Title: A Decentralized, Double-blinded, Randomized, 18 month, Parallel-group, Superiority Study to evaluate the impact of Complement Theory's Live Coactive Exercise Coaching and Personalized Digital Application on Cancer Survivors' Quality of Life

Pro00077693

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Section 1: PROTOCOL SUMMARY

1.1 Protocol Synopsis

- **Primary and Secondary objectives and endpoints**
    - Primary Objective - To measure the impact of Complement Theory's Program on Quality of Life of cancer survivors as measured by FACT-G questionnaire.
    - Secondary Objectives:
        - Quantify the effect of CT's program on employee absenteeism by tracking changes in the number of sick days taken by participants.
        - Determine the program's impact on employee presenteeism by assessing changes in work motivation and employee performance review scores.
    - Exploratory Objective
        - To quantify the impact of Complement Theory's Program on total healthcare expenditure in cancer survivors.
        - Assess the impact of CT's Program on the progression and recurrence rates of prostate, colorectal, and lung cancers, by evaluating changes in tumor size and biomarker levels, including Blood pressure, PSA or protein, in addition to monitoring actual recurrence rates.
- **Overall Design**
    - Several key aspects of the trial design are summarized below:

Trial Model	Randomized control trial with two parallel groups: one active comparator (control) and one test group.
Test Intervention	Live Coactive Coaching program, focusing on Exercise and Meditation, along with app-guided

	evidence-based information on Diet, Sleep, and other lifestyle practices for 48 weeks (12 months)
Active Comparator (Control)	48 weeks access to Digital application with expert guidelines on lifestyle modification focusing on exercise, meditation, as well as information on diet, sleep and other lifestyle practices. Does not include live coaching and personalization.
Trial Intervention Assignment Method	Randomization
Population Type	Adult survivor
Population Diagnosis	Active Cancer (Breast, Prostate, Colorectal, Lung and Other) Stage 1-4
Population Age	21 yrs and above
Site Distribution	Digital Recruitment of participants who can be anywhere in the US

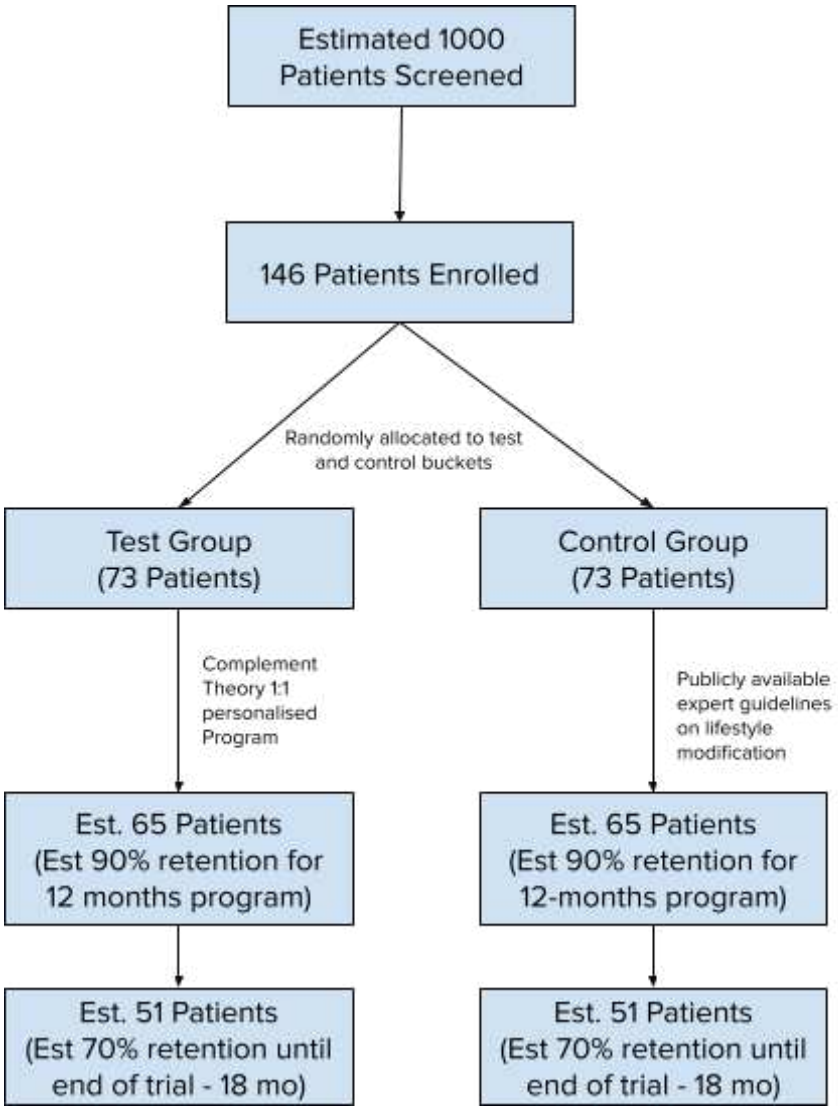
- **Number of Arms**
    - Two - One active comparator (control) and one test
- **Blinding**
    - The study will be double-blind: Participants and the Principal Investigator will not be made aware of treatment assignment.
    - Both the groups shall be given access to the app. The contents shall be different for active comparator and the test group.
- **No of Participants**
    - 146 (73 Maximum to be assigned randomly each to control and treatment)
- **Arms and Duration**

- Treatment Group
    - Participants will get access to Complement Theory's 12 month Live Coactive Coaching program, focusing on Exercise and Meditation and supplemented with evidence-based information on Diet, Sleep, and other lifestyle practices, adjunct to the core treatment.
    - Each week, up to five sessions of 45 minutes each will be offered, with a recommendation for participants to engage in a minimum of three sessions to ensure adequate program exposure and benefits.
    - Each session will consist of 30 Minutes of Physical Exercise and 7 minutes of meditation. Each session will be a combination session focused on Aerobic and Strength, with flexibility and balance exercises included as supplements.
    - Participants will be allocated to Low / Moderate intensity programs based on their specific medical profile, ensuring that the exercises and meditation practices are safe, effective, and aligned with their health status and cancer treatment plan.
- Active Comparator (Control) Group
    - Participants in this group will receive access to a curated collection of publicly available guidelines for lifestyle modification. These resources, presented through a digital application, will focus on exercise, meditation, diet, and sleep, but without the live coaching or program personalization.
    - This comparison aims to evaluate the impact of personalized, interactive live Coactive coaching against self-guided learning using standard guidelines.
- The overall duration for an individual participant is anticipated to be 12 months for the active phase, with a 6 month follow-up period for long-term data collection.

- **Committees**:

- Throughout the study, safety oversight will be provided by the Trial Monitoring Committee (TMC), composed of oncologists, cancer exercise specialists and biostatisticians.
- All participants enrolled in the study will be included in the safety analysis. The Trial Monitoring Committee will be responsible for reviewing relevant safety findings related to study outcomes.

1.2 Trial Schema



1.3 Schedule of Activities

- Step 1: Enrollment and Intervention
  - Screening (including baseline assessment)

    - Randomization by recruitment to test or control groups
    - Informed Consent
    - Access to control and test programs
    - Regular Assessments up to 18 months
- Step 2: Data Analysis
    - Interim Data analysis will be 3 months, 6 months, 12 months and 18 months data.
- Step 3: Publication
    - Publication on protocol analysis and outcomes data is expected at 12 months and the end of 18 months

Section 2: INTRODUCTION

2.1 Purpose of Trial

The randomized controlled trial (RCT) aims to evaluate the efficacy of Complement Theory's (CT) personalized and interactive, evidence-backed lifestyle program in reducing healthcare costs and improving health outcomes for survivors across all major cancer types.

Distinct from conventional interventions, CT's program offers live coactive coaching through a mobile app, concentrating on Exercise and Meditation, and is enriched with evidence-based advice on Diet, Sleep, and comprehensive lifestyle modifications. This trial is pivotal in assessing the program's effectiveness against an active comparator–expert-recommended lifestyle modification resources suitable for cancer survivors--to isolate the impact of coaching and personalization.

The primary objective is to investigate whether CT's novel approach can more effectively reduce healthcare utilization, through reduction of hospitalizations, urgent care visits, and outpatient visits. Furthermore, the trial seeks to measure adherence to treatment, and significant health outcomes, including improvements in Quality of Life Scores (QoLS) to

provide a holistic evaluation of the program's impact on patient care and well-being. As an exploratory effort, the trial will also measure cancer progression, recurrence in Prostate and Colorectal cancer survivors alone.

