A Taxonomy of Imaging Trials

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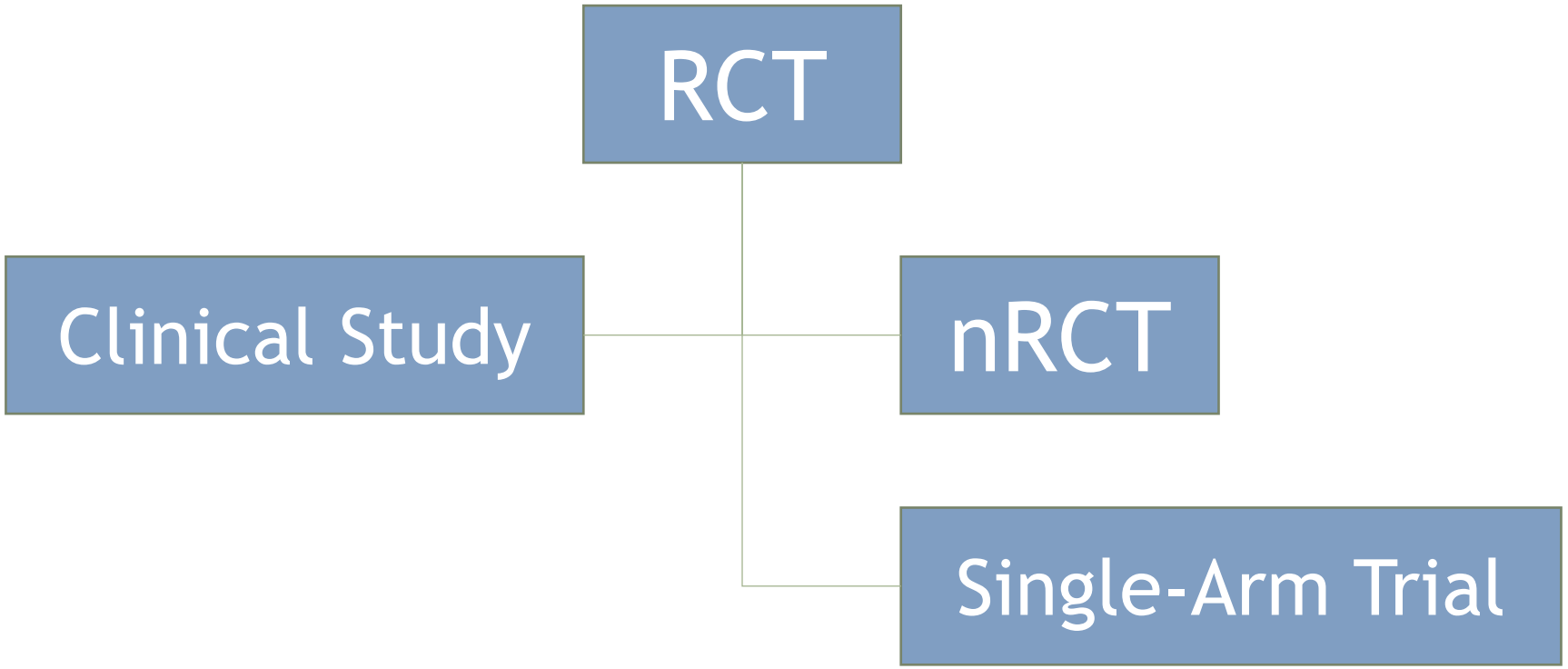
Taxonomy Imaging Trials



My Credo

Clinical trials
should help
in making decisions
about clinical interventions

So, my question:

How will your trial help future patients?

My Warning

- Many different classifications for clinical trials
- The one presented here is based on the flow of participants

Teaching Goals

- After this session, students should be able to explain the following differences:

• trial	observational study
• randomized	non-randomized
• single-arm	two-arm
• longitudinal	cross-sectional
• retrospective	prospective
• study population	study group
• outcome	effect
• primary outcome	secondary outcomes

Session Outline

1. Randomized Clinical Trial (RCT)
2. RCT components
3. Observational Clinical Studies
4. Non-Randomized Clinical Trial (nRCT)
5. Single-Arm Trial
6. Trial and Study Qualifiers
7. Diagnostic Accuracy Trial

1.
RCT: An Example


Technologists administer
a low-dose CT to screen
for lung cancer.

Claim: CT Lung Cancer Screening Saves Lives

Clinical Questions : PICO format

- P: Patient population
- I: Intervention
- C: Comparator
- O: Outcome

Lung Cancer Screening: PICO format

- P: (Former) smokers 55-74 ; 30 pack-years
- I: Screening with Low-Dose CT
- C: Screening with Chest Radiography
- O: Lung-cancer Mortality

Lung Cancer Screening: PICO format

- P: (Former) smokers 55-74 ; 30 pack-years
- I: Screening with Low-Dose CT
- C: Screening with Chest Radiography
- O: Total Mortality

Lung Cancer Screening: PICO format

- P: (Former) smokers 55-74 ; 30 pack-years
- I: Screening with Low-Dose CT
- C: No Screening
- O: Total Mortality

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Reduced Lung-Cancer Mortality with Low-Dose Computed Tomographic Screening

The National Lung Screening Trial Research Team*

ABSTRACT

BACKGROUND

The aggressive and heterogeneous nature of lung cancer has thwarted efforts to reduce mortality from this cancer through the use of screening. The advent of low-dose helical computed tomography (CT) altered the landscape of lung-cancer screening, with studies indicating that low-dose CT detects many tumors at early stages. The National Lung Screening Trial (NLST) was conducted to determine whether screening with low-dose CT could reduce mortality from lung cancer.

METHODS

From August 2002 through April 2004, we enrolled 53,454 persons at high risk for lung cancer at 33 U.S. medical centers. Participants were randomly assigned to undergo three annual screenings with either low-dose CT (26,722 participants) or single-view posteroanterior chest radiography (26,732). Data were collected on cases of lung cancer and deaths from lung cancer that occurred through December 31, 2009.

