Protocol Title:
Feasibility and Acceptability of Click's Ecological momentary assessment (EMA) and text message intervention for STRESS management (FACE STRESS study).

Protocol Number: DL-FACE-101

Amendment Number: N/A

Device: N/A

Study Phase: N/A

Sponsor Name: Click Therapeutics, Inc

Legal Registered Address:
80 White St., 3rd Floor
New York, NY 10013

Manufacturer: Click Therapeutics, Inc

Regulatory Agency Identifier Number(s)
NCT04907942

[redacted]

Sponsor Signatory:

[redacted]

6/30/2020

Date

Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Original Protocol	06/25/2020
Amendment	N/A

Table of Contents

1. Protocol Summary **6**
1.1. Synopsis 6
1.2. Schema 8
1.3. Schedule of Assessments (SoA) 8
2. Introduction **10**
2.1. Study Rationale 10
2.2. Background 10
2.3. Benefit/Risk Assessment 12
3. Objectives and Endpoints **13**
4. Study Design **14**
4.1. Overall Design 14
4.2. Scientific Rationale for Study Design 14
4.2. Justification for Dose 15
4.3. End of Study Definition 15
5. Study Population **16**
5.1. Inclusion Criteria 16
5.2. Exclusion Criteria 16
5.3. Lifestyle Considerations 16
5.4. Screen Failures 16
5.5. Recruitment 16
6. Study Intervention and Concomitant Therapy **17**
6.1. Study Intervention Administered 17
6.2. Preparation/Handling/Storage/Accountability 17
6.3. Measures to Minimize Bias: Blinding 18
6.4. Study Intervention Compliance 18
6.5. Dose Modification 18
6.6. Continued Access to Study Intervention after the End of the Study 18
6.7. Treatment of Overdose 18
6.8. Concomitant Therapy 18
7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal **19**
7.1. Discontinuation of Study 19
7.2. Participant Discontinuation/Withdrawal from the Study 19
7.3. Lost to Follow up 19
8. Study Assessments and Procedures **20**
8.1. Efficacy Assessments 20
8.2. Safety Assessments 22

8.3. Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Safety Reporting 23
8.4. Pharmacokinetics 27
8.5. Genetics and/or Pharmacogenomics 27
8.6. Biomarkers 27
9. Statistical Considerations 28
9.1. Statistical Hypotheses 28
9.2. Sample Size Determination 28
9.3. Analysis Sets 28
9.4. Statistical Analyses 28
9.5. Interim Analysis 29
10. Supporting Documentation and Operational Considerations 30
10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations 30
10.2. Appendix 2: Clinical Laboratory Tests 33
10.3. Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting 34
10.4. Appendix 4: Contraceptive and Barrier Guidance 38
10.5. Appendix 5: AEs, ADEs, SAEs, SADEs, USADEs and Device Complaints and Nonconformances: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting in Device Studies 39
Appendix 6: Abbreviations and Definitions 43

1. Protocol Summary

1.1. Synopsis

Protocol Title:
Feasibility and Acceptability of Click's EMA and text message intervention for STRESS management (FACE STRESS study).

Rationale:
The purpose of the proposed study is to explore feasibility, acceptability, and initial efficacy of an Ecological Momentary Assessment (EMA) and text message intervention for stress management.

Objectives and Outcomes

Objectives	Outcomes
Primary	
● Feasibility of recruitment including eligibility rates and acceptance rates ● Feasibility of delivering the intervention via text message ● Acceptability of the intervention including dropout rates, percentage of completed assessments, adherence, and estimates of satisfaction	The main outcome of the FACE STRESS study is to evaluate **feasibility and acceptability** of an EMA and EMA plus text message intervention. Specifically, we will evaluate: ● number of interested individuals who contact Click Therapeutics because their interest in participating in the study ● the number of eligible individuals after the initial screening ● time taken to recruit the sample ● retention rates ● the number and percentage of participants responding to any EMA text over the 3-week study ● Satisfaction will be measured using both open-ended questions and likert-scaled questions to examine the

	acceptability and utility of the both EMA and intervention texts.
Secondary	
● Explore indicators of the EMA and text message intervention efficacy ● The effect sizes on reductions in perceived stress and other psychological symptoms will be estimated in the EMA and EMA+ intervention groups at post-intervention, 1, 3 and 6-month time-points.	Secondary outcomes will measure: ● Perceived stress and psychological overload ● symptoms of anxiety and depression ● symptoms of PTSD ● positive and negative affects ● resilience ● psychological well-being

Overall Design:

Brief Summary:
The purpose of this study is to evaluate feasibility and acceptability of an EMA compared with an EMA plus text message intervention in participants with higher-than-average perceived stress.

Study details include:
Study Duration: 7 months
Intervention Duration: 3 weeks

Number of Participants: 70
Up to 120 participants will be screened to achieve 70 enrolled to the study (see Section 9.2).

Groups and Duration: 2 groups (EMA alone or EMA plus text message intervention); 3 weeks

Data Monitoring Committee/Data Safety Monitoring Board: N/A

1.2. Schema

N/A

1.3. Schedule of Assessments (SoA)

Procedure	Pre-Enrollment	Day 1	Days 2-4	Days 5-25	Day 26	1 Mo. Post-Study	3 Mos.	6 Mos.	E/D[1]
Telephone Contact	X								X
Inclusion and Exclusion Criteria	X								
Demography	X								
Informed Consent		X							
Baseline Assessment			X						
EMA+Interven-tion				X					
Post Intervention Assessment					X				
Follow Up Assessment						X	X	X	

Procedure	Pre-Enrollment	Day 1	Days 2-4	Days 5-25	Day 26	1 Mo. Post-Study	3 Mos.	6 Mos.	E/D[1]
AE/SAE Reporting		X	X	X	X	X	X	X	X

1. Early Discontinuation

2. Introduction

Click Therapeutics digital therapeutic software applications are integrated with the unique feature of a personalized messaging system. Personalized messages provide the opportunity to tailor the intervention to the specific needs of the individual patient. This study will be pivotal in addressing the feasibility of adding to Click's platform a stand-alone text message intervention for stress management. Many patients with psychiatric and medical conditions suffer with chronic stress which exacerbate course and progression of the disease. A stand-alone text message intervention will represent an important feature to add to Click's platform across indications to target patients with high levels of stress.

