Protocol Title:

Testing scalable, IVR-supported cancer prevention interventions in the rural Alabama Black Belt

Study Protocol & Statistical Analysis Plan

NCT03903874

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Testing scalable, IVR-supported cancer prevention interventions in the rural Alabama Black Belt

Principal Investigator: Dori Pekmezi, PhD

Sponsor: NCI

National Clinical Trial (NCT) Identified Number: 03903874

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Table of Contents

STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and applicable United States (US) Code of Federal Regulations (CFR). The Principal Investigator will assure that no deviation from, or changes to, the protocol will take place without prior documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial subjects. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the local Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from subjects who provided consent, using a previously approved consent form.

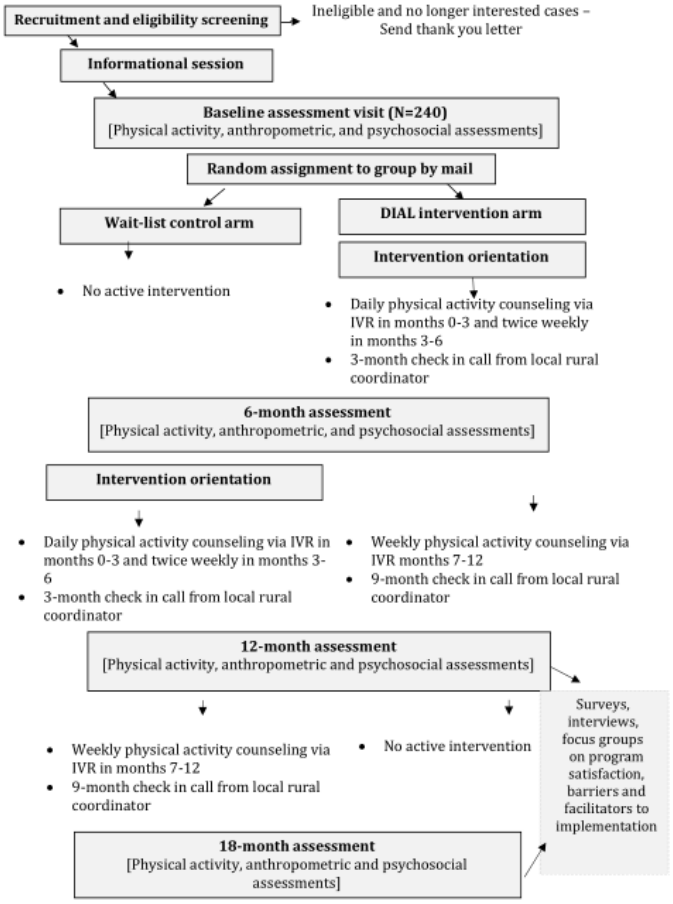
1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Testing scalable, IVR-supported cancer prevention interventions in the rural Alabama Black Belt
Study Description:	This protocol involves a randomized controlled trial (N=240) to test the efficacy of the Deep south Active Lifestyle (DIAL intervention) telephone-based physical activity counseling intervention vs. a wait list condition. Assessments of MVPA and psychosocial variables will occur at baseline, 6, 12, and 18 months. Primary aim. Test the efficacy of DIAL intervention vs. wait list control. Hypotheses are that the participants receiving DIAL intervention will report significantly greater increases in MVPA (based on 7-Day Physical Activity Recalls, accelerometers) from baseline to 6 and 12 months than the wait list control arm. Exploratory Aims. Examine 1) Intervention effects on physical performance and psychosocial variables (anxiety, depression, fatigue, sleep disturbance; corroborate self report sleep improvements from pilot with accelerometry); 2) Changes in MVPA from 12-18 months to assess long term (6 months post-intervention) maintenance in the intervention arm and ascertain replicability of intervention effects in wait list control arm; 3) Intervention costs; 4) Potential mediators (social support from family, friends, CHAs, theoretical constructs directly targeted by the intervention) and moderators (education, neighborhood/environmental features) of treatment efficacy; 5) Potential barriers/ facilitators to widespread implementation of DIAL intervention in rural Black belt counties by Deep South Network for Cancer Control.

Objectives:	This proposal tests an intervention which acts on multiple levels of the socio-ecological model and uses IVR technology to enhance the potential for scaling and sustainability for broad use in populations at high risk for sedentary behavior (residents of rural Black counties in the Deep South).
Endpoints:	Changes in physical activity (as measured by 7-Day Physical Activity Recall interview) over time.
Study Population:	Adults
Phase:	2/3
Description of Study Intervention:	Deep south Interactive voice response system Active Lifestyle (DIAL) intervention. Participants will receive 12 months of automated physical activity phone counseling. Participants will report their physical activity to the IVR system each day for 3 months, twice/week in months 3-6, and once/week in months 6-12 and receive progress feedback via IVR system, along with community health worker support.
Study Duration:	5 year project period
Subject Duration:	18 months

1.2 SCHEDULE OF ACTIVITIES (SOA)



2 INTRODUCTION

2.1 STUDY RATIONALE

The rates of physical inactivity and related cancer incidence and mortality are disproportionately high in the Deep South region in the United States, a rural, medically underserved region with a large African American population compared with the rest of the nation. Given this region's lower rates of literacy and internet access, interactive voice response (IVR) system–automated telephone-based interventions have the potential to help overcome physical activity intervention barriers (literacy, internet access, costs, and transportation) but have yet to be extended to rural, underserved populations, such as in the Deep South.