2.2 Summary of Benefits and Risks

Benefit Summary

- Immediate Potential Benefits
    - Improved Physical Health: Participants may experience improvements in physical health through regular exercise coaching provided by a live coach in conjunction with the digital application. Numerous studies[1,2] across cancer types have shown increased physical activity levels lead to enhanced health, improved strength and flexibility, and better overall physical function, yet only 15%[3] patients follow recommended physical activity levels.
    - Reduced Symptom Burden: Cancer survivors often experience symptoms such as fatigue, pain, and nausea as a result of their disease and treatment. Engaging in regular exercise has been shown to alleviate these symptoms and improve overall well-being. By participating in the trial, individuals may experience a reduction in symptom severity and an improvement in their daily functioning.
    - Enhanced Emotional Well-being: Physical activity is associated with numerous psychological benefits, including reduced stress, anxiety, and depression. The personalized exercise coaching delivered by a live coach may help participants manage emotional distress and improve their mood and overall psychological well-being.
    - Improved Quality of Life: Engaging in regular exercise, meditation, and experiencing improvements in physical and emotional health can contribute to a better quality of life over the long term. By participating in

the trial and adopting healthy exercise habits, individuals may enjoy a higher quality of life and greater satisfaction with their overall well-being.

- Medium-Long-Range Potential Benefits
    - Reduced Healthcare Utilization: By incorporating exercise into their daily routine and experiencing improvements in health outcomes, participants may reduce their reliance on healthcare services such as hospitalizations, urgent care visits, and outpatient appointments. This could lead to cost savings for both the individual and the healthcare system over the long term.
    - Empowerment and Self-management: Participating in the trial and receiving personalized exercise coaching empowers individuals to take an active role in managing their health and well-being. Learning skills and strategies for incorporating exercise into their lifestyle can help participants feel more in control of their health and better equipped to cope with the challenges of cancer treatment and survivorship.
    - Improved Treatment Outcomes: The program aims to positively impact cancer progression, and recurrence compared to survivors receiving standard care. By measuring changes in levels of biomarkers, size of tumors and incidence of cancer recurrence, the intervention seeks to improve overall treatment outcomes.

Risk Summary and Mitigation Strategy

- Trial-specific Discussion of Intervention Risks and Mitigations
    - Risk of Injury or Exacerbation of Health Conditions: Even though physical activity is considered safe for Cancer, engaging in physical exercise, especially for individuals undergoing cancer treatment, carries a small risk of injury or exacerbation of existing health conditions for survivors with existing comorbidities. Participants may experience muscle strains, joint

injuries, or fatigue, particularly if they engage in exercises beyond their physical capabilities.

- Mitigation Strategy: To mitigate this risk, the intervention takes into account participants' medical history, current health status, and physical fitness levels through an Intake Screening Form, which assigns them to Low intensity or Moderate intensity groups. The live coach in conjunction with the digital application will provide personalized exercise plans tailored to each participant's needs and capabilities Additionally, participants will receive education and guidance on proper exercise techniques, warm-up and cool-down procedures, and signs of overexertion or injury.

- Trial-specific Discussion of Procedure Risks and Mitigations
  - Some key risks associated with trial procedures in this trial: Engaging in the trial procedures, such as completing assessments, using the software app, may impose a burden on participants, particularly those undergoing cancer treatment or managing other health issues.
  - Mitigation Strategy: To mitigate participant burden, we will have trained personnel to help with data entry virtually as needed. Additionally, we will offer flexible scheduling to help alleviate the burden and enhance participant retention.

Overall Benefit: Risk Conclusion

The evaluation of our proposed trial, which integrates live coactive coaching with a software solution for cancer survivors, demonstrates a significant favorable balance between minimal risks and anticipated benefits. The residual risks are minimized through tailored safety measures and are outweighed by the expected benefits of improved physical health, decreased symptom burden, and enhanced quality of life.

Supporting this favorable assessment, a substantial body of research not only confirms the safety of exercise but also endorses the significance of physical activity and lifestyle

changes in cancer management. This evidence base, coupled with medical endorsement of physical activity for enhancing survivor outcomes, bolsters confidence in the trial's approach.

To ensure ongoing safety and integrity, risks and benefits will be continuously assessed, adjusting protocols as necessary to safeguard participant well-being. This trial aligns with best practices in cancer treatment and reflects a commitment to advancing survivor care through evidence-based lifestyle interventions.

Section 3: TRIAL OBJECTIVES, ENDPOINTS AND ESTIMANDS

Trial Objective 1: Impact of Complement Theory's Program on Quality of Life
Clinical Question: How does participation in Complement Theory's program affect Quality of Life Scores (as measured by FACT-G) in cancer survivors compared to those receiving standard care?

- Endpoint(s): Measured through change in FACT-G scores which is designed to assess various dimensions of quality of life including pain levels and sleep quality.
- Estimand(s): The mean difference in change in scores between the intervention and control groups at specified time points during and after the intervention period.

Trial Objective 2: Effect on Employee Absenteeism
Clinical Question: How does participation in the Complement Theory program influence the number of leave days taken by employed cancer survivors due to health issues?

- Endpoint(s): Number of leave days (including sick leave, short-term disability, and long-term disability) taken by participants during the trial period.
- Estimand(s): The difference in the average number of leave days between the intervention and control groups over the trial period.

Trial Objective 3: Impact on Employee Presenteeism

Clinical Question: What is the effect of Complement Theory's program on motivation to work and performance review scores among employed cancer survivors?

- Endpoint(s):
    - Motivation to work: Assessed through self-reported scales or questionnaires.
    - Performance review scores: Obtained from employer records or self-reported performance evaluations.
- Estimand(s): The difference in mean scores of motivation and performance reviews between the intervention and control groups over the trial period.

Exploratory Objective(s):

Impact on rates of cancer progression, and recurrence

Clinical Question: What is the effect of Complement Theory's program on progression and recurrence of prostate, lung and colorectal cancers?

- Endpoint(s):
    - Cancer progression: Measured by changes in tumor size and changes in levels of biomarkers.
    - Recurrence: Incidence of cancer recurrence.
- Estimand(s): Directional trends evaluating the difference in proportions or rates of cancer progression and recurrence between the intervention and control groups during and post-trial follow-up.

Rationale for Excluding Breast Cancer from Exploratory Objective:

- Breast cancer, in particular, exhibits a longer average timeframe for recurrence when compared to prostate, lung and colorectal cancers. This longer latency could extend beyond the scope of our study's follow-up period, making it

challenging to accurately measure the program's impact on recurrence rates within the study's duration.

- By focusing on prostate, lung and colorectal cancers, we aim to assess the program's impact on cancers with more predictable progression patterns and well-established biomarkers, enabling a clearer evaluation of the Complement Theory's potential benefits in these specific cancer populations.

Impact on Total Healthcare Expenditure

Clinical Question: Does participation in Complement Theory's 12-month Live coactive Coaching program, focusing on Exercise and Meditation and supplemented with evidence-based information on Diet, Sleep, and other lifestyle practices, adjunct to the core treatment, lead to a reduction in total healthcare expenditure for cancer survivors?

- Endpoint(s): Total healthcare expenditure, including hospitalization costs, medication expenses, outpatient visits, and any other related healthcare services that we planned and unplanned, cancer and non-cancer, over the trial period.
- Estimand(s): The difference in mean total healthcare expenditure between the intervention and control groups over a specified period (e.g., at 12 months and 18 months from baseline).

3.1 Summary of objectives, endpoints and estimands:

	Trial Objective	Clinical Question	Endpoint(s)	Estimand(s)

1	Impact on Quality of Life	How does participation in Complement Theory's program affect Quality of Life Scores (QoLS) in cancer survivors compared to those receiving standard care?	Measured through change in FACT-G score which is designed to assess various dimensions of quality of life, including physical well-being, pain levels, sleep quality.	Mean difference in change in scores between groups
2	Effect on Employee Absenteeism	How does participation in Complement Theory's program influence employee absenteeism due to health issues?	Number of leave days taken (sick leave, short/long-term disability)	Difference in average number of leave days between groups
3	Impact on Employee Presenteeism	What is the effect of Complement Theory's program on motivation to work and performance review scores among employed cancer survivors?	- Motivation to work - Performance review scores	Difference in change of mean scores of motivation and performance between groups

N/A	Impact on Cancer Progression, and Recurrence	What is the effect of Complement Theory's program on cancer progression, and recurrence on prostate lung and colorectal cancer?	- Cancer progression (biomarkers) - Change in tumor size - Recurrence (incidence of cancer recurrence)	Directional trends evaluating the difference in proportions or rates of cancer progression and recurrence between the intervention and control groups during and post-trial follow-up.
N/A	Impact on Total Healthcare Expenditure	Does participation in Complement Theory's 12-month program lead to reduced healthcare expenditure?	Total healthcare expenditure as defined as: (hospitalization, medication, outpatient visits, ER Visits)	Difference in mean total healthcare expenditure between groups

Section 4: TRIAL DESIGN

4.1 Description of Trial Design

- **Description of Intervention Model**
    - This randomized control trial features two parallel groups: an active comparator (control) group and a treatment group, aiming for a total of 146 participants diagnosed with one of the following cancers - Breast, Colorectal, Prostate Lung and Other Cancer.