2.1. Study Rationale

The overarching goal of Face Stress study is to explore feasibility and acceptability and initial efficacy of an EMA and text message intervention for stress management as a digital intervention. As the current pandemic has the potential of causing an increase in mental health problems in people who will be affected by Covid-19 for various reasons and in-person counselling and support are not possible, evaluating the feasibility of using a text messaging intervention to manage stress could be the stepping stone to provide support and reach a broader population. Based on this premise, our main research questions are: 1) Will it be feasible to deliver an EMA and text message intervention for the management of stress?; 2) Will participants find the EMA delivery and SMS content acceptable (satisfactory); 3) Efficacy question: will the text message intervention result in improved resilience and/or reduced psychological distress?

2.2. Background

The covid-19 pandemic represents an historic event with the potential to cause enormous psychological distress both because of the fear of the virus and its health implications, and because it requires major life adjustments (i.e. social distancing, isolation, unemployment etc.) which pose further strain on people's mental health. A recent review of the available literature reported that in the general population symptoms of distress and self-reported stress (8-28%) are common psychological reactions to the COVID-19 pandemic. A survey including 52,730 participants living in the Wuhan region in China, found that 35% of the respondents experienced psychological distress.

How individuals respond to stressful and traumatic experiences over time have been evaluated in longitudinal studies aiming at identifying stress and resilience trajectories. Evidence supports an adapting response with most individuals showing patterns of resilience and gradual recovery (3). However, about 38% of people experiencing traumatic and stressful situations show persistent chronic stress or a delayed stress response. Even though these studies have been helpful in pointing out that most people are indeed resilient, they present several limitations due to the use of traditional assessment methods. Such measures are collected infrequently and require participants to recall past events, feelings, and states, increasing the likelihood of bias and

limiting the ability to detect points of inflection where actual change occurs. Thus, little is known about specific turning points in these trajectories and possible predictors of such turning points in both observational and interventional studies.

Ecologically valid assessment methods have been developed to address the issues represented by the customary recall measures. Ecological Momentary Assessment (EMA) involves measuring psychological processes repeatedly in real time as they occur in the natural environment. EMA encompasses diverse assessment techniques including diaries, behavioral observation, and self-monitoring. EMA presents the advantage of minimizing recall bias, while improving generalizability and ecological validity. It also allows the identification of microprocesses that influence behaviors in real-world contexts.

Several contributions reported that during the 2003 SARS epidemic, individuals who presented high levels of stress continued showing stress symptoms longer after the successful containment of the disease. A survey conducted on the general population, 4 months after resolution of the SARS crisis in Taiwan found that the prevalence of psychiatric morbidity was 11.7%. Lee et al. (7) showed that SARS survivors not only had higher stress levels during the outbreak, compared with control subjects (PSS-10 scores = 19.8 and 17.9, respectively; $P < 0.01$), but this also persisted 1 year later (PSS-10 scores = 19.9 and 17.3, respectively; $P < 0.01$). At 1 year, about 64% of participants scored above the GHQ-12 cut-off suggesting the presence of psychiatric morbidity (7). Health care workers had stress levels similar to those of non-health care workers, but showed significantly higher stress levels a year later (PSS-10 score = 22.8, compared with PSS-10 score = 18.4; $P < 0.05$) and had higher depression, anxiety, posttraumatic symptoms, and GHQ-12 scores (7). Likewise, individuals who had been quarantined, or worked in high-risk locations such as SARS wards, or had friends or close relatives who contracted SARS, were 2 to 3 times more likely to have high PTSD symptoms, than those without these exposures 3 years later. In the light of these findings and the knowledge that about 1/3 of individuals affected by stressful life events show a chronic or delayed stress trajectory, we can assume that, without intervening, millions of survivors in the 216 countries affected will progress to develop psychiatric morbidity.

To overcome the actual challenge of delivering counseling and psychological support in person, text messaging interventions could represent a convenient and easy solution to adopt. Text message interventions have been widely used to support healthy behavior change such as smoking cessation, weight loss and health promotion. Evidence shows that text messaging interventions are effective in promoting behavior change. For example, a three-arm randomized trial compared self-reported alcohol use three months after emergency department visits, during which 765 young adults reported hazardous drinking. The number of self-reported binge drinking days decreased from baseline to three months in the real-time feedback group compared to text message drinking assessments without feedback or a control condition. A health text-messaging program including a range of health topics and information was effective in increasing health awareness in college students. Previous research provided evidence that text messages intervention including psychoeducation, reminders, and links to informative materials can be effective in improving individuals' mental health. For example, a text message intervention was found to be effective in improving parental competence and parental distress (estimated mean difference, -2.39 points; 95% CI, -4.37 to -0.40 points; $P = .02$) compared to

controls. Agyapong et al sent supportive text messages twice a day to a sample of 54 patients with depressive symptoms over a 3-month period. During this period, patients in the intervention group had significantly lower scores on the Beck Depression Inventory-II than control groups (8.5, standard deviation [SD] 8.0 vs. 16.7, SD 10.3, *P*=.003). In Canada, a supportive text message (Text4Mood) program was recently launched to support mental health during COVID-19. Within 1 week of the launch of Text4Hope, 32,805 subscribers had signed up to the program showing the relevance and timely importance of text messaging intervention.

