about mental health symptoms in others or oneself. These effects are expected to be short-lived and can be considered only minimally higher than what would occur in regular life without any study participation. The risks associated with learning about one's one mental health symptoms by completing the online psychosis self-screener cannot be foreseen. While this could lead to distress, psychoeducational material and referral sources will be provided and disclaimers will be provided as part of the screener. Should safety concerns arise during the screening process, appropriate authorities will be contacted as would be done for any other clinic referral as per treatment as usual.

18. RESEARCH RELATED HARM/INJURY

- *Describe the availability of medical or psychological resources that subjects might need as a result of anticipated problems that may be known to be associated with the research.*
- *If the research is greater than minimal risk, explain any medical treatments that are available if research-related injury occurs, who will provide it, what will be provided, and who will pay for it.*

Potential risks are minimal and are related to participating in a digital media campaign, completing an optional demographic/needs assessment, and psychosis self-screener. For some individuals there may be a gain in their understanding of their or their loved one's illness and illness development. Moreover, as a result of study participation, subjects may gain or seek additional information about mental health or seek referral for further evaluation or treatment, which may be beneficial to them. Given the minimal risk nature of the study, these benefits outweigh any possible foreseen risks.

19. POTENTIAL BENEFIT TO SUBJECTS

- *Explain what benefits might be derived from participation in the study, noting in particular the benefit over standard treatment (e.g. a once-a-day administration instead of four times a day, an oral formulation over an IV administration).*
- *Also state if there are no known benefits to subjects, but detail the value of knowledge to be gained*

For some individuals there may be a gain in their understanding of their or their loved one's illness and illness development. Moreover, as a result of study participation, subjects may gain or seek additional information about mental health or seek referral for further evaluation or treatment, which may be beneficial to them. Given the minimal risk nature of the study, these benefits outweigh any possible foreseen risks.

20. PROVISIONS TO PROTECT PRIVACY INTERESTS OF SUBJECTS

- *Describe the methods used to identify potential research subjects, obtain consent and gather information about subjects to ensure that their privacy is not invaded.*
- *In addition consider privacy protections that may be needed due to communications with subjects (such as phone messages or mail).*

Referrals for the study will come from self-response to the search engine ads. Those individual who interact with research staff via phone, text, email, live chat, or two way video will be greeted by a member of the study team who will inform users that as part of efforts to improve services, we'll be using some of the information provided to connect them to local care.

Participant's online activity will remain anonymous unless they chose to provide contact information to research staff. In such cases, individuals will be screened for FEP as per standard clinical screening procedures. During the screening process research staff will inform participants that information provided to research staff will be recorded and that they may opt out verbally of they wish.

Clinical research material will be obtained through a variety of mechanisms. Participants may choose to complete our online demographic survey/needs assessment as well as the psychosis screener (PQ-B). Participants who choose to leave contact information will be contacted via their preferred method including email, phone, and text. Participants may also choose to interact with research staff directly via live chat and two way video available on our campaign website. All information gained from theses interactions

will be recorded by research staff and kept confidential. Any notes and test results obtained as part of the engagement and referral process will be treated with the same stringent confidentiality as treatment as usual. Investigators will collect the results of the referral and eligibility assessment.

21. COSTS TO SUBJECTS

- *Describe any foreseeable costs that subjects may incur through participation in the research*
- *Indicate whether research procedures will be billed to insurance or paid for by the research study.*

Participants will not be billed for participation in the study.

22. PAYMENT TO SUBJECTS

- *Describe the amount of payment to subjects, in what form payment will be received and the timing of the payments.*

Participants will not be reimbursed for primary study aims.
Participants who agree to participate in our optional open-ended qualitative interview will be offered 50$ for their participation. Participants will be reimbursed through electronic cards (Clin Cards) or Amazon gift cards.