RESULTS

The rate of adherence to screening was more than 90%. The rate of positive screening tests was 24.2% with low-dose CT and 6.9% with radiography over all three rounds. A total of 96.4% of the positive screening results in the low-dose CT group and 94.5% in the radiography group were false positive results. The incidence of lung cancer was 645 cases per 100,000 person-years (1060 cancers) in the low-dose CT group, as compared with 572 cases per 100,000 person-years (941 cancers) in the radiography group (rate ratio, 1.13; 95% confidence interval [CI], 1.03 to 1.23). There were 247 deaths from lung cancer per 100,000 person-years in the low-dose CT group and 309 deaths per 100,000 person-years in the radiography group, representing a relative reduction in mortality from lung cancer with low-dose CT screening of 20.0% (95% CI, 6.8 to 26.7; P=0.004). The rate of death from any cause was reduced in the low-dose CT group, as compared with the radiography group, by 6.7% (95% CI, 1.2 to 13.6; P=0.02).

CONCLUSIONS

Screening with the use of low-dose CT reduces mortality from lung cancer. (Funded by the National Cancer Institute; National Lung Screening Trial ClinicalTrials.gov number, NCT00047385.)

The members of the writing team (who are listed in the Appendix) assume responsibility for the integrity of the article. Address reprint requests to Dr. Christine D. Berg at the Early Detection Research Group, Division of Cancer Prevention, National Cancer Institute, 6130 Executive Blvd., Suite 3112, Bethesda, MD 20892-7346, or at bergc@mail.nih.gov.

*A complete list of members of the National Lung Screening Trial research team is provided in the Supplementary Appendix, available at NEJM.org.

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Lung cancer is an aggressive and heterogeneous disease.[1,2] Advances in surgical, radiotherapeutic, and chemotherapeutic approaches have been made, but the long-term survival rate remains low.[3] After the Surgeon General's 1964 report on smoking and health, mortality from lung cancer among men peaked and then fell; among women, the peak occurred later and a slight decline has occurred more recently.[4] Even though the rate of heavy smoking continues to decline in the United States,[5] 94 million current or former smokers remain at elevated risk for the disease,[6] and lung cancer remains the leading cause of death from cancer in this country.[3] The prevalence of smoking is substantially higher in developing countries than in the United States, and the worldwide burden of lung cancer is projected to rise considerably during the coming years.[7]

Although effective mass screening of high-risk groups could potentially be of benefit, randomized trials of screening with the use of chest radiography with or without cytologic analysis of sputum specimens have shown no reduction in lung-cancer mortality.[8] Molecular markers in blood, sputum, and bronchial brushings have been studied but are currently unsuitable for clinical application.[8] Advances in multidetector computed tomography (CT), however, have made high-resolution volumetric imaging possible in a single breath hold at acceptable levels of radiation exposure,[9] allowing its use for certain lung-specific applications. Several observational studies have shown that low-dose helical CT of the lung detects more nodules and lung cancers, including early-stage cancers, than does chest radiography.[8] Therefore, the National Cancer Institute (NCI) funded the National Lung Screening Trial (NLST), a randomized trial, to determine whether screening with low-dose CT, as compared with chest radiography, would reduce mortality from lung cancer among high-risk persons. The NLST was initiated in 2002.[10] In October 2010, the available data showed that there was a significant reduction with low-dose CT screening in the rates of both death from lung cancer and death from any cause. We report here the findings of the NLST, including the performance characteristics of the screening techniques, the approaches used for and the results of diagnostic evaluation of positive screening results, the characteristics of the lung-cancer cases, and mortality. A comprehensive description of the design and operations of the trial, including the collection of the data and the acquisition variables of the screening techniques, has been published previously.[10]

METHODS

TRIAL OVERSIGHT

The NLST, a randomized trial of screening with the use of low-dose CT as compared with screening with the use of chest radiography, was a collaborative effort of the Lung Screening Study (LSS), administered by the NCI Division of Cancer Prevention, and the American College of Radiology Imaging Network (ACRIN), sponsored by the NCI Division of Cancer Treatment and Diagnosis, Cancer Imaging Program. Chest radiography was chosen as the screening method for the control group because radiographic screening was being compared with community care (care that a participant usually receives) in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial (ClinicalTrials.gov number, NCT00002540).[11] The NLST was approved by the institutional review board at each of the 33 participating medical institutions. The study was conducted in accordance with the protocol; both the protocol and the statistical analysis plan are available with the full text of this article at NEJM.org.

PARTICIPANTS

We enrolled participants from August 2002 through April 2004; screening took place from August 2002 through September 2007. Participants were followed for events that occurred through December 31, 2009 (Fig. 1 in the Supplementary Appendix, available at NEJM.org).

Eligible participants were between 55 and 74 years of age at the time of randomization, had a history of cigarette smoking of at least 30 pack-years, and, if former smokers, had quit within the previous 15 years. Persons who had previously received a diagnosis of lung cancer, had undergone chest CT within 18 months before enrollment, had hemoptysis, or had an unexplained weight loss of more than 6.8 kg (15 lb) in the preceding year were excluded. A total of 53,454 persons were enrolled; 26,722 were randomly assigned to screening with low-dose CT and 26,732 to screening with chest radiography. Previously published articles describing the NLST[10,12] reported an enroll-