2.3. Benefit/Risk Assessment

Some participants may experience discomfort when completing assessments related to their stress levels and emotional well-being. Although participation in this study may reduce stress and improve emotional well-being, we recognize that individuals experiencing high stress may conversely face the risk of symptomatic worsening. Both text message platforms are two-way. This will allow for review of the evaluation of content and assessment to determine if participants are experiencing a worsening of stress and are in need of further support.

3. Objectives and Endpoints

Objectives	Outcomes
Primary	
● Feasibility of recruitment including eligibility rates and acceptance rates ● Feasibility of delivering the intervention via text message ● Acceptability of the intervention including dropout rates, percentage of completed assessments, adherence, and estimates of satisfaction	The main outcome of the FACE STRESS study is to evaluate **feasibility and acceptability** of an EMA and EMA plus text message intervention. Specifically, we will evaluate: ● proportion of individuals who will contact us because interested to participate ● the number of eligible individuals after the initial screening ● time taken to recruit the sample ● retention rates ● the number and percentage of participants responding to any EMA text over the 3-week study ● Satisfaction will be measured using both open-ended questions and likert-scaled questions to examine the acceptability and utility of the both EMA and intervention texts.
Secondary	
● Explore indicators of the EMA and text message intervention efficacy The effect sizes on reductions in perceived stress and other psychological symptoms will be estimated in the EMA and EMA+intervention groups at post-intervention, 1, 3 and 6-month time-points.	Secondary outcomes will measure: ● Perceived stress and psychological overload ● symptoms of anxiety and depression ● symptoms of PTSD ● positive and negative affects ● resilience ● psychological well-being

4. Study Design

4.1. Overall Design

This study is a pilot randomized controlled trial with embedded qualitative research. Eligible participants who complete an informed consent form will be randomized to receive 3 weeks of EMA or 3 weeks of EMA plus the text message intervention for stress management based on a 1:1 allocation using random block sizes of 2.

Eligible participants will sign the consent form online before moving on to complete their baseline assessment. All participants will receive a copy of their signed consent form and will be provided with the research personnel's contact details. Participants who do not complete the baseline survey within 3 days from enrollment will be excluded from the study. Once their baseline is completed, participants will be randomized to receive:

- **Control**: 3 weeks of EMA, consisting of 2 text messages per day delivered at random times during waking hours to prompt participants to complete the survey
- **Intervention**:
    - 1 week of EMA, consisting of 2 text messages per day delivered at random times during waking hours to prompt participants to complete the survey followed by
    - 2 additional weeks of EMA in combination with 2 text messages per day with content related to stress management techniques.

At the end of the 3 weeks, participants in both groups will complete a post-intervention survey designed to evaluate participant satisfaction and to gather information for the purposes of improving the content of the text-message intervention. Changes in levels of psychological distress and well-being from baseline will be also evaluated.

At 1, 3 and 6-months post intervention, participants will be contacted via text message to complete a follow up survey. The follow up survey will include the same information collected at baseline with the exclusion of age, race, gender and adverse childhood events.

Participants from either group will be informed that they can withdraw from the study at any time without giving a reason by replying 'STOP' to any of the messages, or by contacting a member of the research team. No further information will be collected from participants who withdraw from the study.

Participants in the control group will be offered the opportunity to receive the intervention after the 6 months follow-up period. No data will be collected from this intervention.

4.2. Scientific Rationale for Study Design

This is a research study designed to explore feasibility and acceptability and initial efficacy of an EMA and text message intervention for stress management as a digital intervention.

4.2. Justification for Dose

N/A

4.3. End of Study Definition

The end of trial date is defined as the date at which all subjects have completed all activities shown in the Schedule of Assessments, all data has been entered, all data queries have been resolved, and the database has been locked.

5. Study Population

70 participants will be randomized to control (n=35) or intervention group (n=35)

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Age 22 or older
2. Must reside in an Easter Standard Time or Central Standard Time zone
3. Able to read and write in English as demonstrated by review and completion of an Informed Consent Form
4. Own an SMS enable smartphone (Android or iPhone OS4)
5. Scoring >5 on the 4-item Perceived Stress Scale (reflecting higher-than-average perceived stress; 15, 16)

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Reported cognitive impairment and/or psychiatric disorders of the psychotic spectrum
2. Enrolled in another support study
3. Currently receiving psychotherapy through telehealth
4. PHQ-9 score of 20 or greater.

5.3. Lifestyle Considerations

N/A

5.4. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

5.5. Recruitment

Between 70 and 120 participants will be recruited by advertisements posted on an internet job board, in order to randomize 70 participants. [redacted]

6. Study Intervention and Concomitant Therapy

The study intervention is described below.

6.1. Study Intervention Administered

Text messages were developed by the principal investigator who is a trained clinical psychologist and cognitive behavioral therapist. The development of the text message library followed

6.2. Preparation/Handling/Storage/Accountability

Consent and welcome and intervention text messages will be delivered remotely using a web-based SMS messaging platform. To send and receive messages, a third-party web-based text messaging platform was used as the Internet gateway. Participants' cell phone numbers will be registered in the web-based text messaging platform at baseline. EMA and standard surveys will be collected through [redacted] a HIPPA approved secure survey platform that enables direct texting. The company is GDPR Compliant; data is stored securely and encrypted in transit, at rest, and on all backups to reduce the risk of data security breach. In addition, the company leverage [redacted] security features to further lock down access to data.