23. CONSENT PROCESS

If obtaining consent for this study, describe:

- *Who will be obtaining consent*
- *Where consent will be obtained*
- *Any waiting period available between informing the prospective participant and obtaining consent*
- *Steps that will be taken to assure the participants' understanding*
- *Any tools that will be utilized during the consent process*
- *Information about how the consent will be documented in writing. If using a standard consent form, indicate such.*
- *Procedures for maintaining informed consent.*

See below

In the state of NY, any participants under the age of 18 are considered children. If your study involves children, additional information should be provided to describe:

- *How parental permission will be obtained*
- *From how many parents will parental permission be obtained*
- *Whether permission will be obtained from individuals other than parents, and if so, who will be allowed to provide permission. The process used to determine these individual's authority to consent for the child should be provided*
- *Whether or not assent will be obtained from the child*
- *How will assent be documented*
- *Whether child subjects may be expected to attain legal age to consent to the procedures for research prior to the completion of their participation in the research. If so, describe the process that will be used to obtain their legal consent to continue participation in the study. Indicate what will occur if consent is not obtained from the now-adult subjects.*

Please see above

If the study involves cognitively impaired adults, additional information should be provided to describe:

- *The process to determine whether an individual is capable of consent*
- *Indicate who will make this assessment*
- *The plan should indicate that documentation of the determination and assessment will be placed in the medical record, when applicable, in addition to the research record.*
- *If permission of a legally authorized representative will be obtained,*
  - *list the individuals from who permission will be obtained in order of priority*
  - *Describe the process for assent of subjects; indicate whether assent will be required of all, some or none of the subjects. If some, which subjects will be required to assent and which will not.*
  - *If assent will not be obtained from some or all subjects, provide an explanation as to why not*
  - *Describe whether assent will be documented and the process to document assent*
  - *Indicate if the subject could regain capacity and at what point you would obtain their consent for continued participation in the study*

N/A

If the study will enroll non-English speaking subjects:

- *Indicate what language(s) other than English are understood by prospective subjects or representatives*
- *Indicate whether or not consent forms will be translated into a language other than English*

- *Describe the process to ensure that the oral and written information provided to those subjects will be in that language*
- *If non-English speaking subjects will be excluded, provide a justification for doing so*

N/A

24. WAIVER OR ALTERATION OF THE CONSENT PROCESS ☐ N/A

Complete this section if you are seeking an alteration or complete waiver of the consent process.

- *Describe the possible risks of harm to the subjects involved in this study and explain why the study involves no more than minimal risk to the subject:*
- *Explain why the waiver/ alteration will not adversely affect the rights and welfare of subjects*
- *Explain why it is impracticable to conduct this research if informed consent is required*
- *If appropriate, explain how the subjects will be provided with additional pertinent information after participation. If not appropriate to do so, explain why.*

Complete this section if you are obtaining informed consent but you are requesting a waiver of the documentation of consent (i.e., verbal consent will be obtained). *To proceed with a waiver based on these criteria, each subject must be asked whether they wish to have documentation linking them to this study.* ***Only complete subsection 1 OR subsection 2.***

SUBSECTION 1

- *Explain how the only record linking the subject to the research would be the consent document.*
- *Explain how the principal risk of this study would be the potential harm resulting from a breach in the confidentiality*
- *Indicate whether or not subjects will be provided with a written statement regarding the research.*

Referrals for the study will come from self-response to the search engine ads. Those individual who interact with research staff via phone, text, email, live chat, or two way video will be greeted by a member of the study team who will inform users that as part of efforts to improve services, we'll be using some of the information provided to connect them to local care. If the individual does not want their information shared they can opt out. Verbal consent will be documented by research staff. Patients who on initial evaluation are deemed not to be capable of giving verbal informed consent will not be evaluated further for the

study. Patients who are deemed capable of giving verbal informed consent will then be provided with a full and complete description of the study. Participant's online activity will remain anonymous unless they chose to provide contact information to research staff. In such cases, individuals will be screened for FEP as per standard clinical screening procedures. Research staff will request permission to re-contact those referred to OTNY post intake to determine enrollment status. Given that participants may be located throughout NYS, the verbal informed consent process will occur over the phone or online via two way video. Participants will not be provided a written statement regarding research. Verbal consent will be obtained from participants prior to sending audio recordings of participant interviews to a Northwell approved transcription service (Perry Johnson & Associates) in order to analyze qualitative interviews conducted throughout the trial. If any participant refuses to provide consent or we are unable to re-contact to obtain verbal consent/authorization, their data will not be sent for transcription.

SUBSECTION 2

- *Describe the possible risks of harm to the subjects involved in this study and explain why the study involves no more than minimal risk.*
- *Confirm that the research only involves procedure for which consent is not normally required outside the research context.*
- *Indicate whether or not subjects will be provided with a written statement regarding the research.*

N/A

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25. WAIVER OF HIPAA AUTHORIZATION ☒ N/A

Complete this section if you seek to obtain a full waiver of HIPAA authorization to use and/or disclose protected health information.