2.2 BACKGROUND

Our research team developed a tailored, IVR-supported physical activity intervention for cancer risk reduction in the Deep South. The development of the Deep South Interactive Voice Response System–Supported Active Lifestyle (DIAL) intervention was guided by extensive formative research (11 focus groups with African American community health advisors and community members) on physical activity intervention preferences and barriers in our target population. Results from the subsequent pilot randomized controlled trial with 63 participants supported the feasibility and acceptability of the DIAL intervention. Pilot trial findings and participant feedback guided intervention refinement (providing more accountability and encouragement) in preparation for scale-up.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

The risks associated with the proposed study are minimal since a physical activity generally promotes good health, especially in a sample of healthy adults. Participants may find moderate intensity physical activity uncomfortable and may experience sprains, other soft tissue injuries, or bone injuries. However, risks associated with moderate intensity physical activity at Centers for Disease Control/American College of Sports Medicine recommended levels are rare. Due to the low level of risk, CDC/ACSM have recommended moderate intensity physical activity for adults with no prior history of cardiovascular risk or orthopedic impediments. Risk minimization protocol is derived from the American College of Sports Medicine's Guidelines for Exercise Testing and Prescription. Prior to enrollment, participants will be screened for cardiovascular risk factors and orthopedic problems affecting ability to safely perform moderate intensity physical activity. We will use an ACSM recommended screening instrument: Physical Activity Readiness Questionnaire (PAR-Q). The PAR-Q asks about cardiovascular and orthopedic risk factors for adverse events from moderate intensity physical activity.

After enrollment, participants will be provided with an exercise prescription that emphasizes safety with the following features: 1) training in assessing moderate intensity activity using a number of strategies (e.g., Rating of Perceived Exertion [RPE], target heart rate monitoring), 2) instructions to perform activity in the moderate range of exertion (i.e., 64% to 76% of maximal heart rate, 3) gradual increases in activity from week to week (i.e., 20% per week) until reaching the CDC/ACSM guidelines, 4) warm-up and cool-down as part of each activity, and 5) flexibility training after activity. These instructions will be provided as part of intervention orientation and each participant will also be provided with related written materials. Moreover, in each IVR call,

participants will be asked whether they have experienced any physical symptoms or complaints that could interfere with their physical activity program. If they respond 'yes' to this question, they are told to stop exercising and contact their personal physician to discuss the health issues further. The research staff will run weekly reports on reported health events and will follow up with a telephone call to the participant and discontinue physical activity intervention until physician clearance is provided. All health occurrences will be recorded and regularly reviewed by the study team and the UAB Institutional Review Board Office.

It is possible that specific survey items could be perceived as embarrassing or an invasion of privacy; thus, participants will be informed that they can refuse to answer any questions without penalty. Another unlikely risk is that, while the intervention is provided free of charge, participants may incur costs associated with the intervention (IVR calls) if using a cell phone with limited minutes plan. Participants will be cautioned against this risk by staff at the study information session and intervention orientation and staff will help participants with limited minutes problem solve how to conduct IVR calls without incurring costs (i.e., use landline) on a case-by-case basis.

2.3.2 KNOWN POTENTIAL BENEFITS

Regular physical activity is a key modifiable risk factor for several cancers (breast, colon).16 Since underserved (rural, African American) populations, particularly in the Deep South, report high rates of inactivity and are disproportionately affected by such cancers, they have even a higher likelihood of benefiting from receiving such physical activity interventions. However, no promise of a direct benefit will be made to the participants. Results from this study may be beneficial to future participants.

3 STUDY DESIGN

3.1 OVERALL DESIGN

The current study will test the efficacy of a 12-month multi-level, Interactive Voice Response system-supported physical activity intervention vs. a waitlist control condition. Primary endpoints are changes in moderate intensity or greater aerobic physical activity from baseline to 6 months and 12 months. Secondary endpoints include examining effects on physical performance and related psychosocial variables; intervention costs, changes in physical activity from 12-18 months, potential mediators/moderators of intervention efficacy, and barriers and facilitators to the implementation and sustainability of the DIAL intervention. This two armed randomized controlled trial will enroll a sample of 240 underactive adults from rural Black Belt (Marengo, Choctaw, Sumter, Hale, Greene, Dallas) counties in Alabama. Interested individuals will attend study information sessions hosted by local county coordinators to learn more about the study and complete brief screening interviews.