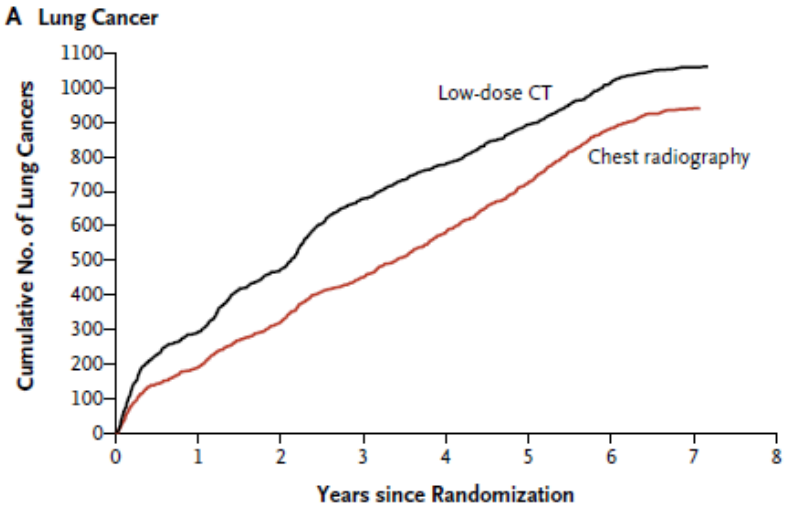
Table 1. Selected Baseline Characteristics of the Study Participants.*

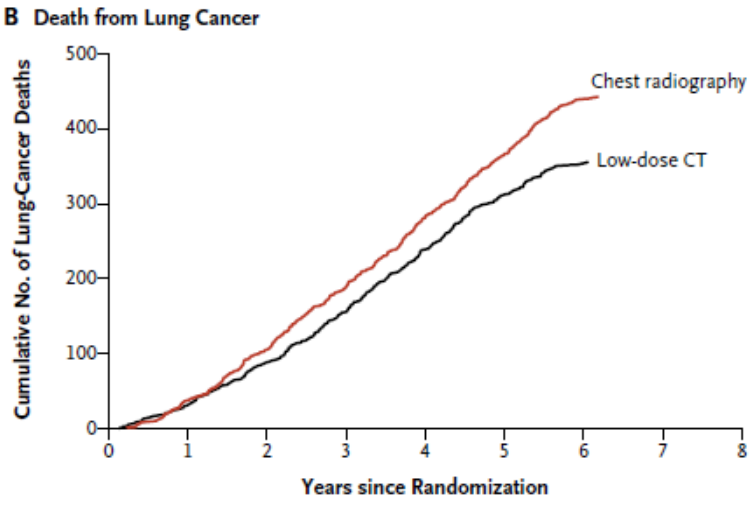
Characteristic	Low-Dose CT Group (N=26,722)	Radiography Group (N=26,732)
	number (percent)	
Age at randomization		
<55 yr†	2 (<0.1)	4 (<0.1)
55–59 yr	11,440 (42.8)	11,420 (42.7)
60–64 yr	8,170 (30.6)	8,198 (30.7)
65–69 yr	4,756 (17.8)	4,762 (17.8)
70–74 yr	2,353 (8.8)	2,345 (8.8)
≥75 yr†	1 (<0.1)	3 (<0.1)
Sex		
Male	15,770 (59.0)	15,762 (59.0)
Female	10,952 (41.0)	10,970 (41.0)
Race or ethnic group‡		
White	24,289 (90.9)	24,260 (90.8)
Black	1,195 (4.5)	1,181 (4.4)
Asian	559 (2.1)	536 (2.0)
American Indian or Alaska Native	92 (0.3)	98 (0.4)
Native Hawaiian or other Pacific Islander	91 (0.3)	102 (0.4)
More than one race or ethnic group	333 (1.2)	346 (1.3)
Data missing	163 (0.6)	209 (0.8)
Hispanic ethnic group‡		
Hispanic or Latino	479 (1.8)	456 (1.7)
Neither Hispanic nor Latino	26,079 (97.6)	26,039 (97.4)
Data missing	164 (0.6)	237 (0.9)
Smoking status		
Current	12,862 (48.1)	12,900 (48.3)
Former	13,860 (51.9)	13,832 (51.7)

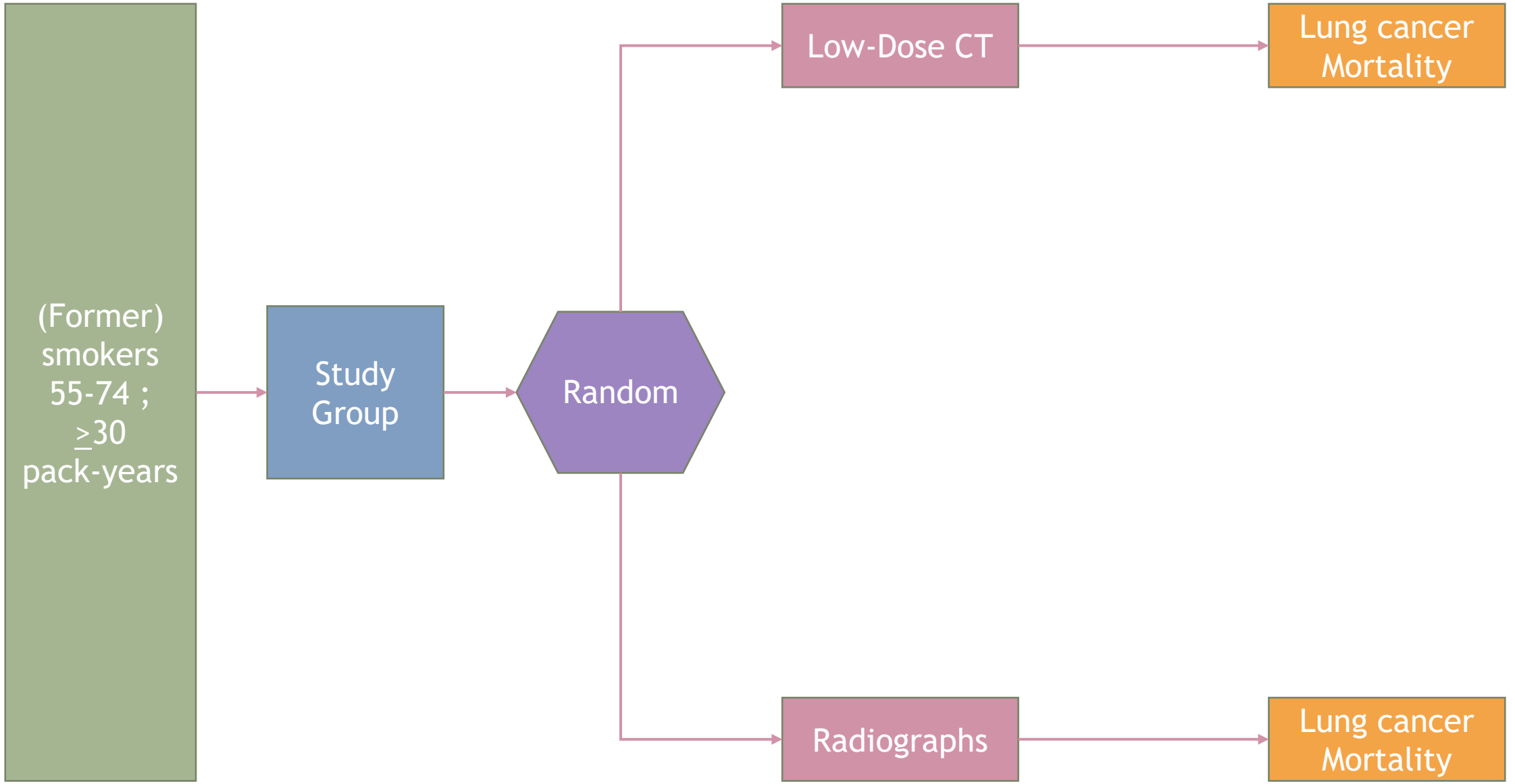
* CT denotes computed tomography.
† Patients in this age range were ineligible for inclusion in the screening trial but were enrolled and were included in all analyses.
‡ Race or ethnic group was self-reported.