Text message send times and delivery status will be recorded. Participants will be informed that this is a one-way message program and not to reply, however record will be kept of any incoming messages from participants. A record of the number of times each participant attempts to contact the research team and the method of contact (i.e. via phone, email, text message) will also be kept.

Participants who text-back will be sent an automated text message as follows 'From FACE stress: This is an automated reply. If this is an emergency and you are in need of immediate help call 911'. In addition, the content of the message will be reviewed by the research team who will determine an appropriate response including:

- No action required (e.g. text is related to content or acknowledgement)
- Action required on a study-related problem (e.g. participant reporting a technical problem or texting to withdraw from study)
- Action required on a different problem (e.g. text indicating high distress; response will be determined on a case-by-case basis and reviewed by the Principal Investigator and Medical Monitor)

6.3. Measures to Minimize Bias: Blinding

N/A

6.4. Study Intervention Compliance

Subjects will receive study intervention via text messages.
Subjects may remain in the trial, even if they are nonadherent with the digital intervention treatment.
A record of the digital intervention administered to each participant will be maintained.
Intervention start and stop dates will also be recorded.

6.5. Dose Modification

N/A

6.6. Continued Access to Study Intervention after the End of the Study

Participants in the control group will be offered the opportunity to receive the intervention at the end of the study (after 6 months follow up). No data will be collected from this intervention.

6.7. Treatment of Overdose

N/A

6.8. Concomitant Therapy

N/A

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1. Discontinuation of Study

If the study intervention is permanently discontinued, any reported AEs/SAEs will be collected at the time of discontinuation.

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons. This is expected to be uncommon.
- If a participant withdraws or is withdrawn from the Study, the sponsor will stop collecting new data from the participant, however, the sponsor may retain and continue to use any data collected before the participant withdraws or is withdrawn from the study.
- At the time of discontinuation from the study an early discontinuation visit will be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

7.3. Lost to Follow up

A participant will be considered lost to follow-up if he or she repeatedly fails to complete EMA and follow up surveys and is unable to be contacted by the study staff.
The following actions must be taken if a participant fails to complete 2 consecutive days of EMA survey:

- The study staff must attempt to contact the participant and address the missed survey and whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, an email to the participant's last known email address). These contact attempts should be documented in the participant's study record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- Outcomes are self-reported by the subject through an electronic system. Study staff will review surveys and assessments for completeness.
- Immediate safety concerns will be addressed by the Principal Investigator immediately upon occurrence or awareness to determine if the participant should continue or discontinue study
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The study coordinator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