If still eligible and interested, participants will complete the informed consent process and be scheduled for an assessment visit. At this visit, participants will complete measurements (height, weight, waist circumference, 2 Minute Step Test, psychosocial surveys in REDCap) at a community location with their local county coordinator. Accelerometers will be distributed with instructions and a live demonstration of proper wear. Trained UAB staff will coordinate accelerometer data collection (device initialization, delivery, maintenance, etc). Participants will wear the accelerometer for 7 days. Once valid wear protocol is confirmed, participants will complete 7-Day Physical Activity Recall interviews by phone with trained, blinded UAB research

staff. After all assessment measures are complete, participants will be randomly assigned to a group. Intervention participants will receive orientation to the IVR system and begin the physical activity intervention and the Waitlist Control participants will be encouraged to maintain their normal routine until 6 month assessments. At 6-, 12-, and 18- months, participants will repeat accelerometer wear protocols, 7-Day Physical Activity Recall interviews (by phone), and in-person assessment visits (weight, waist circumference, 2 Minute Step Test, psychosocial surveys) with local staff. Psychosocial surveys will also be distributed at 3-months to a assess potential mediators/ moderators of treatment efficacy. Participants will also complete surveys and exit interviews to assess program satisfaction and solicit feedback for improvement (at 12 months for the intervention arm and 18 months for the waitlist control arm). The wait-control group will be offered the 12 month DIAL intervention (same as intervention arm) after the 6 month assessment.

Throughout the project period, UAB research staff and Office of Community Outreach and Engagement county coordinators will report study progress via weekly emails and Zoom meetings. Surveys and in-depth qualitative interviews with participating Office of Community Outreach and Engagement county coordinators will be held to reflect on barriers and facilitators to implementing IVR-supported cancer prevention interventions in rural Black Belt counties, as well as issues surrounding sustainability and future large scale dissemination.

3.2 END OF STUDY DEFINITION

2024-11-26 (Final data collection date for primary outcome measure)

4 STUDY POPULATION

4.1 INCLUSION CRITERIA

Eligibility criteria include adults who are >18 years old, insufficiently active (engaging in moderate-vigorous physical activity< 60 minutes per week), residents of participating rural Black Belt (Marengo, Choctaw, Sumter, Hale, Greene, Dallas) counties, BMI 18.5-45, no serious medical condition that would make physical activity unsafe (history of heart disease, myocardial infarction, angina, stroke, or orthopedic conditions which limit mobility), not planning to move from the area within the next 18 months, able to speak and read English, willing to be randomized to either study arm and adhere to study protocol, and able to regularly access a telephone (own a cell phone or work/home landline) to complete IVR calls.

4.2 EXCLUSION CRITERIA

Items from the Physical Activity Readiness Questionnaire (PAR-Q) on cardiovascular/ musculoskeletal risk factors will be included in this screening, as recommended by the American College of Sports Medicine for moderate intensity physical activity.81,82 Endorsing an item on the PAR-Q will be grounds for ineligibility.

4.3 SCREEN FAILURES

Ineligible respondents will be thanked for their time and given exclusion reasons. Reasons for ineligibility/disinterest will be tracked for CONSORT diagrams.

4.4 STRATEGIES FOR RECRUITMENT AND RETENTION

Recruitment will take place in rural Black Belt AL counties and be led by Claudia Hardy, Community Health Educator, and her team at the Office of Community Outreach and Engagement in the UAB Comprehensive Cancer Center, including county coordinators. Study staff will distribute study flyers, and host study information sessions via Zoom or in local community meeting spaces as feasible (e.g., county health departments, church fellowship halls, etc) in which individuals will receive a study description and be screened for eligibility. We will also consider strategically placed local newspaper and radio advertisements to promote awareness of the study. All recruitment materials will state that transportation and childcare expenses for assessment visits will be covered, as these strategies increased minority participation in our past studies .Moreover, assessments will be completed by local county coordinators (trusted individuals in the community) in convenient community locations.

Retention efforts will include appointment reminders, flexible scheduling,honoraria/nonmonetary incentives, and holiday cards. In the case of 2 or more missed IVR intervention calls, staff will contact the participant to determine the reason why and retrieve missing data. If unable to reach by telephone, a letter will be sent. Moreover, to maintain engagement in the wait list control condition, these participants will be involved in monthly virtual events on cancer topics other than physical activity (e.g., screening) during the wait period.

5 STUDY INTERVENTION

5.1 STUDY INTERVENTION(S) ADMINISTRATION

5.1.1 STUDY INTERVENTION DESCRIPTION

The 12-month multi-level DIAL intervention is based in social ecological model and emphasizes individual, interpersonal, community/ organizational, and policy approaches to increasing PA. Individual and interpersonal strategies are grounded in Social Cognitive Theory (SCT). Participants will report PA and key SCT constructs (self-efficacy, social support, outcome expectations, enjoyment) and receive tailored counseling via IVR. Interpersonal and community/organizational strategies will include support from local coordinators (problem solving barriers, leading walking groups) and monthly newsletters.