Table 2. Results of Three Rounds of Screening.*

Screening Round	Low-Dose CT				Chest Radiography			
	Total No. Screened	Positive Result	Clinically Significant Abnormality Not Suspicious for Lung Cancer	No or Minor Abnormality	Total No. Screened	Positive Result	Clinically Significant Abnormality Not Suspicious for Lung Cancer	No or Minor Abnormality
	no. (% of screened)				*no. (% of screened)*			
T0	26,309	7191 (27.3)	2695 (10.2)	16,423 (62.4)	26,035	2387 (9.2)	785 (3.0)	22,863 (87.8)
T1	24,715	6901 (27.9)	1519 (6.1)	16,295 (65.9)	24,089	1482 (6.2)	429 (1.8)	22,178 (92.1)
T2	24,102	4054 (16.8)	1408 (5.8)	18,640 (77.3)	23,346	1174 (5.0)	361 (1.5)	21,811 (93.4)



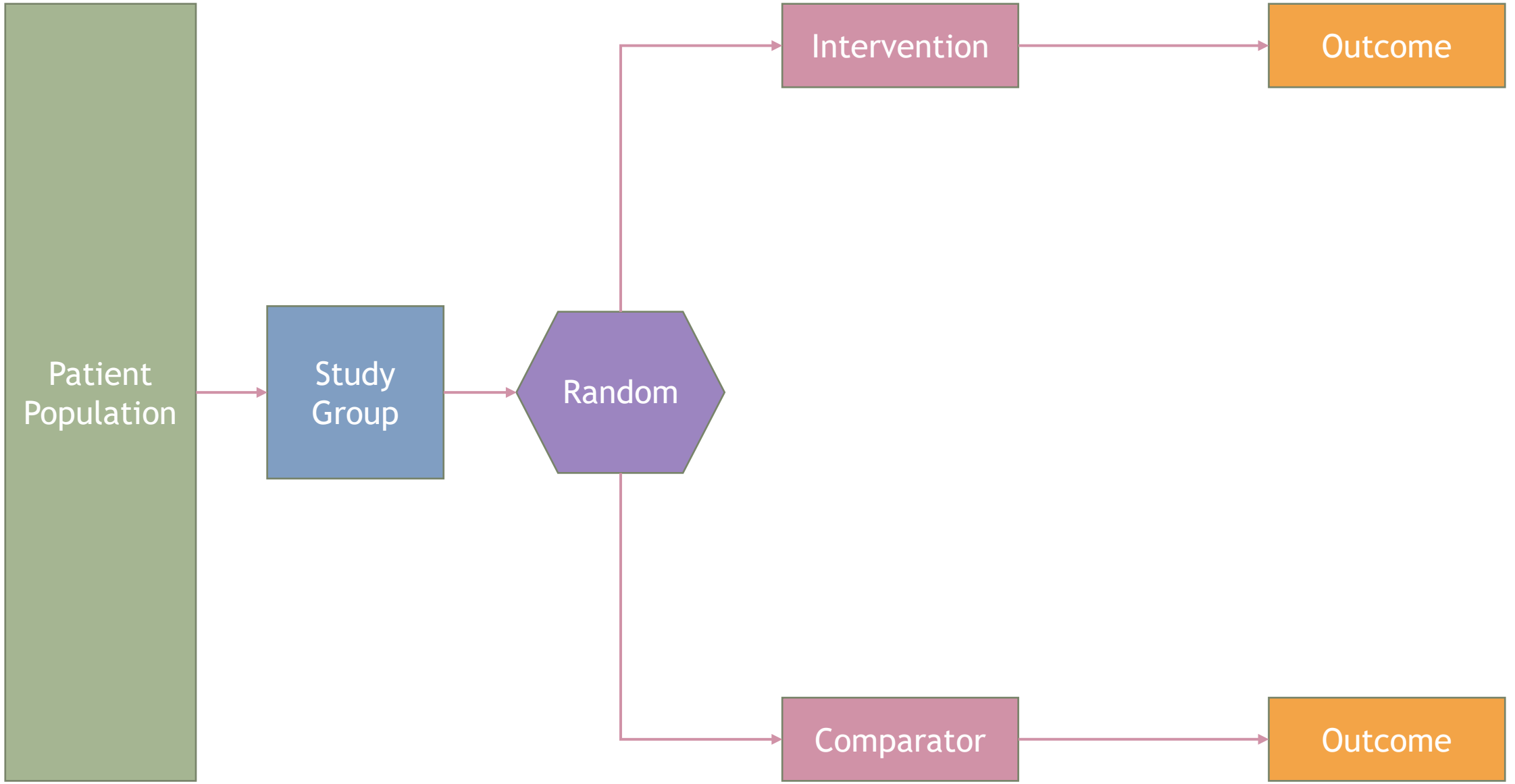


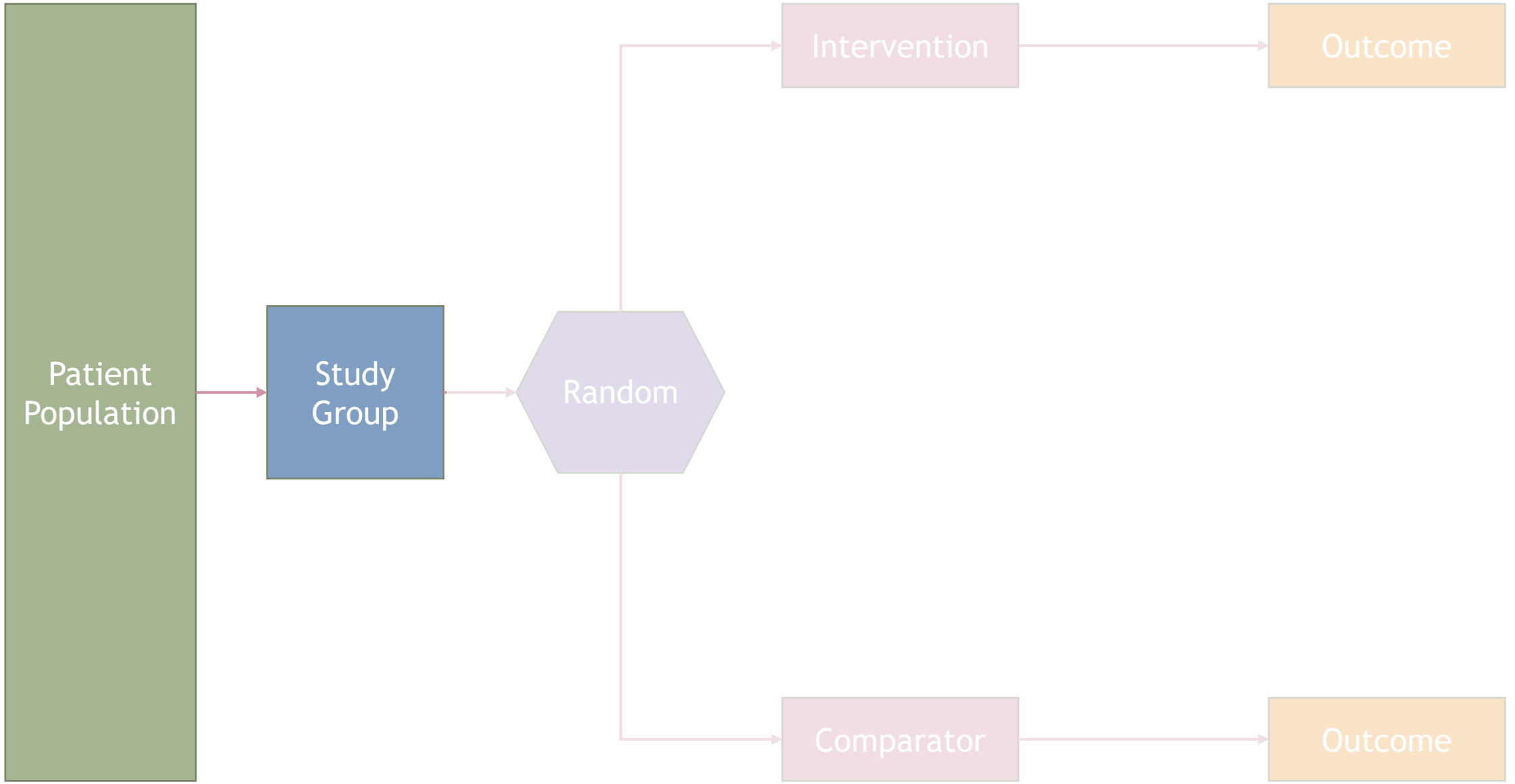

(Former) smokers 55-74 ; ≥30 pack-years
Study Group
Random
Low-Dose CT
Lung cancer Mortality
Radiographs
Lung cancer Mortality

2.
RCT: the components

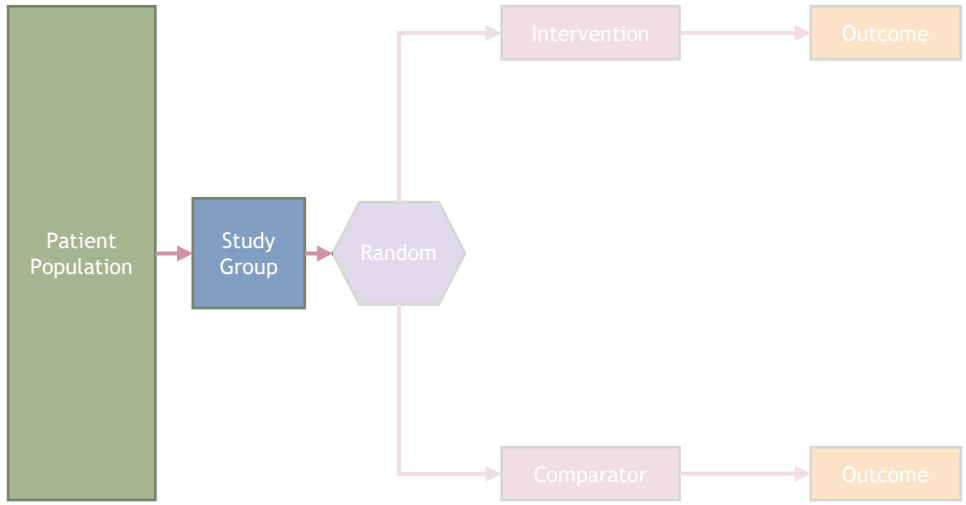
RCT

- Randomized Clinical Trial
- Randomized Controlled Trial
- Randomized Control Trial

