LDCT Mega Trial (LIFEMAP Trial): Detailed Study Design & Statistical Analysis Plan (Draft)

Sponsor/Organizer: LIFEMAP Foundation (working name)
Planned launch: Protocol v1.0 discussion — Nov 6, 2025 (AHA Scientific Sessions satellite)
Overall design: Pragmatic, multicenter, randomized outcomes trial assessing whether **one-time LDCT with AI-guided, image-informed prevention** reduces mortality vs. usual care

Executive Summary for the LDCT …

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1) Rationale & Prior Evidence

- **Lung cancer screening:** NLST showed **20% lower lung-cancer mortality** with LDCT vs chest x-ray and **~6.7% lower all-cause mortality** at 6.5 years. NELSON confirmed a **24% reduction in lung-cancer mortality in men** and larger in women at 10 years; the trial was **powered (80%)** to detect ≥25% reduction. Systematic reviews and UKLS/MILD reinforce sustained mortality benefits with LDCT.
- **Cardiovascular outcomes from imaging-guided strategies:** In **SCOT-HEART**, adding coronary CT angiography to standard care **reduced fatal or non-fatal MI (HR≈0.59)** at 5 years; longer follow-up continues to show event reduction signals.
- **Policy backdrop:** USPSTF Grade-B LDCT screening (50–80 y, ≥20 pack-years) indicates favorable benefit-harm balance within high-risk populations; our trial extends the concept to **multi-disease prevention** triggered by a **single LDCT**.
  Implication: A one-time, AI-quantified **multi-disease LDCT** can reasonably lower **lung-cancer mortality** and plausibly lower **CVD mortality** via image-guided preventive therapy (lipids, BP, smoking cessation, osteoporosis therapy, hepatometabolic care). The co-occurrence of risks in mid-to-older adults makes a **combined mortality endpoint** clinically coherent.

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2) Objectives & Endpoints

Primary Objective

Demonstrate **≥20% relative reduction** in **combined disease-specific mortality** (cardiovascular + lung-cancer mortality) over **5 years** with **one-time LDCT plus predefined image-guided care pathways**, versus usual care.

Rationale: NLST/NELSON support ≥20% reductions in lung-cancer mortality; SCOT-HEART supports sizeable reductions in CHD events with imaging-guided management. Co-primary on all-cause mortality is feasible given total N and long follow-up.

Co-Primary Endpoints

1. **Combined disease-specific mortality** (adjudicated deaths from CVD or lung cancer) to 5 years.
2. **All-cause mortality** to 5 years.

(Multiplicity handled with a **fallback/Hochberg** or **alpha-split** procedure; see §7.)

Key Secondary Endpoints

- **Lung-cancer-specific mortality**; **CVD mortality** (separately).
- **Major adverse cardiovascular events (MACE)** (CV death, MI, stroke, urgent revascularization).
- **Late-stage (III/IV) lung cancer incidence**, **time-to-treatment**, COPD exacerbations, hip/vertebral fractures, clinically significant hepatic outcomes.
- **Health economics** (cost/QALY), **equity** (uptake in underserved groups), **safety/harms** (radiation, downstream invasive procedures), and **quality of life**.

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3) Trial Design

- **Design:** Individually randomized, open-label, blinded endpoint evaluation (**PROBE**). Parallel two-arm design.
- **Population:** Adults **45–75 y** (broad risk), enriched for cardiopulmonary risk factors via pragmatic EHR flags (e.g., smoking history, hypertension, diabetes, prior ED visits for chest or respiratory symptoms), yet inclusive to maximize generalizability and equity.
- **Arms (1:1):**
    - **Intervention:** Single **non-contrast LDCT** (harmonized protocol). AI-assisted quantification returns a **multi-system report** (CAC & cardiac chamber metrics; emphysema/COPD indices; lung nodules per volume/doubling time; vertebral bone proxy; hepatic steatosis; body composition). **Standardized care pathways** (below) are communicated to PCPs and patients with facilitated navigation.
    - **Control: Usual care** per prevailing guidelines (including standard LDCT screening eligibility; no trial-driven LDCT).
- **Sites:** Academic & community hospitals, integrated delivery networks, and **autonomous/micro-staffed LDCT pods** in community settings.
- **Follow-up:** Scheduled outreach (telehealth allowed) at **90 days**, **1 y**, then **annual** to **5 y**, passive follow-up to 10 y via EHR/registries.