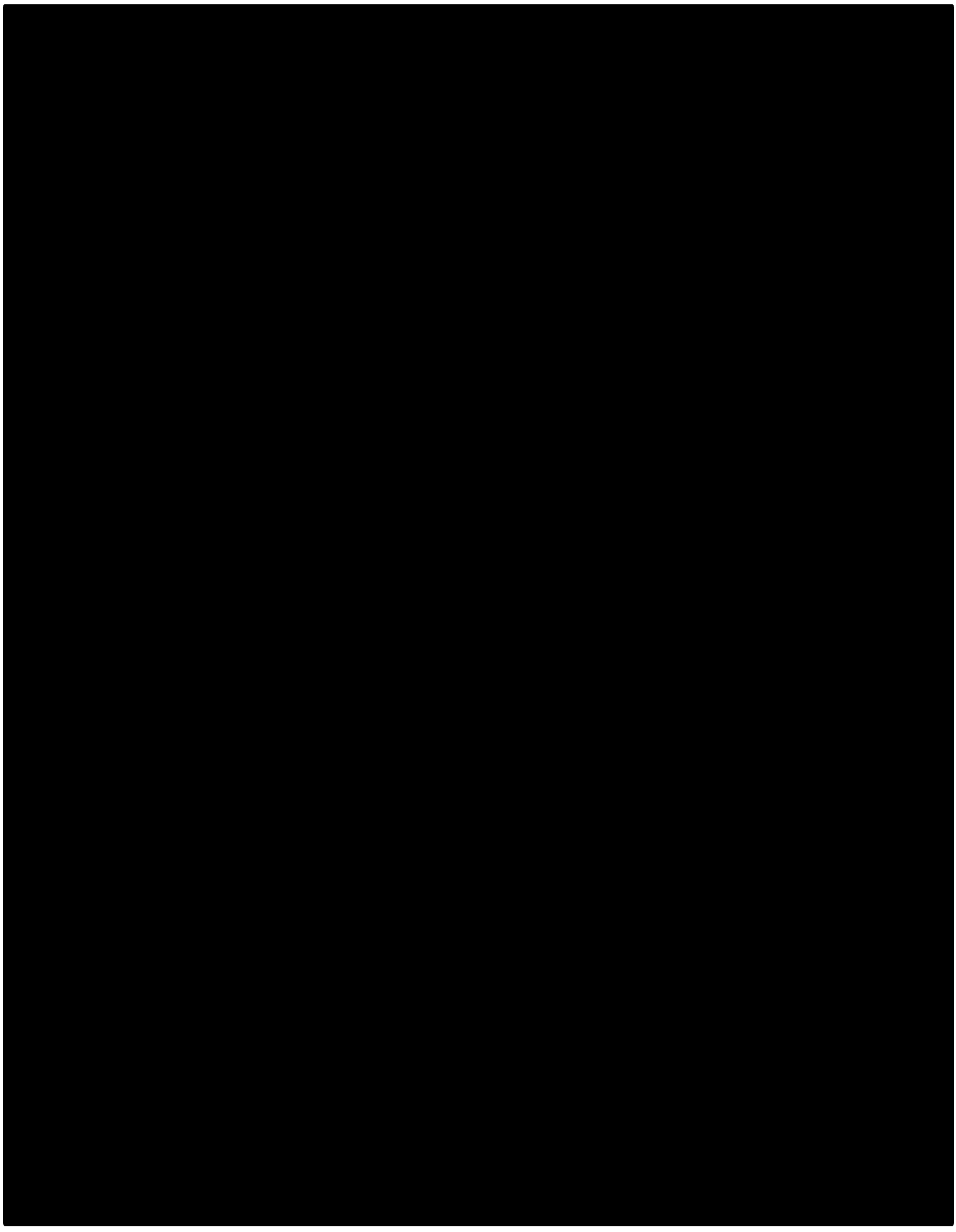
8.1. Efficacy Assessments

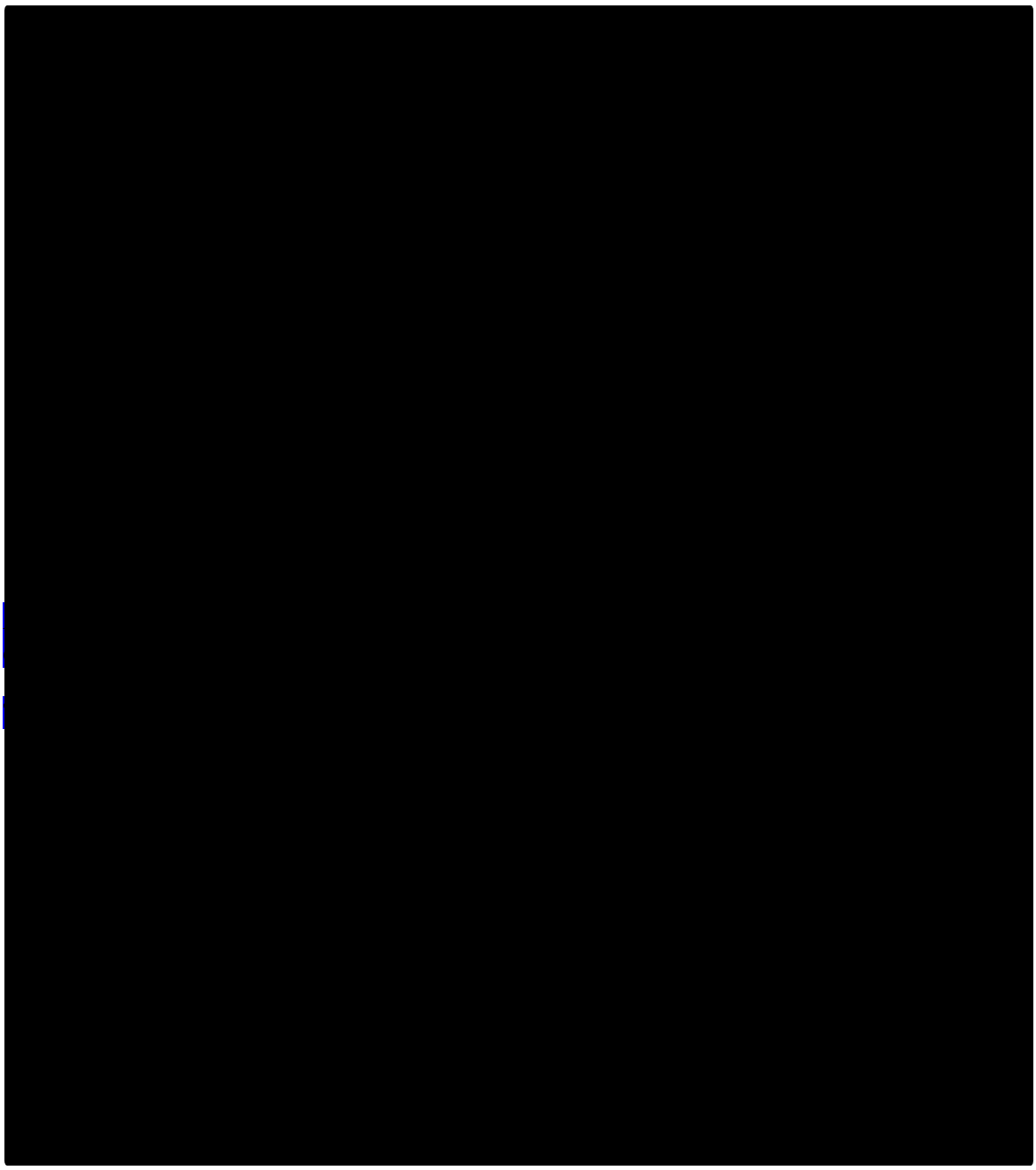
Participants will be recruited by advertisements posted on an internet job board. Screening assessments will occur remotely via phone to evaluate eligibility.

Planned time points for all efficacy assessments are provided in the SoA.

- **Standard assessment.** Participants will be evaluated at baseline, post-intervention and at 1, 3 and 6 months follow up.
    - Baseline assessment will include:
        - *sociodemographic information* (age, race, gender, employment status, annual income, zip code, living situation, health insurance);

[redacted]





8.2. Safety Assessments

- AEs and SAEs will be collected at each contact point with the participant, beginning when the consent form is signed, and throughout the participants participation in the study. Safety events will be reported through an electronic reporting system and evaluated by the Principal Investigator.
- AEs and SAEs that are collected via the text messaging platform will be recorded and evaluated. Specifically, adverse events will be reported and categorized with respect to

their likely relationship to the intervention (i.e. definitely, possibly, not related). Adverse events that might be reasonably related to SMS text messaging include hand or finger pain, or involvement in an accident as a result of sending or receiving a text relating to the study.