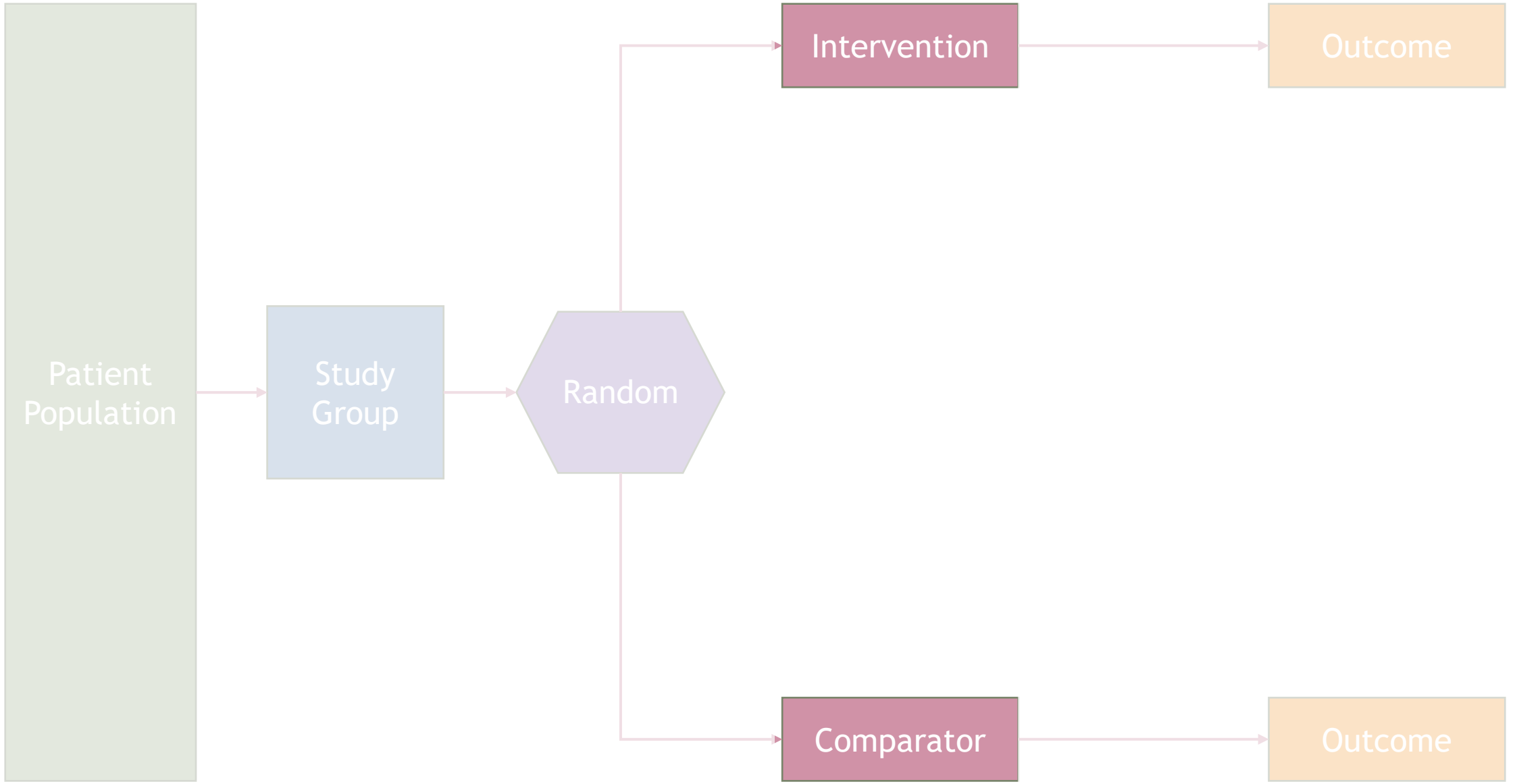

Patient Population
Study Group
Random
Intervention
Outcome
Comparator
Outcome


Patient Population
Study Group
Random
Intervention
Outcome
Comparator
Outcome

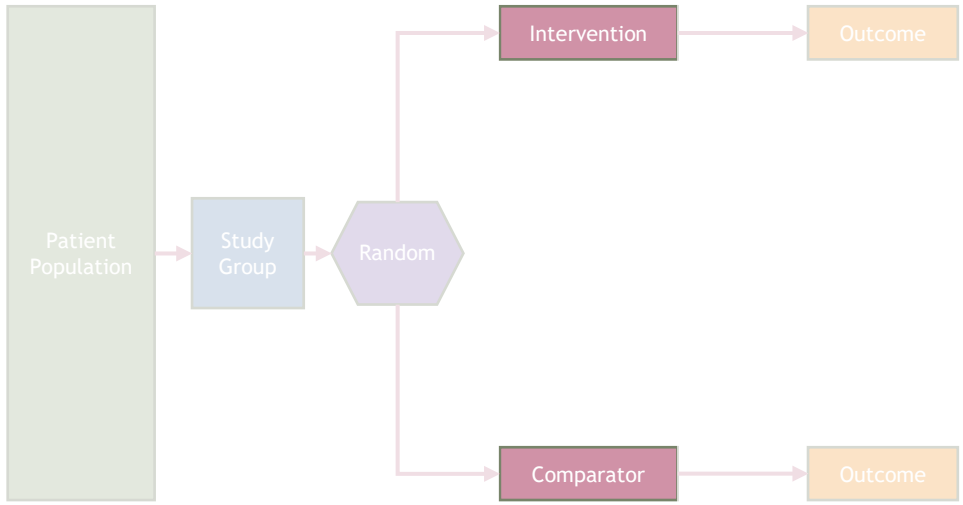
Patient Population versus Study Group



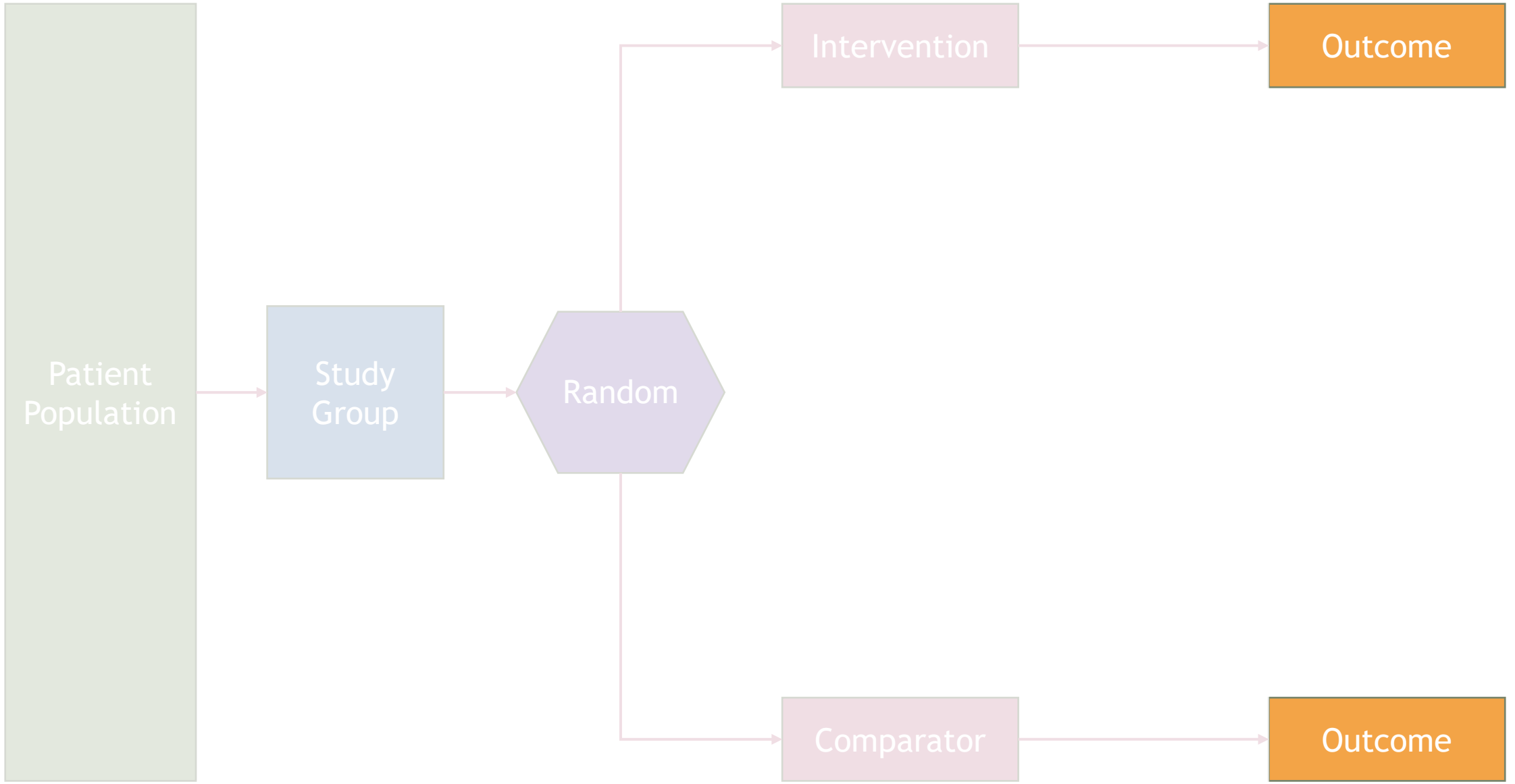
- Inclusion criteria
  - Define the *intended-use population*
- Exclusion criteria