5.1.2 DOSING AND ADMINISTRATION

*P*articipants will complete IVR calls each day for 3 months, twice/week in months 4-6, and once/week in months 7-12.

5.2 MEASURES TO MINIMIZE BIAS: RANDOMIZATION

Dr. Oster (biostatistician) will prepare a closed envelope blocked randomization for the two treatment arms stratified by county and BMI group (BMI<30 and BMI>30, as this variable is known to be related to activity levels) using Proc Plan in SAS® Ver. 9.4.

5.3 STUDY INTERVENTION COMPLIANCE

A treatment fidelity plan based on the NIH's Behavioral Change Consortium framework will involve scripted treatment manuals, audio-recording of participant encounters, etc. Research staff will perform weekly IVR system audits to ensure that the IVR system is functioning properly; monitor the help line daily, which will be used by participants to report problems with DIAL system; and manually inspect feedback letters for accuracy before mailing to participants.

5.4 CONCOMITANT THERAPY

n/a

6 STUDY INTERVENTION DISCONTINUATION AND SUBJECT DISCONTINUATION/WITHDRAWAL

6.1 DISCONTINUATION OF STUDY INTERVENTION

n/a

6.2 SUBJECT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Subjects are free to withdraw from participation in the study at any time upon request.
An investigator may discontinue or withdraw a subject from the study for the following reasons:

- Significant study intervention non-compliance
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the subject

Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

6.3 LOST TO FOLLOW-UP

A subject will be considered lost to follow-up if he or she fails to return for 2 scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a subject fails to be available for a required study visit:

- The site will attempt to contact the subject and reschedule the missed visit and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain if the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's study file.
- Should the subject continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

7 STUDY ASSESSMENTS AND PROCEDURES

7.1 STUDY ASSESSMENTS

The main outcome is minutes per week of moderate- to vigorous-intensity physical activity. The 7-day PAR interview is administered by trained research staff, who will contact participants by telephone and ask about the amount, intensity, and types of physical activities over the past 7 days.

ActiGraph GT3X accelerometers are worn continuously for 7 days during waking (on the nondominant hip) and sleeping (on the nondominant wrist) hours at baseline and at 6, 12, and 18 months. This device measures movement, intensity of physical activity, and sleep efficiency, latency, and number of awakenings.

The secondary outcomes include physical performance and anthropometrics. Physical performance is assessed with the Two Minute Step Test, in which participants step in place as fast as possible for 2 minutes while lifting the knees to a premeasured height midway between the upper tips of their patella and iliac crest when standing. A score is calculated based on the number of times the right knee meets the marked height, which can be used to estimate the current level of physical function and predict future physical independence. Anthropometric measurements include height, weight, and waist circumference. Height will be measured without shoes and with a portable stadiometer (Seca 213). Weight will be measured without shoes and in light clothing with a digital scale (Healthometer, model no: 349KLX) that is zeroed before each measurement. Waist circumference will be measured with a Gulick II tension-controlled tape measure (County Technology, Gary Mills). The tape is positioned around the natural waist, just above the iliac crest. The measurement is recorded to the nearest 0.1 cm upon exhalation.

Psychosocial factors will also be assessed at baseline and at 6, 12, and 18 months using Patient-Reported Outcome Measurement Information System scales for anxiety, depression, fatigue, and sleep disturbance with previously demonstrated validity and reliability.

Social Cognitive Theory measures will be assessed in person at the 4 assessment visits and by mail at 3 months (for mediation analyses). The measures include the 10-item self-regulation scale (α=.78), 13-item social support for exercise scale (α=.61-.9), 9-item outcome expectations scale (α=.89), 18-item physical activity enjoyment scale with high internal consistency and test-retest reliability, 10-item walking self-efficacy scale (α=.82), and the 12-item exercise confidence scale (α=.92).

Secondary measures at baseline, 6 months, and 12 months were included in the cost-effectiveness analyses. We will use a health care utilization survey that captures information on physician and emergency room visits and hospitalizations; the EuroQol-5 Dimension, which estimates utility weights to estimate quality-adjusted life years (QALYs); and a set of questions to measure time spent and expenses related to participation and time devoted to physical activity.

An 18-item measure adapted from similar past studies will assess participant satisfaction with the DIAL intervention and request suggestions for program improvement at 12 and 18 months. Finally, a similar survey will be administered at 18 months to the rural county coordinators to

examine stakeholders' perspectives on acceptability, barriers to and facilitators of implementation, and sustainability of the DIAL intervention in the Deep South.