    - The treatment group will be given live coactive coaching and personalized digital application program focused on Exercise and Meditation, supplemented with evidence-based facts on Diet, Sleep, and other lifestyle practices
    - On the other hand, the control group will be given a digital application with expert guidelines on lifestyle modification, available publicly but with no live coaching and personalization.
    - In essence, this is a superiority trial aimed at establishing that CT's program is more effective in improving outcomes.
- **Description of Trial Duration**
    - The overall duration for an individual participant is anticipated to be 48 weeks (minimum 3, up to 5 days per week, 45 mins each session) for the active phase, with a 6 month follow-up period for long-term data collection.
    - This duration allows for a comprehensive assessment of the intervention's immediate and sustained impacts on health outcomes and healthcare costs.
- **Method of Assignment to Trial Intervention**
    - Participants in each group will be recruited transparently through online advertisements while ensuring balanced representation across cancer types.
    - Blinding: The participants will not be aware if they are in control or test group.
    - Number of Arms: Two – one control and one treatment group.

4.2 Rationale for Trial Design

- **Rationale for intervention model**
    - The chosen randomized control trial (RCT) model with an active comparator allows for a direct and meaningful comparison between Complement Theory’s live coactive guidance with a physical coach and personalized program and the standard guidance available to cancer survivors. This

model is particularly suited to our objectives as it accommodates the evaluation of a complex intervention involving live coactive coaching and digital support, unlike traditional drug trials. This approach ensures that any observed differences in outcomes can be attributed with greater certainty to the unique components of the Complement Theory program, thereby providing a clear assessment of its added value over standard care practices.

- **Rationale for duration**
    - The trial duration has been carefully selected to ensure sufficient time to observe meaningful changes in Quality of Life, Presenteeism and Absenteeism. A 12-month intervention period, followed by a 6 month-long follow-up, allows us to capture both the immediate and sustained impacts of lifestyle modifications on health outcomes. As an exploratory effort, the extended follow-up period enhances our ability to monitor long-term effects, particularly relevant for outcomes like cancer recurrence and cancer progression in three cancer types (prostate, lung and colorectal). The durations for these exploratory metrics in Breast cancer are much longer and hence not considered.
- **Rationale for Endpoints**
    - The trial endpoints have been selected for their clinical relevance and their capacity to provide reliable and valid measurements of the intervention's effect. Quality of Life provides a patient-centered measure that is both prognostically important and assessable in the short term. Both the control and treatment groups are offered exercise oncology guidance, however our hypothesis is that CT’s live coactive coaching is expected to have better Quality of Life is measured measured through the FACT-G questionnaire. FACT-G also helps us measure the impact on Pain, Fatigue and Sleep Quality, providing a comprehensive assessment of well-being among cancer survivors. Lastly, measures of employee absenteeism and

presenteeism are particularly relevant to both employers and employees, providing insight into the program's potential to improve work-related outcomes in addition to health parameters.

- **Rationale for Comparator**
    - The control group's engagement with a digital application with publicly available expert guidelines on lifestyle modification represents current non-pharmacological supportive care options available to cancer survivors.
    - This comparator was selected to underscore the added value and distinct benefits of Complement Theory’s personalized and interactive wellness approach against more generic and self-guided lifestyle resources.

4.3 Access to Trial Intervention After End of Trial

- Post-trial, participants will have the opportunity to continue accessing the Complement Theory’s program Free of Cost. Details on extended access will be communicated towards the trial's conclusion.

4.4 Start of Trial and End of Trial

- Start of Trial: Defined by the first participant's enrollment (FPI).
- End of Trial: Marked by the last scheduled follow-up of the final participant, with an anticipated end date eighteen months post final participant enrollment to allow comprehensive long-term outcome analysis.
- Early Termination: Criteria for early trial termination will include lack of efficacy, safety concerns, or regulatory guidance, detailed in Section 10.5 with responsibilities clearly outlined for both sponsor and investigator.

Section 5: TRIAL POPULATION

5.1 Selection of Trial Population

- Participants for this trial will be identified through targeted online advertisements on platforms such as Facebook and Google. This approach ensures an unbiased recruitment process, enhancing our chances of assembling a representative

sample of the U.S. cancer survivor population. Consequently, we do not intend to impose specific gender or race quotas.

5.2 Rationale for Trial Population

- We have specifically chosen cancer survivors aged 21 yrs and above who have received cancer treatment (ie either surgery, chemotherapy, radiation, or immunotherapy) within the past six months. This demographic is selected based on evidence suggesting they stand to significantly benefit from our intervention in terms of improved health outcomes, aligning with employer interests.

5.3 Inclusion Criteria

- Cancer Type : Breast, Prostate, Colorectal, Lung and Other Cancers
    - Other Cancers here refers all other cancer types apart from Breast, Prostate, Colorectal and Lung Cancer
- Cancer Stage: Stage 1 to 4
- Treatment Status: Has undergone any cancer-related treatment in last 12 months
- Age : 21 yrs and above
- Permission to access to last 1 year digital health records
- Access to smartphone or a tablet

5.4 Exclusion Criteria

- Excludes individuals who have undergone surgery within the last 4 weeks or will undergo surgency in the next 4 weeks
- Participants declared medically unfit by their physicians to do physical exercise
- ECOG Score 3, 4 or 5

5.5 Lifestyle Considerations

- No lifestyle restrictions during the trial

5.6 Screen Failures

- Documentation: All screen failures will be documented, including the specific reason(s) for the failure. This information is crucial for trial records and may inform future trial design adjustments or participant recruitment strategies.
- Immediate Notification: Participants who do not meet the eligibility criteria at screening will be promptly informed of their screen failure status. The participant can also get detailed explanation regarding the specific criteria not met by writing to trial support team (mentioned on the landing page).
- Rescreening may be considered under the following conditions:
    - Reversible Conditions: If the screen failure is due to a reversible condition or temporary circumstance that rendered the participant ineligible (e.g., recent surgery), rescreening may be acceptable once the condition has resolved.
    - Updated Information: If new medical information becomes available that could change the initial screening outcome (e.g., updated diagnostic tests, revised cancer staging), rescreening is permissible.
    - All such participants would be able to write to trial support team to get rescreened.

Section 6: TRIAL INTERVENTION AND CONCOMITANT THERAPY

6.1 Schedule of Events

Schedule of events for test/treatment group:

Intervention or Assessment (Test)	**Baseline (Day -30 to -1)**	**Week 1/3/5/7/9/11/13/15/17/19/21/23/ ... /47**	**Week 2/4/6/8/10/12/14/16/18/20/22/24/ ... / 48**	**Month 1-6 (Every 30 days)**	**Month 7-18 (Every 30 days)**
Live Coactive Lifestyle Coaching		X	X		

- 3-5 days per week, 45 mins each					
Async access to Lifestyle modification content curated by CT		X	X		
Informed Consent	X				
Eligibility Criteria Assessment	X				
Demographic Details	X				
EHR Access Consent	X				
Claims Data Access	X		X		X
QoLS (FACT-G Form)	X		X		X
Weight	X		X		X
Motivation to work	X	X			X
Employee Performance Review	X	X			X
Absenteeism Questions	X	X			X
Claim data validation with				X	X

survivor					
Cancer Progression Status				X	X

Schedule of events for active comparator (control) group:

Intervention or Assessment (Test)	**Baseline (Day -30 to -1)**	**Week 1/3/5/7/9/11/13/ 15/17/19/21/23/ ... /47**	**Week 2/4/6/8/10/12/14/ 16/18/20/22/24/ ... /48**	**Month 1-6 (Every 30 days)**	**Month 7-18 (Every 30 days)**
Async access to publically available lifestyle modification guidance		X	X		
Informed Consent	X				
Eligibility Criteria Assessment	X				
Demographic Details	X				
EHR Access Consent	X		X		X
Claims Data Access	X		X		X
QoLS (FACT-G Form)	X		X		X
Weight	X		X		X
Motivation to work	X	X			X
Employee Performance Review	X	X			X
Absenteeism Questions	X	X			X
Claim data validation with survivor				X	X
Cancer Progression Status				X	X

6.2 Rationale for Trial Intervention

Previous studies have shown that exercise at recommended levels can lead to 35-45%[5,6] recurrence reduction among cancer patients, and 40-50% cancer mortality reduction[5,6]. Patients report improvements in physical function, symptom management, and quality of life without significant adverse effects. Meditation has shown to reduce depression and increase in NK cells production[7]. However, less than 15%[3] of cancer patients practice clinically recommended regimen. We hypothesize that Live coactive instructions that are personalized will increase the adherence to exercise and related lifestyle modifications such as meditation & nutrition, and will enable the benefits outlined above.