  - Not everyone in the intended-use population can participate in trial
  - Limit membership *study group*


Patient Population
Study Group
Random
Intervention
Outcome
Comparator
Outcome

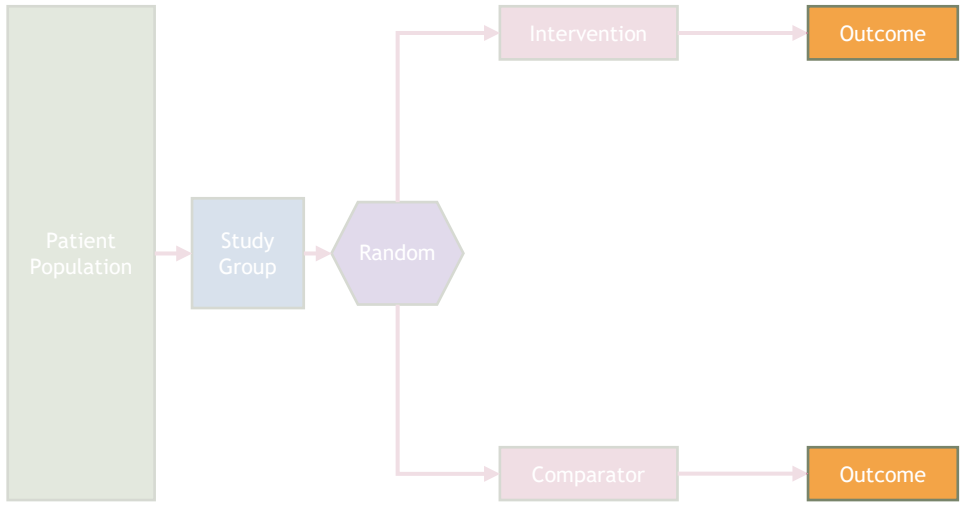
Intervention versus Comparator



- Intervention
  - Intervention under evaluation
- Comparator
  - Alternative to the intervention
  - In principle: Current best alternative / standard of care / usual care
  - Could be: No intervention at all