The research staff will complete the three components of the Rural Active Living Assessment (RALA) for each county at baseline. This assessment consists of the street segment assessment to evaluate factors such as walkability, safety features, and terrain of individual, specific street segments; the town-wide assessment that examines community characteristics such as population, total area, and the presence of recreation activities; and finally, the program and policy assessment, which identifies community programs and policies that support physical activity.

7.2 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

7.2.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

7.2.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse event (of note, the term "life-threatening" refers to an event in which the subject was at risk of death at the time of the event, rather than to an event which hypothetically might have caused death if it were more severe)
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- or a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

7.2.3 CLASSIFICATION OF AN ADVERSE EVENT

7.2.3.1 SEVERITY OF EVENT

For adverse events (AEs), the following guidelines will be used to describe severity:

- **Mild** – Events require minimal or no treatment and do not interfere with the subject's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a subject's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious."

7.2.3.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the subject based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Related** – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
- **Not Related** – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

7.2.3.3 EXPECTEDNESS

The Principal Investigator will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

7.2.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study subject presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the subject is screened will be considered as baseline and not reported as an AE. However, if the study subject's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The Study Coordinator will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the Study Coordinator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

7.2.5 ADVERSE AND SERIOUS ADVERSE EVENT REPORTING

All serious adverse events must be reported to the IRB according to regulatory requirements. The Principal Investigator will immediately report to the sponsor any serious adverse event, whether or not considered study intervention related, including those listed in the protocol or package insert and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the study intervention and the event. In that case, the investigator must immediately report the event to the sponsor.

All serious adverse events (SAEs) will be followed until satisfactory resolution or until the Principal Investigator deems the event to be chronic or the subject is stable. Other supporting documentation of the event may be requested and should be provided as soon as possible.

7.3 UNANTICIPATED PROBLEMS

7.3.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to subjects or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

7.3.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB within 10 working days of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB within 10 working days of the investigator becoming aware of the problem.

8 STATISTICAL CONSIDERATIONS

8.1 STATISTICAL HYPOTHESES

- Primary Efficacy Endpoint(s):

The main outcome is minutes per week of moderate- to vigorous-intensity physical activity. The 7-day PAR interview is administered by trained research staff, who will contact participants by telephone and ask about the amount, intensity, and types of physical activities over the past 7 days. The 7-day PAR has demonstrated reliability, congruent validity, and internal consistency. The instrument is sensitive to moderate changes in physical activity over time and has been validated by telephone. Moreover, these self-reported data will provide useful insights regarding the specific types of physical activities occurring in rural counties.

ActiGraph GT3X accelerometers are worn continuously for 7 days during waking (on the nondominant hip) and sleeping (on the nondominant wrist) hours at baseline and at 6, 12, and 18 months. This device measures movement, intensity of physical activity, and sleep efficiency, latency, and number of awakenings. The devices have been validated using heart rate telemetry and total energy expenditure and have been shown to provide valid estimates of sleep. A minimum threshold of 1952 counts per minute will be used for moderate- to vigorous-intensity physical activity with an epoch of 30 seconds. The minimum valid wear time has been set at 4 days of at least 600 minutes of wear. This objectively measured data will be used to corroborate self-reported PAR data

- Secondary Efficacy Endpoint(s):

The secondary outcomes include physical performance and anthropometrics. Physical performance is assessed with the Two Minute Step Test, in which participants step in place as fast as possible for 2 minutes while lifting the knees to a premeasured height midway between the upper tips of their patella and iliac crest when standing. A score is calculated based on the number of times the right knee meets the marked height, which can be used to estimate the current level of physical function and predict future physical independence. Anthropometric measurements include height, weight, and waist circumference. Height will be measured without shoes and with a portable stadiometer (Seca 213). Weight will be measured without shoes and in light clothing with a digital scale (Healthometer, model no: 349KLX) that is zeroed before each measurement. Waist circumference will be measured with a Gulick II tension-controlled tape measure (County Technology, Gary Mills). The tape is positioned around the natural waist, just above the iliac crest. The measurement is recorded to the nearest 0.1 cm upon exhalation.

Psychosocial factors will also be assessed at baseline and at 6, 12, and 18 months using Patient-Reported Outcome Measurement Information System scales for anxiety, depression, fatigue, and sleep disturbance with previously demonstrated validity and reliability (α=.95, .98, .84, and .83, respectively).

SCT measures will be assessed in person at the 4 assessment visits and by mail at 3 months (for mediation analyses). The measures include the 10-item self-regulation scale (α=.78), 13-item social support for exercise scale (α=.61-.91), 9-item outcome expectations scale (α=.89), 18-item physical

activity enjoyment scale with high internal consistency and test-retest reliability, 10-item walking self-efficacy scale (α=.82), and the 12-item exercise confidence scale (α=.92).

Secondary measures at baseline, 6 months, and 12 months were included in the cost-effectiveness analyses. We will use a health care utilization survey that captures information on physician and emergency room visits and hospitalizations; the EuroQol-5 Dimension, which estimates utility weights to estimate quality-adjusted life years (QALYs); and a set of questions to measure time spent and expenses related to participation and time devoted to physical activity.