6.3 Dosing and Administration

Details for Trial Intervention (Test Group):

- Timing of Intervention: Participants can log in at their convenience, with the flexibility to schedule exercise coaching sessions according to their preferences and availability.
- Intervention Structure: Over the course of 12-months or 48 weeks, each participant will participate in 3-5 weekly live sessions. Each session, spanning approximately 45 minutes, combines 30 minutes of targeted exercise with 7 minutes of meditation. Each session will be supervised live by a coactive coach for each participant. The program is strategically developed to progressively escalate in intensity:
    - Each session will consist of an optimal combination of Aerobic and Strength exercises.
    - Flexibility and Balance exercises will be included as supplemental exercises in the sessions.

<u>12 Months Program Structure</u>

Months 1 and 2

- Initially participants will be given 1:1 coaching to ensure that the participants get immediate feedback as well as modifications as needed.
- 10 workouts will be presented to the participants in Month 1 and 2. Each workout will be repeated 4 times, hence completing 40 days of workouts.
- The first 2 weeks will be “Light”: allowing the participants to complete the 10 workouts in flow while building confidence without pushing too hard or feeling too sore.
- The second 2 weeks will be “Light/Moderate”: allowing the participant to repeat the same 10 workouts, feel more confident in their ability to finish each workout because they are not brand new, but also experience a slight challenge on the body with the order in which the workouts are laid out.
- The third 2 weeks will be “Moderate”: the participants are expected to begin to feel stronger and more capable at this point which allows them to push a little harder and enjoy the challenge without burnout.
- The fourth 2 weeks will be “Moderate/Hard”: the participant by now should be experiencing what it’s like for the body to master the foundational goals above.

Month 3, 4, 5 and 6

- Next set of 10 workouts will be introduced in months 3 and 4, and likewise in months 5 and 6.

Month 6 to 12

- Based on their ability and progress, participants will be slowly graduated from 1:1 coactive sessions to Group-coactive sessions.

- Planned Route of Administration: The intervention will be administered remotely via the online platform, accessible through mobile devices.
- Specific Instructions: Participants will receive login credentials and instructions for accessing the software upon enrollment in the trial. They will be guided through the process of scheduling and participating in live exercise sessions, including how to navigate the platform and interact with their exercise coach.
- Delayed or Missed Intervention: Participants who miss scheduled exercise coaching sessions will have the opportunity to reschedule or make up missed sessions at a later time within the 12-month intervention period.
- Coaching Modifications: The coaching strategy includes personalized exercise recommendations tailored to each participant's unique needs and physical condition.
    - For instance, in cases of severe fatigue post-chemotherapy, coaches may adapt the program to include gentle activities like simple stretching followed by soothing meditation to ensure participant comfort and safety.
- Start and Stop Treatment: Participants are encouraged to engage consistently in the software app throughout the 12-month intervention period. However, they have the flexibility to start and stop treatment as needed, with the option to resume participation at their discretion.
- Dose Reductions: As this intervention does not involve pharmaceuticals, there are no dose reductions; however, adjustments to the frequency, intensity and approach of exercises may be made in response to participant feedback and progress (as suggested above with examples).

Details for Control Product:

- Timing of Intervention: Participants can log in to the app at their convenience to learn about exercise, diet and meditation guidelines.

- Duration: Participants will have access to the Active Comparator for the same 12-month period as the intervention arm.
- Planned Route of Administration: The Active Comparator will be administered remotely via the online platform, mirroring the administration method of the experimental intervention.
- Specific Instructions: Participants will receive login credentials and instructions for accessing the software upon enrollment in the trial.
- Delayed or Missed Doses: Participants in the control arm are free to manage how they like to use the app within the 12-month intervention period.
- Dose Modifications: N/A
- Start and Stop Treatment: Participants in the control arm have the same flexibility to start and stop treatment as those in the intervention arm, with the option to resume participation at their discretion.
- Dose Reductions: N/A

Trial Intervention Dose Modification

- For the intervention provided in this trial, the intervention involves personalized exercise coaching sessions tailored to each participant's needs and capabilities.
- The intensity and frequency of exercise sessions will be adjusted dynamically based on individual responses (such as RPE score), progress, and tolerance, as guided by the exercise coach. Therefore, there are no predefined criteria for dose modification or dose titration.

6.4 Treatment of Overdose

While overdose typically refers to the administration of excessive doses of pharmacological agents, in the case of a software solution, it pertains to the potential for participants to overexert themselves during exercise sessions, leading to adverse effects

such as muscle strains, joint injuries, fatigue, or exacerbation of underlying health conditions.

Given the nature of the trial intervention, there are no specific antidotes or therapies for trial intervention overdose. However, measures will be in place to prevent and manage potential adverse events associated with excessive exercise. These measures include:

- Individualized Exercise Prescription: The software app provides personalized exercise coaching tailored to each participant's fitness level, health status, and exercise tolerance through an intake form. Each patient is categorized into low or moderate based on the form. Exercise sessions will be designed to gradually progress in intensity and duration for each individual based on participants' responses and feedback.
- Monitoring and Supervision: Participants will be closely monitored during exercise sessions by trained exercise coaches who can provide real-time feedback and guidance. Coaches will ensure that participants adhere to safe exercise practices and modify activities as needed to prevent overexertion or injury. The survivor will be filling a RPE (Rating of Perceived Exertion) form after each session and will be given feedback based on the same.
- Participant Education: Participants will receive education and instruction on proper exercise techniques, warm-up and cool-down procedures, and signs of overexertion or injury. They will be encouraged to listen to their bodies and communicate any discomfort or concerns to their exercise coach.
- Flexibility and Adaptability: The solution app offers flexibility in scheduling and adapting exercise sessions to accommodate participants' individual preferences, capabilities, and constraints. Participants have the autonomy to adjust the intensity or duration of exercises based on their comfort level and feedback from the exercise coach.
- Prompt Recognition and Response: In the event of symptoms suggestive of overexertion or adverse effects during exercise sessions, participants will be

instructed to stop the activity immediately and seek appropriate medical attention if necessary. Coaches will be trained to recognize signs of overexertion and intervene promptly to ensure participant safety.

6.5 Preparation, Handling, Storage and Accountability

- **Preparation of Trial Intervention**
    - For both the trial intervention and control product, there are no specific preparation or administration procedures beyond accessing the online platform and following the instructions provided therein. These procedures are straightforward and do not require any specialized preparation or handling by trial personnel.
- **Accountability of Trial Intervention**
    - Distribution of Trial Intervention:
        - The trial intervention will be distributed to participants electronically. Upon enrollment in the trial, participants will receive login credentials and instructions for accessing the digital platform via email or through a secure online portal.
        - Distribution of the trial intervention will be managed by the study coordinators or research personnel responsible for participant enrollment and communication. They will ensure that participants receive the necessary information and support to access the digital platform and engage in exercise coaching sessions.
    - Expectations for Reconciliation:
        - Reconciliation of the trial intervention will involve tracking participant engagement and adherence to the software app through the online platform. Study coordinators or research personnel will monitor participant activity logs and session completion rates to ensure compliance with the trial protocol.
        - Any discrepancies or issues related to participant access or engagement with the digital platform will be documented and

addressed promptly to maintain data integrity and participant accountability.

6.6 Participant Recruitment, Randomization and Blinding

- **Participant Recruitment**
    - Participants will be recruited through a unified online advertisement campaign across platforms such as Facebook and Google. Interested individuals will click on the advertisement, which directs them to a screening form where they provide preliminary information relevant to the study eligibility criteria.
- **Randomization**
    - Screening and Eligibility Confirmation: Upon submission of the screening form, potential participants will undergo an initial eligibility assessment based on predefined inclusion and exclusion criteria.
    - Randomization Approach: Eligible participants will then be randomized into either the treatment or control group. This randomization is performed after the completion of the screening process and is based solely on the cancer type, ensuring an equal distribution of participants across different cancer categories within both groups.
    - Implementation Details: The randomization process will be conducted using a computer-generated random allocation sequence to ensure impartiality and minimize selection bias.
- **Blinding and Unblinding**
    - Efforts will be made to ensure that the trial intervention and control products are as indistinguishable as possible to maintain the integrity of blinding. This includes measures such as:
        - Standardization of software: Both the trial intervention and control software products will be delivered through the same app to minimize visual differences that could indicate the treatment assignment.

        - Blinding of personnel: Personnel involved in the administration, assessment, and monitoring of participants will be blinded to the treatment assignment whenever possible. This includes investigators, outcome assessors, data analysts, and other relevant staff.

6.7 Trial Intervention Compliance

Measures will be employed to ensure and document trial intervention compliance.

