

LDCT Mega Trial (LIFEMAP Trial?)

Study Design and Statistical Analysis Plan

Sponsor/Organizer: LIFEMAP Foundation (working name)

Planned launch: Protocol discussion – November 6, 2025 (AHA Scientific Sessions Satellite, New Orleans)

Design Type: Pragmatic, multicenter, randomized outcomes trial assessing whether one-time LDCT with AI-guided, image-informed prevention reduces mortality vs. usual care

1. Rationale and Prior Evidence

Despite advances in treatment, the leading causes of death—cardiovascular disease (CVD), cancer, chronic respiratory disease, and metabolic disorders—are still detected too late in most patients. Major imaging trials such as the National Lung Screening Trial (NLST), NELSON, and SCOT-HEART have each shown mortality reductions when imaging is used proactively. However, no study has yet integrated multi-disease risk detection and prevention from a single LDCT platform. The LDCT Mega Trial aims to demonstrate that combining AI-based quantification across cardiac, pulmonary, hepatic, skeletal, and metabolic systems can yield greater absolute mortality benefits, with CVD mortality reduction expected to exceed that of lung cancer.

2. Implication

A one-time, AI-quantified multi-disease LDCT is expected to produce larger absolute mortality and morbidity reductions from cardiovascular disease than from lung cancer because the scan simultaneously detects and stratifies coronary and cardiothoracic risk (CAC, chamber enlargement/LVH), emphysema/COPD burden, osteoporotic bone proxies, and hepatic steatosis—each linked to proven, guideline-directed therapies that lower events. The intervention arm operationalizes image-guided intensification (statins/ezetimibe/PCSK9; optimized BP regimens; SGLT2i/GLP-1 RA for adverse adiposity/diabetes; smoking cessation escalation by emphysema severity; osteoporosis treatment; targeted work-ups for actionable nodules) and care navigation, yielding near-term CVD event reductions, stage-shifted lung cancer, fewer COPD exacerbations, fewer fragility fractures, and improved hepatometabolic outcomes. Given the high co-occurrence of these risks in mid-to-older adults, a combined disease-specific endpoint (CV + lung cancer mortality) is clinically and statistically coherent, with anticipated spillover benefits on all-cause mortality and unplanned hospitalizations.

3. Objectives and Endpoints

Primary Objective: Demonstrate $\geq 20\%$ relative reduction in combined disease-specific mortality (CVD + lung cancer) over 5 years with one-time LDCT plus predefined image-guided care pathways versus usual care.

LIFEMAP: Low-Dose Imaging for Early Multi-disease Assessment and Prevention

Co-Primary Endpoints: Combined disease-specific mortality and all-cause mortality.

Secondary Endpoints: MACE, lung-cancer mortality, COPD exacerbations, fractures, hepatic outcomes, cost-effectiveness, and equity metrics.

4. Trial Design

Design: Individually randomized, open-label, blinded-endpoint (PROBE) study.

Population: Adults 45–75 years, inclusive of diverse ethnic and socioeconomic backgrounds.

Sample Size: 100,000 participants (50,000 per arm).

Intervention: One-time non-contrast LDCT with AI-based quantification linked to evidence-based preventive pathways.

Control: Usual care per existing guidelines.

Follow-Up: Annual visits for 5 years; passive follow-up for another 5 years.

5. Image-Guided Care Pathways

- Cardiovascular: Statins, PCSK9, BP optimization, SGLT2i/GLP-1 RA for metabolic risk.
- Pulmonary: Nodule follow-up, smoking cessation intensification, COPD management.
- Bone: Anti-resorptive or anabolic therapy for osteopenia/osteoporosis.
- Liver: Hepatology referral for steatosis or elevated liver attenuation index.
- Equity: Navigation support and cost waivers for underinsured patients.

6. Outcomes and Safety Monitoring

A blinded Clinical Events Committee will adjudicate causes of death and MACE. Safety oversight will include radiation exposure, invasive procedures, and complication rates. A DSMB will monitor interim efficacy and safety with O'Brien-Fleming boundaries.

7. Statistical Framework

Time-to-event analyses will use Cox proportional hazards models and log-rank tests, with HRs and 95% CIs reported. Competing-risk methods (Fine-Gray) will be used for disease-specific mortality. Interim analyses will occur after 50% and 75% of events. Intent-to-treat principle will guide the primary analysis, with sensitivity per-protocol analyses to quantify contamination.

8. Sample Size and Power Calculations

Assuming HR = 0.80 (20% relative reduction) with $\alpha = 0.05$ and power 90%, required deaths $(D) = (Z_{1-\alpha/2} + Z_{1-\beta})^2 / [\ln(HR)]^2 \approx 211$ events. Assuming a 5-year control combined disease-specific mortality of 4%, expected mean event rate = 3.6% across arms. With contamination (10–15%) and 5% attrition, 100,000 participants (50k/arm) ensure more than adequate power for both disease-specific and all-cause mortality endpoints.

Table: Estimated Participants Required for 20% Mortality Reduction (90% Power)

Control Event Rate | Mean | Required N (approx)

3.0% | 2.7% | 7,800

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3.5% | 3.15% | 6,700

4.0% | 3.6% | 5,900

5.0% | 4.5% | 4,700

9. Randomization and Blinding

Randomization: Central, 1:1, stratified by site, age, sex, and smoking status. Endpoint adjudicators and statisticians blinded to group allocation.

10. Data Management

All imaging and clinical data will be stored in a centralized cloud-based data repository. AI models will be locked and validated prior to deployment. Data will be pseudonymized and shared using federated or open-access models after primary results.

11. Health Economics

The trial will collect direct and indirect costs, estimate cost per QALY gained, and evaluate payer-specific budget impact models to support future reimbursement.

12. Equity and Access

The trial will intentionally oversample underrepresented groups. Mobile LDCT pods will reach rural and underserved communities, ensuring equitable participation and downstream access to preventive therapies.

13. Key Milestones

2026-Q1: Protocol finalization and site selection.

2026-Q3: First patient enrollment.

2028–2029: Mid-trial interim analysis.

2030–2031: Completion of primary follow-up.

2031–2035: Extended follow-up, dissemination, and policy engagement.

14. Discussion Points for Steering Committee

- Finalize endpoint hierarchy (disease-specific vs all-cause)
- Define AI thresholds for CAC, emphysema, steatosis, bone density.
- Confirm adjudication charter.
- Approve public awareness campaign for follow-up years 6–10.

15. References

1. National Lung Screening Trial Research Team. N Engl J Med. 2011.
2. NELSON Trial. N Engl J Med. 2020.
3. SCOT-HEART Investigators. Lancet. 2018.
4. UKLS and MILD Trials. Lancet Oncology. 2021.
5. USPSTF Lung Cancer Screening Recommendations. JAMA. 2021.
6. Multi-disease imaging and AI-based prevention literature (2020–2025).