- Planned time points for all safety assessments are provided in the SoA.

8.2.1. Physical Examinations

N/A

8.2.2. Vital Signs

N/A

8.2.3. Electrocardiograms

N/A

8.2.4. Clinical Safety Laboratory Assessments

N/A

8.2.5. Pregnancy Testing

Pregnancy will be self-reported throughout the study. No pregnancy tests will be administered.

8.3. Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Safety Reporting

AEs will be reported by the participant. The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study (see Section 7).

In the unlikely event of an adverse event resulting from participation in this research study, the Click Discovery Lab Standard Operating Procedure will be followed for handling Adverse and Serious Adverse Events. The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

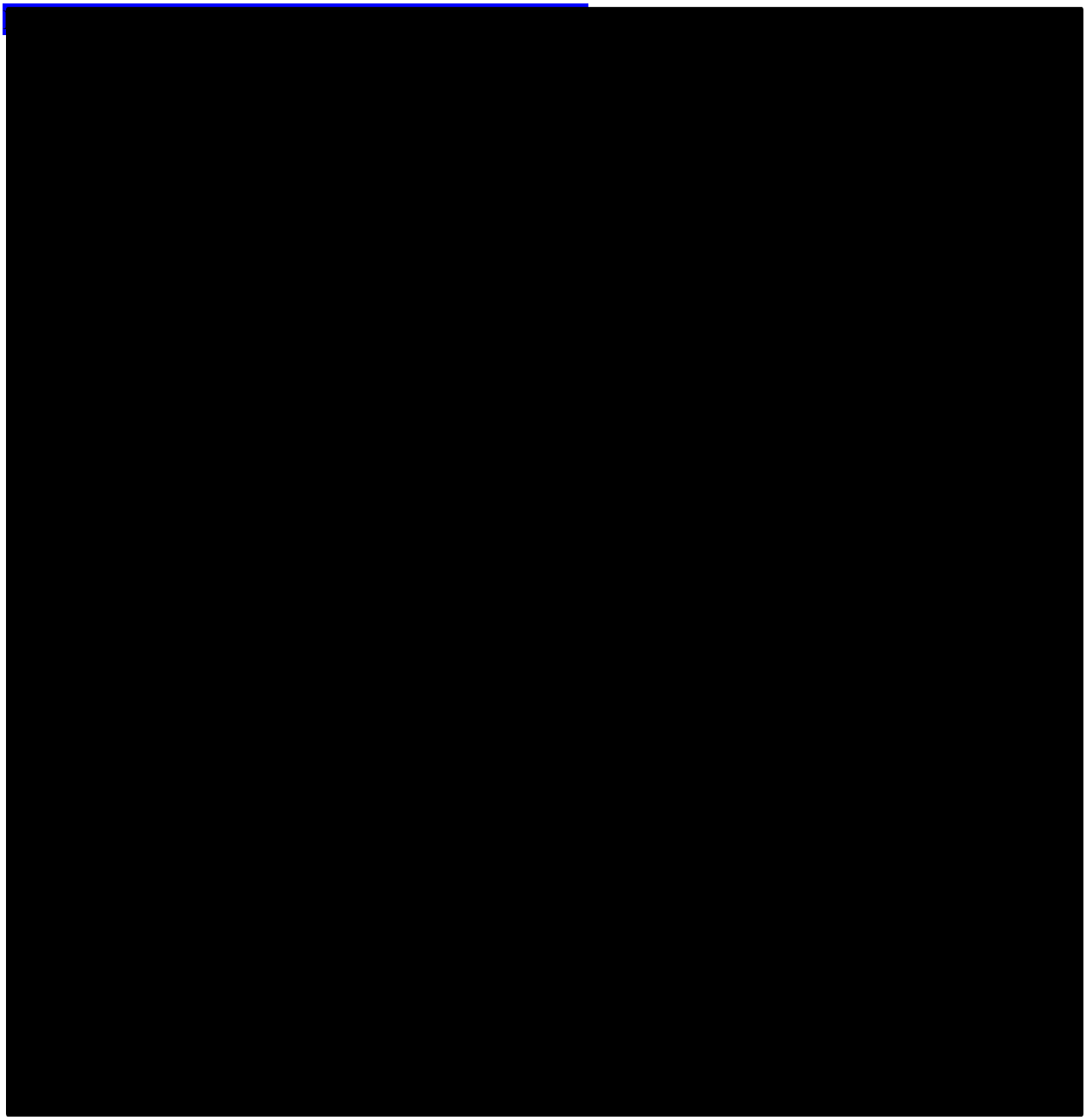
8.3.1. Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected from the signing of the informed consent form (ICF) until the 6 months follow-up as specified in the SoA (Section 1.3).

All SAEs will be recorded and reported to the investigator immediately. Under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to Designated Click Medical Monitor within 24 hours of it being available.

8.3.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.



8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Appendix 3.

8.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and file it and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Pregnancy

Pregnancy will be self-reported by the subject. Pregnant females will not be excluded from participation.

- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the female participant pregnancy.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study may continue the study intervention.

9. Statistical Considerations

9.1. Statistical Hypotheses

The primary hypothesis is that the EMA and text message intervention will be feasible and well accepted as evaluated by participants completing at least 33% of the surveys and a retention rate >= 70%.

9.2. Sample Size Determination

Based on an expected small to moderate effects size (17) of the text message intervention for stress management, a sample size of 70 participants (35 participants per arm) will be sufficient to establish feasibility for a 80% powered main trial with an 80% upper confidence limit (18). About 120 participants will be screened to achieve up to 70 enrolled to the study.