Image-Guided Care Pathways (protocolized)

- **Cardiovascular:** Statins/ezetimibe/PCSK9 per CAC severity; BP targets per guideline with **priority alerts** if LVH/LAE; SGLT2i/GLP-1 RA consideration in diabetics or adverse adiposity; smoking cessation; exercise/weight programs.
- **Pulmonary/Oncology:** Nodule management per Lung-RADS/volume doubling time; smoking cessation intensity by emphysema/COPD metrics; expedited diagnostic pathways.

- **Bone & Liver:** Osteoporosis therapy triggers from LDCT-derived bone proxy; hepatology referral if steatosis thresholds met.
- **Equity/Navigation:** Community health worker support, multilingual education, and **no-cost follow-up** for under-insured participants.

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4) Eligibility (illustrative; to finalize with Steering Committee)

Inclusion: 45–75 y; consent; accessible PCP/telehealth; EHR match for outcomes.
Exclusion: Known active cancer under treatment; recent (≤12 mo) diagnostic chest CT with equivalent reads; life expectancy <5 y; pregnancy; contraindication to downstream diagnostics if strongly anticipated.

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5) Outcomes Ascertainment & Safety

- **Adjudication:** Independent, blinded **Clinical Events Committee** adjudicates cause-specific deaths and MACE using source documents, death registries, and imaging/biopsy reports.
- **Safety: DSMB** oversees radiation exposure metrics, complication rates from downstream procedures, and early imbalances in severe adverse events.
- **Harms minimization:** Nodule management per validated algorithms to limit overdiagnosis; shared decision-making tools.

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6) Statistical Framework

Primary Analyses

- **Time-to-event** comparisons using **Cox proportional hazards** and **log-rank tests**; report **HRs** with 95% CIs.
- **Competing risks**: Fine-Gray models for lung-cancer-specific and CVD-specific mortality.
- **Intent-to-treat** (ITT) primary; **per-protocol** and **as-treated** sensitivity analyses to quantify contamination/drop-in.

Interim Monitoring

- **Event-driven** interims (e.g., at **50% and 75%** of expected deaths) with **O'Brien-Fleming** alpha-spending to preserve 2-sided **α=0.05**. DSMB may recommend early stop for overwhelming efficacy or harm.

Subgroups (pre-specified)

Age bands, sex, race/ethnicity, smoking status/pack-years, baseline CAC strata, emphysema burden, diabetes, socioeconomic and geographic indicators. Hierarchical modeling to limit false discovery.

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7) Multiplicity & Co-Primary Handling

Two approaches (choose one at protocol sign-off):

1. **Alpha-split**: two-sided α=0.04 for combined disease-specific mortality and α=0.01 for all-cause mortality; or
2. **Fallback/Hochberg**: test the endpoint with strongest prior (combined disease-specific) at α=0.05; if significant, test all-cause at α=0.05; otherwise adjust per Hochberg.

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8) Sample Size & Power (≥20% relative reduction)

Let **HR = 0.80** (20% reduction), **two-sided α=0.05**, power **80–95%**. For a log-rank design, the **required number of deaths (D)** is:

$$D = \frac{(Z_{1-\alpha/2} + Z_{1-\beta})^2}{\{\ln(HR)\}^2}$$

- **D (80% power)** ≈ **158** events
- **D (90% power)** ≈ **211** events
- **D (95% power)** ≈ **261** events

(Exact calculations available on request.)

To translate **events → participants**, assume a **5-year control event rate** for the endpoint of interest and apply the **average event incidence across arms** (control rate vs. 0.8× control in intervention), then inflate for **non-adherence, contamination, and loss to follow-up**.

A) Combined Disease-Specific Mortality (CVD + Lung Cancer)

Conservative **5-year control event rate** scenarios in adults 45–75:

Control 5-yr event rate	Mean across arms	N for 90% power (D≈211)
3.0%	2.7%	~7,800
3.5%	3.15%	~6,700
4.0%	3.6%	~5,900
5.0%	4.5%	~4,700

Design recommendation: Power on **combined disease-specific mortality** with **≥90% power** using **N≈8,000–10,000** if the trial's sole aim were this endpoint. However:

- We are enrolling **N = 100,000 (50k/arm)** to (i) enable **all-cause mortality** assessment, (ii) ensure precision in **subgroups/equity** aims, and (iii) withstand **contamination** from opportunistic LDCT outside the trial and **treatment drop-ins**.

B) All-Cause Mortality

If 5-year **all-cause mortality** in 45–75 y averages **~5–8%**, a **20% reduction** would require far fewer than 100k to detect, but **real-world contamination** and **dilution** make the larger **100k** sample appropriate to (a) ensure adequate **all-cause** power, (b) support **interim looks** with conservative spending, and (c) deliver **policy-level certainty**.