An 18-item measure adapted from similar past studies will assess participant satisfaction with the DIAL intervention and request suggestions for program improvement at 12 and 18 months. Finally, a similar survey will be administered at 18 months to the rural county coordinators to examine stakeholders' perspectives on acceptability, barriers to and facilitators of implementation, and sustainability of the DIAL intervention in the Deep South.

The research staff will complete the three components of the Rural Active Living Assessment (RALA) for each county at baseline. This assessment consists of the street segment assessment to evaluate factors such as walkability, safety features, and terrain of individual, specific street segments; the town-wide assessment that examines community characteristics such as population, total area, and the presence of recreation activities; and finally, the program and policy assessment, which identifies community programs and policies that support physical activity. These tools have been successfully used in similar past studies conducted by our research team in the Deep South.

8.2 SAMPLE SIZE DETERMINATION

Results from our previous UAB pilot study indicated an increase in minutes of moderate-to-vigorous physical activity among the DIAL intervention group compared with the control group. The SD of this measure was 90 minutes. Assuming a mean difference of 35 (SD 90) minutes in moderate-to-vigorous physical activity between the two groups from baseline to 6 months, a two-tailed two-group *t* test, and a significance level of 5%, we will have 80% power to detect this difference (with an effect size of 0.388) with 105 participants per arm (210 for the study). Assuming a mean change of 35 (SD 90) minutes in moderate-to-vigorous physical activity from baseline to 6 months for the intervention group, a two-tailed paired *t* test, and a significance level of 5%, we will have 80% power to detect this within-group change (with an effect size of 0.276) with 105 participants. Allowing for 15% attrition, we will recruit 240 participants (120 per arm).

8.3 STATISTICAL ANALYSES

8.3.1 GENERAL APPROACH

Analyses will be performed on an intent-to-treat basis (ie, participants will be analyzed by the arms to which they were randomized). All statistical tests will be two-sided. All analyses will be performed using SAS, and *P*<.05 will be deemed statistically significant.

Although a large amount of missing data is not expected for any of our study variables, a sensitivity analysis may be performed using alternative methods for handling missing data (such as multiple imputation) to assess the most appropriate approach based on the amount of missing data and effect sizes observed.

8.3.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

The primary method of analysis for physical activity, anthropometrics, and psychosocial measures, all of which will be measured at baseline, 6 months, 12 months, and 18 months, will be mixed model repeated measures analyses. Other general linear mixed model techniques may also be used. These analyses will allow us to examine changes from baseline to follow-up (within-group changes) and differences between the study groups simultaneously, while also accounting for the group-by-time interaction as well as any covariates and interactions that are of scientific interest. An appropriate covariance matrix (eg, autoregressive or unstructured) will be selected based on the final data. The Tukey-Kramer multiple comparisons test will be used to determine specific pairwise differences for statistically significant main effects. Some of these models will include the stratification variable of county and confounding variables (as covariates) such as the baseline BMI category, age, gender, and education level. Some of the models that include physical activity as the dependent variable will be adjusted for wear time. Study variables that will be analyzed using these techniques include the change in minutes of moderate-to-vigorous physical activity. Pearson correlation analysis will be performed to assess the relationship between self-reported and measured physical activity.

Distributions of the aforementioned continuous variables will be examined for normality using box plots, normal probability plots, and the Kolmogorov-Smirnov test. Variables that are determined to deviate from a normal distribution will be log-transformed before statistical testing. Nonparametric tests (eg, the Wilcoxon rank-sum test and the Wilcoxon signed-rank test) may also be used to analyze nonnormally distributed data.

8.3.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

We will investigate potential mediators of the intervention effect (*social support*) using a multiple mediation approach in SPSS, in which all potential mediators are tested simultaneously, using a product of the coefficients method with bootstrapped SEs (5000 samples with replacement). The interest is in estimating the path coefficients, effect sizes, and CIs rather than strict hypothesis testing.

Potential moderators and interactions will be assessed as follows. A variable will be considered a moderator if evidence exists of either qualitative or quantitative interaction with the intervention. We will use a similar analytic approach as in the primary aims; models will include the main effects of intervention (DIAL intervention vs control), the potential moderator (eg, education and neighborhood and environmental features), and the interaction between the two. Evidence of moderation exists if the coefficient of the interaction term is statistically different from zero.

Descriptive analyses of quantitative stakeholder acceptability survey items and content analyses of open-ended items from stakeholder acceptability surveys and focus group transcripts will be conducted to inform future efforts toward sustainability and large-scale dissemination in rural counties.