- *Describe the risks to privacy involved in this study and explain why the study involves no more than minimal risk to privacy:*
- *Describe your plan to protect identifiers from improper use or disclosure and to destroy them at the earliest time.*
- *Indicate why it is not possible to seek subjects' authorization for use or disclosure of PHI.*
- *Indicate why it is not possible to conduct this research without use or disclosure of the PHI.*
- *Indicate if PHI will be disclosed outside NSLIJ Health System, and if so, to whom. Note: PHI disclosed outside NSLIJ Health System, without HIPAA authorization needs to be tracked. Please see guidance at www.nslij.com/irb for information about tracking disclosures.*

Participants who are deemed to be likely eligible for a referral to an early intervention clinic (based on their responses to the self-screener and/or live chat with research staff) and who chose not to progress along their pathway to care and/or accept a referral to care, are re-approached by research staff (via the provided contact information) to participate in an additional optional 10 minute qualitative interview.
Verbal consent for completion of this additional interview will be obtained. The goal of the interview will be to explore barriers in the online pathways to care and ultimately improve future iterations of the campaign. Questions will be open ended and explore personal motivations for deciding against pursuing formal care at this time. To then transcribe the interviews for analyses, verbal consent will be obtained from participants prior to sending audio recordings to a Northwell approved transcription service (Perry Johnson & Associates). Given that participants may be located throughout NYS, and that many participants selected to remain anonymous or semi-anonymous, the verbal informed consent process was deemed appropriate and will occur over the phone. If any participant refuses to provide consent, or if we are unable to re-contact a participant to obtain verbal consent/authorization, their data will not be sent for transcription.
The proposed research activity involves no more than minimal risk. The potential risk includes breach of confidentiality as some participants may have chosen to disclose PHI during their interview and voice data represents PHI as well. To minimize these risks, the research team will attempt to edit out any disclosed personal information however we will not be able to alter the voice. No other data or information (besides the audio recordings) will be sent to the transcription team.
All recordings and transcriptions will be stored in a one drive folder dedicated to this research study. The subject name-identification number link will also be kept in this folder. The study material will only be accessible by study personnel who require access to the information.

Complete this section if you seek to obtain a partial waiver of the patient's authorization for screening/recruitment purposes *(i.e., the researcher does not have access to patient records as s/he is not part of the covered entity)*

Note: Information collected through a partial waiver for recruitment cannot be shared or disclosed to any other person or entity.

- *Describe how data will be collected and used:*
- *Indicate why you need the PHI (e.g.PHI is required to determine eligibility, identifiers are necessary to contact the individual to discuss participation, other)*
- *Indicate why the research cannot practicably be conducted without the partial waiver (e.g. no access to medical records or contact information of the targeted*

population, no treating clinician to assist in recruitment of the study population, other)

26. VULNERABLE POPULATIONS:

Indicate whether you will include any of these vulnerable populations. If indicated, submit the appropriate appendix to the IRB for review:

- ☒ *Children or viable neonate*
- ☐ *Cognitively impaired*
- ☐ *Pregnant Women, Fetuses or neonates of uncertain viability or nonviable*
- ☐ *Prisoners*
- ☐ *NSLIJ Employees, residents, fellows, etc*
- ☐ *poor/uninsured*
- ☐ *Students*
- ☐ *Minorities*
- ☐ *Elderly*
- ☐ *Healthy Controls*

If any of these populations are included in the study, describe additional safeguards that will be used to protect their rights and welfare.

Referrals for the study will come from self-response to the search engine ads. Participant's online activity will remain anonymous unless they chose to provide contact information to research staff. It is likely that research staff will interact with minors who are searching for behavioral health information online. In such cases, research staff will encourage parental involvement and will screen individuals for FEP as per standard clinical screening procedures. Children between ages 16-17 searching for behavioral health information or resources will be referred to local care.

27. MULTI-SITE HUMAN RESEARCH (COORDINATING CENTER)

If this is a multi-site study where you are the lead investigator, describe the management of information (e.g. results, new information, unanticipated problems involving risks to subjects or others, or protocol modifications) among sites to protect subjects.

28. REFERENCES/BIBIOGRAPHY

Provide a reasonable list of references directly related to the study. Any diagrams for new medical devices or brief reprints from journals might also prove useful.

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