[redacted]

9.3. Analysis Sets

[redacted]

9.4. Statistical Analyses

Primary outcome.

- *Quantitative analysis*. Feasibility of the intervention will be reported as descriptive statistics, focusing on number of individuals who contact the study team with interest in participation; the number of eligible individuals after the initial screening; time taken to recruit the sample; retention rates; the rate of EMA survey completion. Acceptability will be measured as means and standard deviations of responses to each item within the satisfaction questionnaire, and the proportion of participants giving favorable responses.
- *Qualitative analysis*. A codebook and coding guidelines will be developed for analysis of qualitative feedback. Two researchers will code all transcripts using [redacted] and add to the codebook as needed. Each researcher will then independently identify main themes. Results will be compared and discussed until an agreement will be reached. Representative samples of feedback from open-ended questions will be also used.

Secondary outcomes.

- *Standard responses.* Sociodemographic responses will be described by mean, standard deviation (SD), and range. Mixed-effects models for repeated measure (MMRM) will be used to examine change in secondary outcomes, with outcomes examined as change in scores between baseline and follow-up. Models will include effects for time, group (control/intervention), group x time interactions and baseline values of the outcome variable (to control regression to the mean) and other potential confounders. Per Protocol analysis will be performed. The per protocol population will include all randomized participants excluding those who had protocol violations. A significance level of 0.05 will be used. All analyses will be performed using [redacted]
- *EMA responses.* Variability in momentary responses will be described by each participant's mean, SD, and range of mean square successive difference (34), which is a measure of variability that accounts for the temporal order of responses. Analyses on momentary responses will be conducted using Multilevel Modelling (35) because of the hierarchical structure of the data (level 1 = measurement time, level 2 = measurement day, level 3 = participant) and the aptness for dealing with varying time intervals between assessments and missing data. For depicting systematic (i.e. changing with time) or unsystematic (i.e. symptom variability) inter- and intraindividual variations in symptom severity and coping strategies, intraclass correlation coefficients (ICCs) will be used, while associations of symptomatology, coping efficacy and HCC will be analyzed using multilevel correlation and regression analyses.

9.4.1. Safety Analysis

All AEs will be coded by system organ class and Medical Dictionary for Regulatory Activities (MedDRA) preferred team. All AEs will be coded by system organ class and Medical Dictionary for Regulatory Activities (MedDRA) preferred term All safety analyses will be made on the Safety Population.All safety analyses will be made on the Safety Population.

9.5. Interim Analysis

N/A

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require IRB/IEC approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, and all other applicable local regulations.

10.1.2. Informed Consent Process

- Patients who meet the eligibility criteria will be asked to sign an online consent form. The consent form will describe the potential risks and benefits of study participation as well as the responsibilities of the participants and the investigators.
- Participants must be informed that their participation is voluntary. Participants are required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant.

10.1.3. Data Protection

Study participants will be assigned a unique identifying number (ID). This ID, rather than any PII, will be used to label all hard copy and electronic data. Identifiers and study data will be saved in separate files, accessible only to study staff. As a result, the bulk of the data will be completely anonymized, including records of screening instruments.
However, the consent form and documentation of payment will include both the subject's name and ID. As a result, these documents will be stored separately from other records. All hard copy records will be stored in locked cabinets to which only the study investigators will have access. All electronic records will be stored on an electronically secure database at Click Therapeutics. This database is password protected.

[redacted]

10.1.4. Patient Privacy

Protection of Participant Privacy: Privacy in the context of this study includes confidentiality of data and personal information and in the handling and reporting of data. The investigator will be responsible for ensuring data are stored in a secure area accessible only to study staff. These provisions will be monitored periodically. Clinical research may be a stressful experience for some patients; therefore, sensitivity in recruitment (i.e., including no coercive strategies) will be a high priority.

HIPPA compliance: All projects will obtain an authorization for the Health Insurance Portability and Accountability Act (HIPAA) from the Institutional Review Board (IRB). The authorization is to use or disclose protected health information for research that also includes a research repository, which will be signed by the participant, with a copy kept in the data management system. A copy will also be available to the patient. This authorization will allow the use or sharing of private information including information that is given via written questionnaires from questions regarding demographic and psychological and medical information.

[redacted]

10.1.4.1. Medical Monitor

- Participant safety will be continuously monitored by the Medical Monitor, which includes safety signal detection at any time during the study.
- All safety data collected will be summarized and reviewed by the Medical Monitor for agreement of next steps.
- If at any time during the course of the study, the PI judges that risk to subjects outweighs the potential benefits, either shall have the discretion and responsibility to recommend that the study be terminated.
- Case unblinding may be performed for above reviews if necessary.

10.1.5. Dissemination of Clinical Study Data

N/A

10.1.6. Data Quality Assurance

- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.

10.1.7. Source Documents

Source documents are defined as the electronic survey responses. Electronic survey responses provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents for this study will be collected electronically and will be maintained by the sponsor.

[redacted]

10.2. Appendix 2: Clinical Laboratory Tests

Laboratory tests are not evaluated in this study.

10.3. Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected intervention- intervention interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. “Lack of efficacy” or “failure of expected pharmacological action” also constitutes an AE or SAE.

Events <u>NOT</u> Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant’s condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant’s condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

An SAE is defined as any serious adverse event that, at any dose:

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
  - Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions or development of intervention dependency or intervention abuse.

10.3.3. Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information.

- It is **not** acceptable for the investigator to send photocopies of the participant's medical records in lieu of completion of the required form.
- There may be instances when copies of medical records for certain cases are requested. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

  An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by [X] to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or by telephone.
- Contacts for SAE reporting can be found in the Study Reference Manual.