If, as hypothesized, the DIAL intervention results in significantly greater increases in moderate-to-vigorous physical activity minutes, we will conduct a within-trial cost-effectiveness analysis to determine if the DIAL intervention is cost-effective compared with no active intervention. Perspectives will be those of the health care sector, participants, and society. The time frame will be 6 months. We will estimate the DIAL implementation costs and participants' medical and other costs that may be affected. Effectiveness will be measured by the change in moderate-to-vigorous physical activity minutes and QALY.

Implementation costs will include start-up and ongoing costs necessary to implement the DIAL intervention in other settings and will not include costs of intervention development and research activities (eg, consent process). Start-up costs will include time spent on training by trainers and intervention personnel, materials, space, and other supplies needed. To identify and value the DIAL intervention's ongoing costs, we will develop process maps with intervention staff to identify all key processes (eg, supervision and orienting the participants to the IVR system, preparing, and IVR system tracking and maintenance) and the personnel involved in those processes, and develop a time tracking system to record the time spent in the identified processes. To reduce burden, this system will be used in random weeks by each intervention staff member. County coordinators will also complete time studies to estimate their time. Over the course of the study, we will select 1 week per month randomly for each intervention staff member. Data will then be annualized and combined with hourly wages and fringe benefits of the personnel to value annual personnel costs per activity. Costs of workbooks, handouts and other materials, phone and IVR system, office space, shipping, and others will be tracked and valued using project records or current market prices. Implementation cost data will be summed overall and by intervention-related categories, for example, IVR tracking and maintenance or feedback reporting. We will calculate the average DIAL intervention cost per participant and per minute moderate-to-vigorous physical activity increase.

The implementation costs of participants will include participation time costs, which will be captured with our surveys at baseline, 6 months, and 12 months. Survey questions will ask participants about the time spent reviewing intervention materials and calling into the IVR system and completing surveys and other intervention activities. These activities will also be tracked using the IVR system user data. Time costs will be valued using hourly wages and fringes based on average age and gender groups.

As improving physical activity has effects on well-being and potentially health care use, in the cost-effectiveness analysis, we will estimate medical costs for the DIAL intervention participants and control participants. At baseline, 6 months, and 12 months, we will use a health care utilization survey to capture information on physician and emergency room visits and hospitalizations [*45*]. To calculate medical costs, we will combine self-reported health care use and associated time and out-of-pocket costs and third-party payer unit costs. We will measure the cost of time spent exercising using the self-report 7-day PAR data and accelerometer data. All time costs will be valued using hourly wages and fringes based on average age and gender groups.

Medical and other costs will be added to the implementation costs. Incremental cost-effectiveness ratios (ICERs) will be calculated as the average net cost per minute of moderate-to-vigorous physical activity. In a previous study, physical activity interventions had ICERs of US $0.05-US $0.15 per moderate-to-vigorous physical activity minutes. We will also calculate the ICERs per QALY gained. QALYs will be calculated over a 6-month follow-up period using utility weights derived from the EuroQol-5D. To determine if the DIAL intervention is cost-effective compared with no active intervention, ICERs will be compared with the commonly used threshold of US $50,000-US $100,000 per QALY.

To examine uncertainty, we will sample the replacement costs and outcomes from the two trial arms and calculate the mean costs and outcomes for each bootstrap sample, repeating the procedure 1000 times. Differences in costs and outcomes between the two groups from each sample will be plotted in a cost-effectiveness plane. ICERs will be obtained for each sample, and confidence limits around the ICER will be obtained by taking the values at the 5th and 95th percentile of the distribution. Analyses will be repeated to examine the uncertainty around data inputs, such as hourly wages or medical care costs. In addition, we will construct an acceptability curve by considering the proportion of bootstrap replications for which the ICER falls below the possible thresholds of cost per QALY.

8.3.4 SAFETY ANALYSES

This study involves an educational intervention aimed at promoting physical activity. Thus, it is a minimal risk level study that dictates annual review by the UAB Institutional Review for Human Subjects (IRB) –Expedited Review, as the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. Moreover, this study will receive annual review by the University of Alabama at Birmingham Clinical Trials Review Committee (CTRC) for scientific progress and IRB compliance. Note that research staff will be capturing adverse events that are called into the toll-free study number, as well as captured from IVR calls and at in person assessments. This data and safety monitoring plan has been developed to ensure and maintain the scientific standard and protect the safety of the participants. Dr. Pekmezi is primarily responsible for the plan with oversight from her Co-Investigators, Drs. Demark-Wahnefried, *Baskin,* Pisu, Thirumalai, and Oster, with consultation/guidance from the study physician, Dr. Partridge. The plan calls for monitoring of adverse events, ensuring that the recruitment goals are on target, and protecting data/confidentiality. Based on our preliminary work, and on a vast literature on moderate intensity physical activity, we anticipate that our intervention will be low risk and that negative side effects will be rare. Nonetheless, we will have multiple levels of data safety and monitoring.