- Participant Engagement Metrics: The software platform will be equipped with tracking features to monitor participant engagement. Key metrics may include:
    - Frequency of logins and sessions attended.
    - Duration of each coaching session.
    - Participation in interactive features such as progress tracking and sharing exercise exertion feedback.
- Participant Surveys or Feedback: Program feedback for the intervention will be collected after each session.
- Attendance Records: For live Coactive coaching sessions, attendance records will be maintained to track participant involvement and compliance with scheduled sessions.
- System Logs: The software will generate system logs capturing user activity, such as login times, session durations, and interactions within the software. These logs serve as objective documentation of participant engagement.

Mandatory documents to complete include:

- Patient Reported Outcomes: These outcomes include all primary, secondary and exploratory metrics as highlighted above.
- Participant Engagement Logs: These logs will capture key metrics related to participant engagement and compliance with the software and coaching.
- Attendance Records: Specifically for live coaching sessions, attendance records will document participant attendance and participation.

Source data and records used to document trial intervention compliance will include:

- Digital Platform Data: System logs and engagement metrics generated by the software.
- Participant Surveys/Feedback: Responses collected from participant surveys or feedback forms.
- Attendance Records: Records of participant attendance at live coaching sessions.

6.8 Concomitant Therapy

Complement Theory is an adjunct treatment along with undergoing cancer treatment. Hence, the survivor continues the standard of care as is.

Section 7: DISCONTINUATION OF TRIAL INTERVENTION AND PARTICIPANT WITHDRAWAL FROM TRIAL

7.1 Discontinuation of Trial Intervention

Criteria for Permanent Discontinuation of Trial Intervention

- Participant Withdrawal: Participants may voluntarily withdraw from the trial intervention at any time for any reason. This may include personal preferences, intolerable side effects, or changes in health status that make continued participation undesirable.
- Adverse Events: Participants experiencing serious or intolerable adverse events related to the trial intervention may be discontinued from further participation in the intervention. Adverse events will be carefully monitored and managed.
- Disease Progression: If a participant experiences disease progression or other significant changes in health status that render the trial intervention ineffective or inappropriate, discontinuation from the intervention may be warranted. This may include worsening of cancer symptoms, disease recurrence, or development of new medical conditions impacting intervention efficacy.

- Non-Adherence: Participants who fail to adhere to the trial intervention protocol, including non-compliance with usage instructions for the Live coaching and software, will be discontinued from further participation in the intervention.
- Ineligibility: If a participant is found to be ineligible for continued participation in the trial intervention due to newly discovered medical conditions or other factors, discontinuation from the intervention may be necessary.

Participants who discontinue trial intervention may or may not be allowed to continue the trial, depending on the specific circumstances. In some cases, participants may continue to undergo follow-up assessments and data collection even if they discontinue the intervention. This allows for the evaluation of secondary outcomes, long-term effects, and safety monitoring following discontinuation of the intervention.

Temporary Discontinuation or Interruption of Trial Intervention

- Acute Medical Events: Temporary discontinuation may be warranted in the event of acute medical events such as hospitalization, surgery, or serious adverse reactions requiring immediate medical attention.
- Non-Urgent Medical Procedures: Temporary interruption may be necessary for non-urgent medical procedures that temporarily interfere with the participant's ability to engage with the trial intervention, such as elective surgery or diagnostic procedures.
- Serious Adverse Events: Temporary discontinuation may be indicated in the presence of serious adverse events related to the trial intervention, pending further evaluation and resolution of symptoms.
- Participant Preference: Temporary discontinuation may occur at the participant's request due to personal reasons, travel, or other temporary circumstances that interfere with intervention adherence.

During the period of temporary discontinuation or interruption of trial intervention, the following steps will be taken:

- Documentation: The reason for temporary discontinuation or interruption will be documented in the participant's trial documentation, including the date and duration of interruption.
- Participant Education: Participants will be informed of the temporary discontinuation or interruption and provided with guidance on when and how to resume the intervention, as well as any necessary precautions or restrictions.
- Continued Trial Participation: Participants may continue in the trial during the period of temporary discontinuation or interruption, depending on the nature of the event.
- Assessments: Depending on the nature and duration of the temporary discontinuation, certain trial assessments may continue as scheduled, while others may be temporarily suspended or deferred. Assessments relevant to safety monitoring or primary endpoints will be prioritized, while non-essential assessments may be postponed until the participant resumes the intervention.

Rechallenge

- Participants will be allowed to rejoin the trial if medically permitted.

7.2 Participant Withdrawal from the Trial

1. Voluntary Withdrawal: Participants have the right to withdraw from the trial at any time for any reason without facing any consequences.
2. Inability to Continue: Participants may withdraw if they become unable to continue participating in the trial due to medical reasons, such as worsening health status, or other personal circumstances.
3. Non-compliance: Participants may be withdrawn from the trial if they fail to adhere to the study protocol or follow the instructions provided by the research team.
4. Safety Concerns: Participants may be withdrawn from the trial if there are safety concerns identified during the course of the study, such as the development of

serious adverse events or medical conditions that may compromise their well-being.

7.3 Lost to Follow-Up

1. We will provide clear communication about the importance of follow-up visits with some incentives for participation and maintaining regular contact with participants through phone calls, emails or reminders.
2. Offer flexibility in scheduling
3. Follow up duration will be 4 weeks after a lack of response. We will re-attempt to contact the survivor after a brief 2 week pause after which we will no longer contact the survivor.

Section 8: TRIAL ASSESSMENTS AND PROCEDURES

This section outlines the comprehensive assessments and procedures deployed throughout the trial to ensure accurate, reliable data collection across all specified endpoints, emphasizing adherence to the trial's design and objectives.

Data Collection and Assessment Methods

- Claims Record: To accurately assess the financial impact of the intervention on healthcare expenditures, participants will be requested to provide Claims Records and Explanation of Benefits documentation. This comprehensive data set will encompass costs related to hospitalization, medication, lab visits, and other relevant medical expenses.
- Electronic Health Records (EHR): For a detailed and objective view of medical histories, participants will be asked to access their Electronic Health Records through platforms like MyChart. This step aims to enrich the claims data with additional medical record insights with information like days of hospitalization, disease for which treatment was undertaken, whether it was an Emergency visit or not and so on.
- Patient-Reported Outcomes: In a complementary approach to objective data collection, participants will also self-report on various aspects including healthcare

expenditures, quality of life (measured by FACT-G) and cancer progression status. Furthermore, they will report on absenteeism (detailing the number of leave days taken, including short-term or long-term disability status) and presenteeism (evaluated through work motivation and performance review scores). These self-reported metrics will be securely collected through a digital platform, aiming to supplement and validate the analysis of claims and EHR data.

Live Coaching Consistency

- Training Program for Live Coaches: To ensure uniform delivery of the intervention across participants, live coaches will undergo a standardized training program. This program will cover the intervention's core components, ethical guidelines, communication skills, and use of the digital platform for interaction with participants. Regular refresher sessions and assessments will maintain coaching quality and consistency.

Ensuring Data Integrity and Consistency

- Centralized Data Collection: Utilizing a centralized digital platform for self-reported data and integrating EHR information will ensure data consistency and facilitate real-time monitoring of trial progress.
- Standardized Assessments: All assessments, including all the self-reported metrics, will be conducted following standardized protocols. Instructions on the timing and conditions of assessments will be clearly communicated to participants, and specialized training will be provided to any personnel involved in data collection or analysis.
- Blinding Maintenance: While blinding participants to the intervention details is not feasible, measures will be in place to ensure that data analysts and the Trial Monitoring Committee members are blinded to group assignments to minimize bias in outcome assessment and safety monitoring.

8.1 Screening/Baseline Assessments and Procedures

1. Informed Consent Process:
    - We will obtain informed consent from participants, ensuring they understand the nature of the trial, potential risks and benefits, and their rights as participants.
2. Medical History and Physical Examination:
    - We will collect relevant medical history information, including past medical conditions, current medications, surgical history from the survivor.
3. Work-related Assessments:
    - We will conduct baseline assessment on pre-cancer work data - work hours, number of sick days taken; current status - if and since when they are on short term or long term disability from the survivor
4. Disease Assessment and Staging:
    - We will collect survivor reported disease assessments specific to the cancer types under study, such as tumor staging, biomarker evaluations, or imaging studies to assess baseline disease status and severity.
5. Stratification Variables:
    - See section 5.3 for Trial population variables and section 4.1 for Randomization variables.

8.2 Efficacy Assessments and Procedures

Improvement in Quality of Life (QoLS) as measured by FACT-G questionnaire (Trial Objective 1):

- Endpoint: Change in FACT-G scores measuring quality of life
- Assessment Procedures: Administer the above four questionnaires to assess participants' at baseline and specified time points during and after the intervention period.
- Data Collection: Obtain self-reported scores from participants on Quality of Life.

- Analysis: Calculate the mean difference in change in scores between the intervention and control groups at each time point to evaluate the impact of the intervention.