SAE Reporting via Paper Data Collection Tool

- Email of the SAE paper data collection tool is the preferred method to transmit this information.
- In rare circumstances and in the absence of email, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE data collection tool within the designated reporting time frames.
- Contacts for SAE reporting can be found in the Study Reference Manual.

10.4. Appendix 4: Contraceptive and Barrier Guidance

Not applicable.

10.5. Appendix 5: AEs, ADEs, SAEs, SADEs, USADEs and Device Complaints and Nonconformances: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting in Device Studies

- Both the investigator and the sponsor will comply with all local reporting requirements.
- The detection and documentation procedures described in this protocol apply to all sponsor devices provided for use in the study. See Section 6.1.1 for the list of sponsor devices.

10.5.1. Definition of Device AE and ADE

Device AE and ADE Definition
● An AE is any untoward medical occurrence in a clinical study participant, users, or other persons, temporally associated with the use of study intervention, whether or not considered related to the investigational device. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of an investigational device. This definition includes events related to the investigational device or comparator and events related to the procedures involved. ● An adverse device effect (ADE) is defined as an AE related to the use of an investigational device. This definition includes any AE resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational device as well as any event resulting from use error or from intentional misuse of the investigational device.

10.5.2. Definition of Device SAE, SADE and USADE

A Device SAE is an any serious adverse event that:
a. Led to death
b. Led to serious deterioration in the health of the participant, that either resulted in: ● A life-threatening illness or injury. The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death if it were more severe. ● A permanent impairment of a body structure or a body function. ● Inpatient or prolonged hospitalization. Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE. ● Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function. ● Chronic disease (MDR 2017/745).
c. Led to fetal distress, fetal death, or a congenital abnormality or birth defect
SADE definition
● A SADE is defined as an adverse device effect that has resulted in any of the consequences characteristic of an SAE.

- Any device complaint or nonconformance that might have led to an SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.

Unanticipated SADE (USADE) definition

- An USADE (also identified as UADE in US Regulations 21 CFR 813.3), is defined as a serious adverse device effect that by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report (see Section 2.3).

10.5.3. Recording and Follow-Up of Device AE/SAE/Complaints and Nonconformances

Device AE, SAE, and Device Complaint and Nonconformance Recording

- When an AE/SAE/device complaint or nonconformance occurs, it is the responsibility of the investigator to review all documentation related to the event.
- The investigator will then record all relevant information in the participant's medical records, in accordance with the investigator's normal clinical practice and on the appropriate form.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records in lieu of completion of the AE/SAE/complaint and nonconformance form.
- There may be instances when copies of medical records for certain cases are requested. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- For device complaints and nonconformances, it is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the event.
  - A remedial action is any action other than routine maintenance or servicing of a device where such action is necessary to prevent recurrence of a device event. This includes any amendment to the device design to prevent recurrence.

Assessment of Intensity

The investigator will make an assessment of intensity for each event reported during the study and assign it to one of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. "Severe" is a category used for rating the intensity of an event; both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, **not** when it is rated as severe.

Assessment of Causality
● The investigator is obligated to assess the relationship between study intervention and each occurrence of each event. ● A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship, cannot be ruled out. ● The investigator will use clinical judgment to determine the relationship. ● Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated. ● For each event, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE/device complaint or nonconformance and has provided an assessment of causality. ● There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data. ● The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment. ● The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of Device AE/SAE/Complaint or Nonconformance
● The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested to elucidate the nature and/or causality of the event as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. ● New or updated information will be recorded in the originally completed form. ● The investigator will submit any updated SAE data within 24 hours of receipt of the information.

10.5.4. Reporting of Device AE/SAE/Complaints or Nonconformances

SAE Reporting via an Electronic Data Collection Tool
● The primary mechanism for reporting an SAE will be the electronic data collection tool. ● If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next table) to report the event within 24 hours. ● The site will enter the data into the electronic system as soon as it becomes available. ● After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data. ● If a site receives a report of a new event from a study participant or receives updated data on a previously reported event after the electronic data collection tool has

been taken off-line, then the site can report this information on a paper SAE form (see next table) or by telephone. ● Contacts for SAE reporting can be found in the Study Reference Manual.
Device AE/SAE/Complaint or Nonconformances Reporting via Paper Data Collection Tool
● Email transmission of the paper data collection tool is the preferred method to transmit this information. ● In rare circumstances and in the absence of email, notification by telephone is acceptable with a copy of the paper data collection tool sent by overnight mail or courier service. ● Initial notification via telephone does not replace the need for the investigator to complete and sign the paper data collection tool within the designated reporting time frames. ● Contacts for reporting can be found in the Study Reference Manual.

10.5.5. Reporting of SADEs

SADE Reporting
NOTE: There are additional reporting obligations for device nonconformances and complaints that are potentially related to SAEs that must fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to devices being used in clinical studies. ● Any device event that is associated with an SAE must be reported to the sponsor within 24 hours after the investigator determines that the event meets the definition of a device complaint or nonconformance. ● The sponsor will review all device events and determine and document in writing whether they could have led to an SAE. These device events will be reported to the regulatory authorities and IRBs/IECs as required by national regulations. ● Contacts for SAE reporting can be found in the Study Reference Manual.

Appendix 6: Abbreviations and Definitions

Abbreviation	Definition
ADE	Adverse device effects
AE	Adverse event
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
EMA	Ecological Momentary Assessment
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committees
IRB	Institutional Review Boards
SADE	Serious adverse device effect
SAE	Serious adverse events
SoA	Schedule of Assessments
USADE	Unanticipated serious adverse device effect