

# The National Lung Screening Trial (NLST)

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May 21, 2012

# Today's talk

- NLST: an overview
- Typical challenges in cancer screening RCTs
  - Starting a trial in the presence of “certainty”
  - Starting a trial in the presence of “uncertainty”
  - Collaboration
  - Recruitment
  - Reporting when you actually find a benefit

# NLST: an overview

- US RCT of lung cancer screening among heavy/long-term smokers
- Collaboration of two groups:
  - Lung Screening Study (NCI/DCP; gov't contracts)
  - American College of Radiology Imaging Network (ACRIN) (NCI/DCTD, cooperative agreement)

# NLST: an overview

- Arms:
  - Intervention:
    - Low radiation dose computed tomography (LDCT)
  - Comparison:
    - Single view chest x-ray (CXR)

# NLST: an overview

- Participants
  - n=53,464 (M and F)
  - 55-74 years old at randomization
  - 30 pack-years of cigarette smoking history
  - Former smokers: quit < 15 years prior to baseline
  - Asymptomatic for lung cancer

# NLST: an overview

- Years

- Planning: 1999-2002
- Recruitment: 2002-2004
- Follow-up: 2002-2010
- Stopped: October, 2010

- Results

- 20% reduction in lung cancer mortality with LDCT screening, relative to chest x-ray screening
- 95% CI: 6.7-26.7

## Challenge #1

What do you do when people are already certain of the answer?

# Starting a trial in the presence of “certainty”

- Evidence of a benefit: reduction in disease-specific mortality
- Intermediate endpoints:
  - ↑ in early stage cancers
  - ↑ case survival
- Do not guarantee a mortality benefit
  - Lead-time bias, length sampling bias, overdiagnosis

# Starting a trial in the presence of “certainty”

- Favorable intermediate endpoints will be used by proponents of screening as evidence of certainty of a benefit

## NLST's solution:

- Educate, educate, educate
- Make nice with the researchers who think available evidence was definitive
- When necessary, shout louder
- Be persistent, as the truth will win out

## Challenge #2

What do you do when one modality is undergoing evaluation in an RCT and another, more promising, modality comes along?

# Starting a trial in the presence of “uncertainty”

- In 1999, a small single-arm study of LDCT had demonstrated, relative to CXR:
  - Greater detection of early stage lung cancers
  - Better lung cancer survival
- Viewed by some as definitive evidence
  - RCT therefore was unethical
- Others believed that stronger evidence was needed

# Starting a trial in the presence of “uncertainty”

- But
  - CXR was under study in PLCO
  - The answer was not expected for many years (12 as it turned out)

## NLST's solution:

- Use CXR as the comparison arm in NLST
  - If PLCO found a benefit of CXR,
    - it would become standard of care
  - If PLCO did not find a benefit of CXR,
    - Fair to assume that CXR=nothing
  - What if PLCO had found harm with CXR?

# NLST's solution:

- If
  - PLCO had found a benefit
  - CXR had not been included in NLST
- Then
  - NLST would have been useless

## Challenge #3

What do you do when no one owns the intervention of interest?

What do you do when everyone wants to play, but the cost of playing is high?

# Two interested US parties

- Interested party #1
  - The Lung Screening Study (LSS)
    - Conducted the feasibility study
    - 7 years of documented success in the conduct of screening RCTs
    - Major medical centers, academic institutions

# Two interested US parties

- Interested party #2
  - ACRIN
    - Radiologists
    - Previously involved in non-RCT screening research

# NCI's solution

- LSS and ACRIN collaborated
  - Harmonized on primary and some secondary outcomes
  - Negative aspect
    - Made NLST a much more complex undertaking
  - Positive aspect
    - More experts working to solve the question at hand

## Challenge #4

What do you do when you have to  
enroll a lot of smokers  
(both current and former)  
in a cancer screening RCT?

# Recruitment

- Most researchers assume smokers are less interested in their health
  - Probably not so, just have different concerns
- Their reasons for joining cancer screening RCTs are probably different than those of non-smokers
- How do you find enough participants?

# NLST's solution

- Direct mail
  - Mail to many more people than you need (assume response rate < 1%)
- Go to bars and casinos
  - That is, go to the places where smokers go
- Provide smoking cessation resources

# NLST's solution

- Craft appropriate recruitment materials
  - Don't preach about smoking

## Challenge #5

What do you do when you find a benefit?

# You actually found a benefit!

- There will be a media blitz
- The wrong message will be relayed in many instances
- Some people will act as if you've found the cure for cancer

# You actually found a benefit!

- Questions will be asked
  - What should people do now?
    - Those who meet the eligibility criteria
    - Those who don't
- Someone will say that your study was not done properly, because the true benefit is much larger than what you observed

# Reporting when you find a benefit

- Need to frame messages very carefully and repeat caveats again and again
- Remember that cancer screening is not treatment
  - Important and unique issues exist

# Remember!

- A recommendation for mass screening will affect many people
  - Healthy population
  - Have it pretty good already
- Few will benefit
  - Rare disease
  - Generally see a small (if any) reduction in risk

# Remember!

- Harm will occur
  - Most harms will occur among those who cannot benefit
  - False positives, overdiagnosis, adverse events of diagnosis and treatment

Thank you!