Reduction in Employee Absenteeism (Trial Objective 2):

- Endpoint: Number of leave days taken by employed cancer survivors due to health issues.
- Assessment Procedures: Track the number of leave days (sick leave, short-term disability, long-term disability) taken by participants in both groups throughout the trial period.
- Data Collection: Obtain leave records from participants' employers or self-reported information from participants.
- Analysis: Compare the average number of leave days between the intervention and control groups to assess the impact of the intervention on reducing absenteeism.

Improvement in Employee Presenteeism (Trial Objective 3):

- Endpoints: Motivation to work (self-reported scales/questionnaires), performance review scores (from employer records or self-reported evaluations).
- Assessment Procedures: Administer self-reported scales/questionnaires to assess participants' motivation to work and obtain performance review scores from employer records or self-reported evaluations.
- Data Collection: Collect self-reported data on motivation to work and obtain performance review scores from participants and their employers.
- Analysis: Compare the mean scores of motivation and performance reviews between the intervention and control groups to evaluate the impact of the intervention on enhancing presenteeism.

8.3 Safety Assessments and Procedures

- Responsibilities

    - The Trial Monitoring Committee will oversee safety assessments and procedures throughout the trial.
- Safety Data Collection
    - Safety data will be collected through self-reported participant interviews.
    - Standardized forms and procedures will be used for consistent data collection across study sites.
- Safety Reporting and Management
    - Procedures will be in place for the timely reporting and management of safety events, including serious adverse events (SAEs) and suspected unexpected serious adverse reactions (SUSARs).
- Safety Monitoring Committee
    - The Trial Monitoring Committee will review safety data periodically, assess participant safety, and provide recommendations to the study team.
- Participant Education and Counseling
    - Participants will receive education and counseling regarding potential safety risks associated with the intervention.
    - Open communication between participants and study staff will be encouraged to facilitate early detection and reporting of safety events.
- Risk Mitigation Strategies
    - Risk mitigation strategies will be implemented to minimize potential safety risks associated with the intervention, such as user training and device monitoring.
    - Adherence to safety protocols will be monitored, and interventions will be implemented to address deviations or non-compliance.
- Regulatory Compliance
    - Compliance with regulatory requirements governing safety reporting will be ensured, including adherence to Good Clinical Practice (GCP) guidelines and ICH regulations.

    - Accurate and comprehensive safety documentation will be maintained, including safety reports and investigator brochures.

8.4 Adverse Events and Serious Adverse Events

A serious adverse event (SAE) in this trial is defined according to the following severity grades:

- Grade 1: Mild discomfort, not interrupting normal activities
- Grade 2: Moderate discomfort, interrupts normal activities but not incapacitating
- Grade 3: Severe, resulting in disability or necessitating medical consultation (SAE)
- Grade 4: Requires hospitalization (SAE)
- Grade 5: Results in death (SAE)

Only events classified as Grade 3, 4, or 5 are considered SAEs within the context of this trial

- Time Period and Frequency for Collecting SAE Information
    - Time period
        - Start: Apr 15, 2024
        - End: Oct 15, 2025
    - Frequency
        - SAEs will be documented as they are reported by participants.
- Recording of SAEs
    - While prior studies suggest minimal evidence of SAEs resulting from exercise, diet, or meditation in cancer survivors, all SAEs encountered during this trial will be meticulously recorded. Participants can report SAEs directly via the app, or coaches may report on their behalf. Reports should include the severity grade, description of the event, and the participant's perspective on whether the SAE was related to trial interventions.
- Follow up of SAEs

    - All participants will continue receiving standard care from their healthcare providers. In the event of an SAE, a dedicated physician will be assigned to assess the situation, provide immediate recommendations, and categorize the cause of the SAE based on discussions with the participant. This classification will also be documented.
- Regulatory Reporting Requirements for SAEs
    - SAEs must be reported to the Institutional Review Board (IRB) within 24 hours of the event's identification. Additionally, the Sponsor will ensure prompt notification of all investigators regarding any SAEs, enabling them to inform participants about potential risks and take any necessary precautions.
- The grading of adverse events is aligned with the Common Toxicity Criteria for Adverse Events (CTCAE) standards, which detail adverse events on a scale from 1 to 5. The complete CTCAE documentation is available on the National Cancer Institute's website: NCI CTCAE Information.

Section 9: STATISTICAL CONSIDERATIONS

The analysis will be conducted on all participant data at the end of 3 months, 6 months, 12 months and 18 months (ie. end of the trial).

9.1 Analysis Sets

- The analysis will include the following datasets:
    - Intent-to-Treat (ITT) set: Including all randomized survivors, regardless of their adherence with the entry criteria. This set will be used for the primary analysis of Quality of Life changes and cancer progression.
    - Per-Protocol (PP) set: Including participants who completed the trial according to the protocol without significant deviations. PP set is a subset of ITT set, excluding survivors with major protocol deviations or those who do not complete the trial. This set will be used to summarize efficacy and support sensitivity analyses.

9.2 Analyses Supporting Primary Objective(s)

The primary analysis will focus on quantifying the impact of **Complement Theory on changes in Quality of Life Score (QoLS), measured by the FACT-G instrument**, over the trial period. Assessments will occur at baseline, 3, 6, 9, 12, and 18 months.

- **Statistical Model, Hypothesis, and Method of Analysis**
    - Primary Estimand (Change in QoLS):
        - Null Hypothesis (H0): There is no difference in the mean change in FACT-G QoLS between participants in the Complement Theory program and those in the control group at specified time points.
        - Alternative Hypothesis (H1): Participants in the Complement Theory program demonstrate a statistically significant improvement in QoLS compared to the control group.
    - Baseline Data Analysis: Baseline demographics and characteristics will be provided and summarized in both treatment and control groups. Standardized mean differences (SMDs) will be calculated as the measure of distance between groups. SMDs of 0.2 to <0.5, 0.5 to <0.8 and ≥0.8 are considered small, medium, and large, respectively. Frequencies and percentage will be provided for the binary variables as well as the categorical variables (Yes/No); mean (standard deviation) and median (range) will be computed for continuous variables.
    - Method of Analysis: Mixed models for repeated measures (MMRM) will be utilized to analyze changes in FACT-G scores over time, accounting for within-subject correlations. This model allows for the inclusion of both fixed effects and random effects to account for individual variability. In addition, covariate-time interaction terms will be included to guarantee the best results. The strength of the effect from each covariate will be evaluated

through the statistical test significance, i.e., P value, at 95% confidence interval.

- **Handling of Intercurrent Events of Primary Estimand(s)**
    - For participants who discontinue the intervention or are non-adherent, we will employ a treatment policy strategy. This means all data collected will be analyzed as per the initial treatment assignment, regardless of the discontinuation or level of adherence, preserving the intention-to-treat principle.
- **Handling of Missing Data**
    - Given the potential for missing QoLS data due to dropout or non-response, a multiple imputation (MI) approach will be adopted. The imputation model will incorporate variables predictive of missingness and outcomes to generate plausible values for missing data.
    - Multivariate imputation by chained equation (MICE) will be used, i.e., filling the missing data multiple times based on the effect from other covariates by constructing a multivariate regression model. MI is superior to single imputation, as it accounts for the uncertainty of missing values in a more robust way. The number of imputations will be 10, i.e., 10 datasets with imputed data will be created. Each imputed dataset gives a point estimate of the regression coefficients as well as its standard deviation, which will be combined across the 10 datasets to obtain the final estimate and their 95% CIs.
    - MICE is flexible and can accommodate variables of different types, as well as complexities such as bounded scales or survey skip patterns, making it well-suited for patient-reported outcomes like QoLS.
- **Sensitivity Analysis**
    - To complement our intention-to-treat (ITT) analysis, a per-protocol analysis will be performed, including only participants who fully adhered to the intervention, to explore the effect of adherence on QoLS improvement.

- **Supplementary Analysis**
    - Efficacy Analysis: survivors in the treatment and control group will be compared for the outcome variables. The comparison will be evaluated based on both SMD and P value. SMD greater than 0.2 will be considered as acceptable differences (section 3.3 indicated the definition of SMD). Descriptive statistics will be compared between treatment groups and control groups, and P values will be calculated using ANOVA tests comparing means of continuous variables, Brown-Mood test to compare the medians, and Chi-Square tests for binary and categorical variables. The differences will be considered as statistically significant within 95% confidence interval, i.e., P value less than 0.05.