Note: In NLST, all-cause mortality reduction was ~6.7% with LDCT vs CXR—not 20%—highlighting that **all-cause** effects are typically smaller than disease-specific effects. Our **100k** design ensures power to detect **more modest all-cause effects** while targeting **≥20%** for combined disease-specific mortality.

C) Inflation Factors (built into N=100,000)

- **Contamination (control LDCT use):** assume **10–15%** → **~10% power dilution**.
- **Adherence gaps (no follow-up care after flagged findings): 10–20%**; mitigated via navigation.
- **Loss to follow-up:** target **<5%** using registry linkage.
- **Site effect/ICC:** Low for mortality; with hundreds of sites, residual clustering effect is negligible on power.

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9) Randomization, Stratification, and Blinding

- **Randomization:** Centralized, 1:1, variable block sizes, stratified by **site**, **sex**, **age band**, and **baseline smoking status**.
- **Blinding:** Endpoint adjudicators/statisticians blinded; treating clinicians and participants necessarily aware.

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10) Data & Imaging Core

- **Acquisition harmonization:** Fixed LDCT parameters (kVp/mAs) by BMI; phantom-based QA.
- **AI pipeline:** Locked algorithms for **CAC**, **chambers/LVH**, **emphysema**, **nodule volume/doubling**, **vertebral bone proxy**, **hepatic attenuation**; real-time quality flags.
- **Data governance:** Pseudonymization, federated ingestion where required; pre-specified **de-identified data releases**.

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11) Health Economics & Policy

- **Prospective resource capture** (imaging, procedures, meds, admissions).

- **Cost-utility (QALY)** and **budget impact** by payer segment.
- **Value dossiers** aligned with guideline and coverage stakeholders to accelerate **post-trial adoption** if positive.

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12) Equity, Access, and Public Awareness

- **Oversampling** of underserved populations; mobile/drive-thru units to reduce logistical barriers; subsidies where needed.
- **Culturally tailored** education and navigation.
- Years **6–10** include **public-awareness campaigns** to disseminate results and expand access (funded within the nonprofit plan).

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13) Alternative Design (if sites prefer staged roll-out)

Stepped-wedge cluster RCT (by site, quarterly steps). Pros: operationally friendly, all sites eventually deliver LDCT; Cons: larger variance and sensitivity to secular trends, requires robust modeling and **ICC** assumptions. Given low ICC for mortality, either design is viable; **individually randomized PROBE** remains simplest and most interpretable for regulators and payers.

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14) Operational Milestones (abridged)

- **M0–M6:** Finalize protocol, core labs, DSMB; site RFPs; training; master IRB.
- **M6–M18:** Ramp to **≥100 sites**; **first-patient-in** by M9; QA dashboards live.
- **M18–M48:** Peak enrollment; first interim at ~50% events; payer & policy touchpoints.
- **M60:** Primary analyses; manuscripts and policy briefs.
- **Years 6–10:** Extended follow-up, HEOR, and public-awareness scale-up.

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15) What We Need From the Group on Nov 6

1. Final selection of **co-primary strategy** (alpha-split vs fallback).
2. Agreement on **care-path thresholds** (e.g., CAC strata, emphysema cut-points, bone and liver triggers).
3. Confirmation of **adjudication charter** and **interim rules**.
4. Buy-in to **navigation resources** to minimize adherence loss.
5. Site commitments and **targeted subgroup oversampling** plans.

Key References

- NLST (NEJM 2011): LDCT reduced lung-cancer mortality by **20%**; all-cause mortality by **~6.7%** vs CXR. New England Journal of Medicine
- NELSON (NEJM 2020): LDCT reduced lung-cancer mortality; trial powered for **≥25%** reduction at 10 y. New England Journal of Medicine+1
- UKLS/MILD & reviews: Long-term mortality benefits of LDCT screening. PMC+1
- SCOT-HEART (NEJM/Lancet): CTA-guided care **reduced MI** over 5–10 y, supporting imaging-guided prevention. New England Journal of Medicine+2PubMed+2
- USPSTF LDCT recommendations (2021): Grade B. USPSTF+2USPSTF+2

Appendix A — Back-of-Envelope Power Checks (for Steering Review)

- **Event requirement for HR 0.80** (two-sided α=0.05): **D≈211** deaths for **90% power**.
- With **control 5-y event rate** for **combined disease-specific mortality** at **3.0–4.0%**, mean across arms ≈ 2.7–3.6%. You would need **~5,900–7,800** participants total to detect HR 0.80 with 90% power **without** contamination or subgroup aims.
- Our **N=100,000** provides **over-power** to handle contamination, permit **robust all-cause mortality** testing, and enable **dozens of pre-specified subgroup** analyses with policy-relevant precision.