The **adverse event reporting** protocol includes several steps. In each IVR call, participants will be asked if they have experienced any physical symptoms or complaints that could interfere with their PA program. If they respond 'yes', they are told to stop exercising and contact their personal physician to discuss the health issues further. The IVR system will then prompt staff to follow up with a telephone call to the participant within 48 hours and discontinue PA intervention until physician clearance is provided. On a quarterly basis (by mail at 3, 9, 15 months and in person at 6, 12, and 18 month assessments), participants will be asked if they have experienced any physical symptoms or complaints that could interfere with their physical activity program, any serious health events that caused them to seek medical attention, and if any of these resulted in hospitalizations overnight. Details of these events will be recorded. All participants will be instructed to seek immediate care (through their physicians or emergency room) if problems occur. A toll-free number will be provided for communicating these issues with study staff to assure timely response and submission of regulatory work that is required through the UAB IRB. Instructions on the importance of reporting adverse events through the toll-free study number and surveys etc will be included on all study binders, emails, and cover letters that accompany the intervention measures and materials.

All health occurrences will be recorded and regularly reviewed by the study team, including Dr. Partridge (study physician), and the UAB Institutional Review Board Office. The study staff will record all reported events in the adverse event log (including the participant name, date, and event description; minority status and gender also will be included in these reports to allow for detection of differential effects) and immediately notify the PI (Pekmezi) of any unanticipated serious events (including deaths should they occur) that potentially jeopardize participation in the study. Dr. Pekmezi will consult with Dr. Partridge (study physician) on the action that should be taken. This communication will occur within 24 hours (for an unanticipated study death), and 5 business days for an unanticipated serious event. This action and date of implementation also will be recorded in the adverse event log. All serious health events will be reported within 3 business days to the UAB IRB. The research team will participate quarterly in classifying any reported events as "serious" or "non-serious" as well as "non-attributable,"

"possibly attributable" or "attributable" to the intervention. In completing this exercise, the team will be blinded to arm status.

8.3.5 BASELINE DESCRIPTIVE STATISTICS

The characteristics of the study populations will be summarized for each study arm using descriptive statistics, such as means and SD for continuous variables and frequencies and proportions for categorical variables. Unadjusted comparisons of baseline characteristics between study arms and those between participants who completed the study and those who dropped out will be performed using the two-group *t* test for continuous variables and the Pearson chi-square test for categorical variables. Unadjusted within-group changes (from baseline to postintervention) will be assessed using the paired *t* test.

9 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

9.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

9.1.1 INFORMED CONSENT PROCESS

9.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO SUBJECTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the subject and written documentation of informed consent is required prior to conducting procedures.

9.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the subject will be asked to read and review the document. The investigator will explain the research study to the subject and answer any questions that may arise. A verbal explanation will be provided in terms suited to the subject's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research subjects. Subjects will have the opportunity to carefully review the written consent form and ask questions prior to signing. The subjects should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The subject will sign the informed consent document prior to any procedures being done specifically for the study. Subjects must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the subjects for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the subject undergoes any study-specific procedures. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

9.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study subjects and the Institutional Review Board (IRB), will provide the reason(s) for the termination or suspension. Study subjects will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the IRB.

9.1.3 CONFIDENTIALITY AND PRIVACY

Subject confidentiality and privacy is strictly held in trust by the participating investigators and their staff. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Principal Investigator.

All research activities will be conducted in as private a setting as possible.

Representatives of the Institutional Review Board (IRB) may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

The study subject's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB and/or Institutional policies.

Study subject research data, which is for purposes of statistical analysis and scientific reporting, will be stored at the UAB research office. This will not include the subject's contact or identifying information. Rather, individual subjects and their research data will be identified by a unique study identification number. The study data entry and study management systems used by research staff will be secured and password protected.

9.1.4 QUALITY ASSURANCE AND QUALITY CONTROL

The site will perform internal quality management of study conduct, data collection, documentation and completion. Quality control (QC) procedures will be completed by the Data Manager during data entry into the appropriate CRF. Any missing data or data anomalies will be communicated to the Study Coordinator for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements.

The site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and inspection by local and regulatory authorities.

9.1.5 DATA HANDLING AND RECORD KEEPING

9.1.5.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the Principal Investigator. The Principal Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hard copies of source document worksheets will be used for recording data for each subject enrolled in the study. Data recorded in the case report form (CRF) derived from source documents should be consistent with the data recorded on the source documents.

9.1.5.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 3 years after the completion of the study. These documents should be retained for a longer period, however, if required by local regulations.

9.1.6 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol requirements. The noncompliance may be either on the part of the subject, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the Principal Investigator to use continuous vigilance to identify and report deviations within 10 working days of identification of the protocol deviation. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The Principal Investigator is responsible for knowing and adhering to the reviewing IRB requirements.

9.1.7 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be

required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial.

9.2 ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DHHS	Department of Health and Human Services
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IRB	Institutional Review Board
LSMEANS	Least-squares Means
NCT	National Clinical Trial
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOA	Schedule of Activities
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

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