9.3 Analysis Supporting Secondary Objective(s)

- **Secondary Objective 1: Effect on Employee Absenteeism**
    - Statistical Model and Hypothesis:
        - Model: Generalized linear models with a Poisson distribution to compare the number of leave days between groups.
        - Hypothesis: H0: No difference in the number of leave days between groups. H1: A significant reduction in leave days in the intervention group.
    - Handling of Intercurrent Events:
        - Analysis will consider any change in employment status as an intercurrent event, with a modified intention-to-treat analysis excluding participants who lose their job unrelated to health status.
    - Handling of Missing Data:
        - Worst-case scenario imputation for missing absenteeism data, assuming maximum observed absence for missing periods.
    - Sensitivity Analysis:

        - Repeating analyses with and without worst-case imputation to evaluate the impact of different missing data assumptions on the outcome.
- **Secondary Objective 2: Impact on Employee Presenteeism**
    - Statistical Model and Hypothesis:
        - Model: Mixed-effects models to analyze changes in work motivation and performance review scores over time.
        - Hypothesis: H0: No difference in changes in motivation and performance scores between groups. H1: Significant improvement in these measures in the intervention group.
    - Handling of Intercurrent Events:
        - Job changes or significant alterations in work responsibilities will be documented and explored in sensitivity analyses to understand their impact on presenteeism outcomes.
    - Handling of Missing Data:
        - LOCF for interim missing data points in motivation and performance scores, acknowledging potential limitations in this approach.
    - Sensitivity Analysis:
        - Analysis excluding participants with significant job changes during the trial to assess the effect of such changes on presenteeism outcomes.

9.4 Safety Analyses

- We shall continuously monitor and document all serious adverse events (SAEs), categorizing them by severity, causality, and timing relative to the intervention. This includes both anticipated events related to cancer and potential unexpected events related to the intervention.

- Comparative Analysis: Compare the incidence rates of SAEs between the intervention and control groups. This can help ascertain whether the intervention group experiences a higher rate of events, indicating potential safety concerns.
- The Trial Monitoring Committee shall regularly monitor these and can decide to forfeit the trials when there are clear indications that safety of the survivor is in danger due to our intervention
- Along with that we shall utilize QoL and well-being measures to indirectly assess safety, as significant declines could indicate adverse impacts of the intervention.

9.5 Other Analyses

- Futility Analysis: will be accessed to the inability of the clinical trial to achieve the primary and secondary objectives. In that case, both operational and statistical futility will be analyzed. Operational futility includes slow recruitment or slow accumulation of primary endpoints. Statistical futility includes, for the most part, group sequential methods and conditional power.

9.6 Interim Analyses

- Interim analyses are planned to evaluate the primary and secondary objectives' safety and efficacy data. These analyses may also explore data trends that could necessitate adjustments to the trial conduct.
- Statistical Methods:
    - The interim analyses will employ group sequential testing methods with an O’Brien-Fleming spending function to rigorously control the type I error rate across multiple looks at the data.
- Execution:
    - The analyses will be performed by an independent biostatistician from the trial investigators to maintain objectivity.
- Timing and Triggers
    - Scheduled Interim Analyses: Interim analyses are planned at 3 months, 6 months and 12 months of trial commencement.

    - Ad Hoc Requests: Additional interim analyses may be conducted at the request of the Trial Monitoring Committee, particularly if unexpected safety concerns arise.
- Decision Criteria and Oversight
    - Decision Criteria: The criteria for early stopping or trial adaptation include a pre-specified boundary for efficacy (significant improvement in Quality of Life Scores or improvement in health outcomes) or safety concerns (unacceptable adverse events rate).
    - The Trial Monitoring Committee will oversee the interim analyses, reviewing the results to make recommendations on continuing, stopping, or modifying the trial.
    - Blinding Integrity: Individuals analyzing the data may have access to unblinded data; however, measures will be taken to ensure that the trial team remains blinded to maintain the integrity of the trial implementation.
    - Authority to Stop or Modify: The ultimate authority to stop or modify the trial rests with the TMC, in consultation with the principal investigator and the sponsor, based on the interim findings and established stopping guidelines.

9.7 Sample Size Determination

- The metric-wise sample size calculation is provided in the table below on alpha as 0.05 and power of 80% for the one-tail test at enrollment ratio = 1.
- While we are conducting the power analysis and sample size calculation based on several variables (outcomes) of interest, the sample size was computed separately for each parameter in the study and the greatest is used to obtain sample size.
- The analysis (detailed below in table) showed that sample of size of 102 is powerful enough for the analysis to cover 100% of primary and secondary metrics.
- Now since we believe that the long follow-up duration of 6 months for our trial will lead to around 30% drop-offs, we decided a final sample size of 146 (73 control, 73 test).

- So even if get 30% or 44 participants drop off we end up with final sample set of 102 (51 control, 51 test) and would be able to come to statistically significant effects ($p < 0.05$) with respect to 100% of primary and secondary metrics.

Metric Segment	**Sub Metric**	**Control Data**	**Test Data**	**Assumed Variance**	**Sample Size**
Primary Outcome / Concerns					
Quality of Life Improvement	QoLS Score (FACT-G)	70	85	Variance of 20	42 (21 Control, 21 Test)
Secondary Outcome / Concerns					
Presenteeism	Attitude towards work	2	4	Variance of 1.5	16 (8 Control, 8 Test)
	Employee Performance	0.6	0.7	Variance of 20%	102 (51 Control, 51 Test)
Absenteeism	Working Hours	30	40	Variance of 10	28 (14 Control, 14 Test)
	Vacation Days	0.5	0.3	Variance of 0.15	16 (8 Control, 8 Test)
Exploratory Outcomes					
Cancer Care	Cancer Progression Status	0.85	0.88	Variance of 0.04	46 (23 Control, 23 Test)

	Cancer recurrence status	0.3	0.21	Variance of 10%	32 (16 Control, 16 Test)
Medical Expenditure	Total Healthcare Expenditure (Planned + Unplanned)	10000	8000	Variance of 4000	102 (51 Control, 51 Test)
	No of Urgent Care Visits	3	2.5	Variance of 0.5	28 (14 Control, 14 Test)
	No of ED Visits	5	3.45	Variance of 0.8	10 (5 Control, 5 Test)
	No of unplanned outpatient/office visits (other than ED)	4.28	3.5	Variance of 0.8	28 (14 Control, 14 Test)
	Unplanned Hospitalisations	5	4	Variance of 0.8	18 (9 Control, 9 Test)
	Length of hospital stay	3	2	Variance of 0.8	18 (9 Control, 9 Test)
	No of planned outpatient visits	2	1.8	Variance of 0.3	58 (29 Control, 29 Test)
	No of planned hospital visits	1.25	1	Variance of 0.1	10 (5 Control, 5 Test)
	Length of hospital stay	3	2	Variance of 0.8	18 (9 Control, 9 Test)

	Total Prescription Medicine Expenditure	1000	950	Variance of 80	80 (40 Control, 40 Test)

9.9 Protocol Deviations

Protocol deviation begins as soon as the survivor signs the informed consent. Deviations are defined as a departure from approved protocol schedule of events or procedures with or without IRB approval. Protocol deviations will be classified as major or minor dependent per the identifications below.

Major: A major protocol deviation is one that will have a substantive effect on the safety, rights, or well being of subjects, data integrity, or the quality of the intervention product (CT technology).

Minor: A minor protocol deviation is a deviation that does not have a substantive effect on the safety, rights, or well being of subjects, data integrity, or the quality of the intervention product (CT technology).

Below are examples of how each protocol deviation will be coded and classified:

Category	**Description**	**Major/Minor**
Eligibility Criteria	Inclusion or exclusion not met	Major
Informed Consent	Performing study related material prior to obtaining written informed consent	Major
Withdrawal or Termination	Any situation where the study treatment discontinuation criteria are met but the subject is not discontinued from the study and continues to participate	Major

Serious Adverse Event Reporting	Failure to report serious adverse events (SAEs) within 24 hours of awareness	Major
Missed Visits	Failure to attend all 5 sessions in a 7 day period of time	Minor
Out of Window Visits	Make up sessions with live instructor are not rescheduled within a 2 week timeframe	Minor

Every major or minor deviation would be carefully monitored and registered in our database. It will be used on a regular basis, starting with FPI, by the Trial Monitoring Committee (TMC) to review the protocol deviations for that reporting period.

The TMC will identify issues trending on the study. Trends that are deemed critical by the TMC will be evaluated for safety concerns.

Section 10: GENERAL CONSIDERATIONS: REGULATORY, ETHICAL, AND TRIAL OVERSIGHT

10.1 Regulatory and Ethical Considerations

This trial 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 Organisations of Medical Sciences (CIOMS) International Ethical Guidelines
- ICH Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

Investigators' Responsibilities:

- Ensuring that the trial is conducted in accordance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines, and applicable regulatory requirements.
- Obtaining informed consent from all participants prior to their participation in the trial.
- Reporting all serious adverse events (SAEs) to the sponsor promptly and accurately.
- Ensuring the accuracy and completeness of all data collected during the trial.
- Complying with regulatory requirements for the conduct of clinical trials in their jurisdiction.
- Maintaining the confidentiality of participants' data and protecting their rights and well-being throughout the trial.

Sponsor's Responsibilities:

- Designing the trial protocol and ensuring it is scientifically sound and ethically appropriate.
- Obtaining regulatory approval to conduct the trial and ensuring ongoing compliance with regulatory requirements.
- Providing the necessary investigational product and ensuring its quality and supply throughout the trial.
- Monitoring the conduct of the trial to ensure compliance with the protocol, GCP guidelines, and regulatory requirements.
- Collecting, analyzing, and reporting trial data to regulatory authorities and other relevant stakeholders.
- Ensuring that all investigators are adequately trained and informed about their roles and responsibilities.
- Ensuring that appropriate insurance coverage is in place to protect participants and investigators.

- Addressing any safety concerns or protocol deviations promptly and appropriately.
- Ensuring that the trial is conducted in accordance with ethical principles and that participants' rights and well-being are protected.
- Providing financial support for the conduct of the trial, including funding for investigator fees, site costs, and other expenses.

10.2 Committees

The trial will establish an Trial Monitoring Committee (TMC) to oversee the safety and integrity of the trial. The TMC will consist of independent experts in relevant fields such as oncology, biostatistics, and cancer exercise specialists. Their primary role will be to review safety data at regular intervals during the trial to ensure participant safety.

Trial Monitoring Committee will perform safety assessments every 6 months. But they will meet more often if needed such as in case of increase in AEs. The Trial Monitoring Committee will be responsible for making a determination of continuing the study based upon results of the safety assessment.

10.3 Informed Consent Process

The informed consent process will include the following key elements:

- Explanation of the trial: Participants will be provided with detailed information about the purpose, procedures, risks, and potential benefits of the trial.
- Voluntary participation: Participants will be informed that their participation in the trial is entirely voluntary, and they have the right to withdraw at any time without penalty.
- Understanding: The information provided will be presented in a clear and understandable manner, ensuring that participants comprehend the nature of the trial and its implications for their health.

- Confidentiality: Participants will be assured that their personal information will be kept confidential to the extent allowed by law.
- Opportunity for questions: Participants will be given the opportunity to ask questions and seek clarification about any aspect of the trial before providing consent.

Rescreening:

- Participants can be rescreened. Refer section 5.6 for the details.
- Participants who undergo rescreening will not typically be required to complete a new informed consent process if their initial consent remains valid. However, this will be clearly stated in the protocol, and any specific circumstances requiring a new consent will be outlined.

10.4 Data Protection

- Confidentiality Measures: Personal data will be anonymized or pseudonymized whenever possible to protect participant identity. Only authorized personnel will have access to identifiable information, and strict confidentiality protocols will be followed.
- Secure Data Storage: Participant data will be stored securely in electronic databases with restricted access. The databases will be encrypted and password-protected to prevent unauthorized access.
- Limited Access: Only authorized personnel involved in the conduct of the trial will have access to participant data. Access will be granted based on predefined roles and responsibilities, and access logs will be maintained to track data access.
- Data Transfer: When transferring data between sites or to third-party vendors, encryption and secure file transfer protocols will be used to minimize the risk of interception or unauthorized access.
- Training and Awareness: All personnel handling participant data will receive training on data protection policies and procedures. Regular awareness campaigns will be conducted to reinforce the importance of data security.

In the event of a data security breach, the following steps will be taken:

- Immediate Response: Upon discovery of a breach, the responsible personnel will take immediate action to contain the breach and mitigate any potential harm.
- Notification: Relevant stakeholders, including participants, regulatory authorities, and ethics committees, will be promptly notified of the breach in accordance with applicable regulations and guidelines.
- Investigation: A thorough investigation will be conducted to determine the cause and extent of the breach. This may involve forensic analysis of systems and data logs.
- Remediation: Measures will be implemented to address the vulnerabilities that led to the breach, such as software patches, system updates, or changes to procedures.
- Documentation: A detailed report of the breach, including the cause, impact, and remedial actions taken, will be documented for regulatory compliance and future reference.

10.5 Trial Termination

Decision Rights of Sponsor or Designee to Terminate the Trial:

- The sponsor or designee may also terminate the trial if there are safety concerns, lack of efficacy, or other unforeseen circumstances that jeopardize the integrity of the trial or the safety of participants.
- The sponsor holds the decision-making power to suspend or terminate the trial based on recommendations from the Trial Monitoring Committee, IRB and PI.

Section 11: GENERAL CONSIDERATIONS: RISK MANAGEMENT AND QUALITY ASSURANCE

11.1 Quality Tolerance Limits

The purpose of this section is to identify what will trigger internal quality assurance (QA) processes to ensure continuous improvement. The Trial Monitoring Committee will provide the oversight to review the following parameters in the table. The parameter thresholds will be evaluated on a monthly basis. When these thresholds have crossed, the primary QA process employed by the committee will conduct a Root Cause Analysis (RCA). These are the following steps:

1. Collect relevant data
2. Identifying the root causes
3. Find corrective solution
4. Update protocol
5. Implement changes with appropriate change management with relevant stakeholders
6. Monitor if the corrective solution works.

Critical to Quality Factor	**Parameter**	**Definition**	**Justification for Parameter**	**Parameter Threshold**
Safety reporting	Percentage or number of immediately reportable events reported late	Percentage or number of immediately reportable events (e.g., SAEs and other events as defined in the protocol) that are reported more than 1 day after awareness of the event	A high number of late reported, immediately reportable events could impact participant safety due to lack of timely awareness of emerging safety profile	5%

Eligibility criteria	Percentage or number of participants randomized who do not meet inclusion/exclusion criteria	Percentage or number of randomized participants with Protocol Deviations in inclusion/exclusion criteria	A high number of study participants not meeting the entrance criteria could have a significant impact on interpretation of the primary endpoint and overall validity of the trial results.	5%
Intervention handling and administration	Percentage or number of participants with premature discontinuation	Percentage or number of participants who discontinued treatment before the end of the treatment period as defined by protocol	A high number of participants discontinuing treatment could have a significant impact on interpretation of the primary endpoint.	5%
Withdrawal criteria and trial participant retention	Percentage or number of participants with withdrawal of informed consent	Percentage or number of participants with withdrawal of informed consent after treatment allocation	A high number of participants withdrawing informed consent may indicate excessive survivor burden and could significantly impact collection and interpretation of the	5%

			primary endpoint.	
Withdrawal criteria and trial participant retention	Percentage or number of lost to follow-up participants	Percentage or number of participants who are lost to follow-up (i.e., have not continued in the trial until the last planned safety assessment and have not revoked consent nor have been reached by investigator site personnel through normal communication methods). These participants have not completed the trial and their status is unknown	A high number of participants lost to follow-up may indicate excessive participant burden and could impact the collection and interpretation of long-term safety and efficacy data.	10%
Procedures supporting study endpoints and data integrity	Percentage or number of study participants for whom study endpoint data was not collected	Percentage or number of study participants for whom study endpoint data was not collected; this could include	A high number of study participants for whom the failure to collect study endpoint data could impact analysis and interpretation of	15%

		inability to perform study procedure at the protocol-defined time point	study results	
Procedures supporting trial endpoints and data integrity	Percentage or number of participants with "Major" protocol deviations other than eligibility	Percentage or number of participants with protocol deviations during the trial which are not related to protocol inclusion/exclusion criteria (i.e., informed consent, trial intervention, prohibited concomitant medication, trial procedures, safety reporting, and discontinuation)	A high number of study participants with important protocol deviations during the trial could have a significant impact on interpretation of the primary endpoint and overall validity of the trial results. It can also impact participant safety	10%
Procedures supporting trial endpoints and data integrity	Percentage of participants censored in the statistical analysis because they had no bills the	Percentage or number of participants who are at risk of censoring for hospital costs	High number of participants censored for primary objective analysis would translate into smaller than assumed sample	10%

	entire time		size and may impact the interpretation of the efficacy results. Alternatively, final primary objective analysis would be delayed if required sample maturity is not reached within the assumed timelines	
Randomization	Percentage or number of randomized participants who were incorrectly stratified	Percentage or number of randomized participants who were incorrectly stratified	High number of participants who were incorrectly stratified may lead to imbalances in baseline characteristics between treatment arms, introduce biases in the data, and significantly affect the outcome of a trial	10%

11.2 Data Quality Assurance

1. Electronic Data Capture:
    - Since the trial is virtual with survivors located anywhere in the United States, and the intervention is delivered through a in-house custom

HIPAA-compliant software product, we will have a custom form system directly in the same software for survivors to enter self reported data.

2. All Data stored is in AWS with appropriate data redundancy rules in place.
3. Data Validation: Data entered goes through testing (e.g. outliers, missing rows, etc) before being entered into the database.
4. Electronic Health Records and Claims Records: All medical data and billing data will be shared by survivors using their electronic access to their data i.e. medical records, claims data, and prescription drug costs.
    - A clear PDF with instructions and screenshots will be shared for survivors to do this easily.
    - We will recommend survivors give us access for a minimum of 6 months and a maximum of 18 months to minimize streamline survivor workload.

References

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