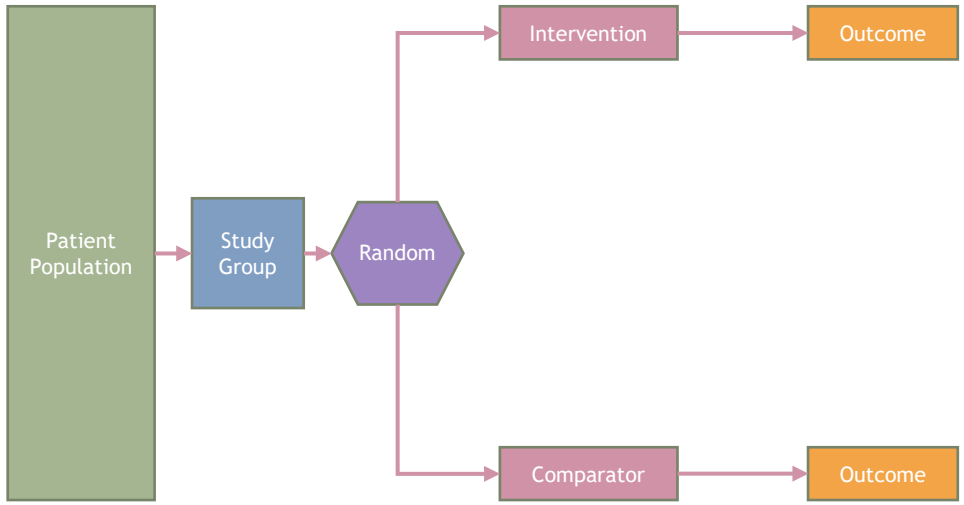

Patient Population
Study Group
Random
Intervention
Outcome
Comparator
Outcome

Outcomes



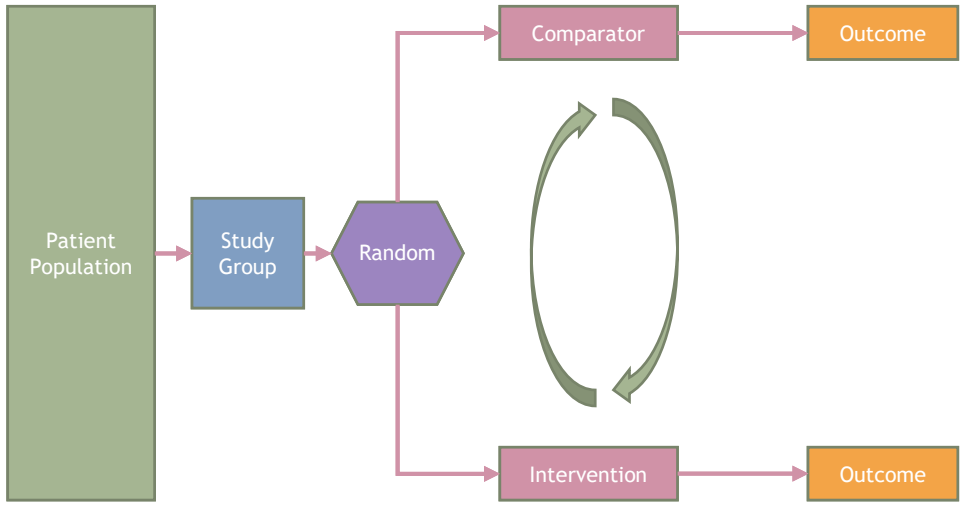
- Primary outcome
  - In principle: Health outcome that matters most to decision-makers
  - Related to “claim”
- Secondary outcomes
  - Other outcomes that matter for decision-making

Analysis



- Should help decision-making
- Focus on *effects*:
  change in outcomes from moving from comparator to intervention
- *Effect:*
  (Estimate of) change in outcomes in intended-use population, based on observations in study group

Exchangeability



- If groups had been swapped, outcomes after intervention/comparator would have been as observed
- Key assumption to infer *effect* of the intervention from an observed *difference* in outcomes between groups
- Plausible in large RCT, questionable otherwise

RCT: Another example

OPEN ACCESS

Original research

Ultra-low-dose CT versus chest X-ray for patients suspected of pulmonary disease at the emergency department: a multicentre randomised clinical trial

Inge A H van den Berk ,[1] Maadrika M N P Kanglie,[1,2] Tjitske S R van Engelen,[3] Josje Altenburg,[4] Jouke T Annema,[4] Ludo F M Beenen ,[1] Bart Boerrigter,[5] Marije K Bomers ,[6] Paul Bresser,[7] Elvin Eryigit,[8] Maarten Groenink,[9] Suzanne M R Hochheimer,[10] Frits Holleman,[3] Jos A J Kooter,[6] Ramon B van Loon ,[11] Mitran Keijzers,[12] Ivo van der Lee,[13] Paul Luijendijk,[11] Lilian J Meijboom ,[8] Saskia Middeldorp,[14] Laura J Schijf,[1] Robin Soetekouw,[15] Ralf W Sprengers,[8] Alexander D Montauban van Swijndregt,[16] Wouter de Monyé,[2] Milan L Ridderikhof ,[17] Michiel M Winter,[9] Shandra Bipat,[1] Marcel G W Dijkgraaf,[18] Patrick M M Bossuyt ,[18] Jan M Prins ,[3] Jaap Stoker,[1] on behalf of the OPTIMACT study group

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/thoraxjnl-2021-218337).

For numbered affiliations see end of article.

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JMP and JS are joint senior authors.

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ABSTRACT

Background Chest CT displays chest pathology better than chest X-ray (CXR). We evaluated the effects on health outcomes of replacing CXR by ultra-low-dose chest-CT (ULDCT) in the diagnostic work-up of patients suspected of non-traumatic pulmonary disease at the emergency department.

Methods Pragmatic, multicentre, non-inferiority randomised clinical trial in patients suspected of non-traumatic pulmonary disease at the emergency department. Between 31 January 2017 and 31 May 2018, every month, participating centres were randomly allocated to using ULDCT or CXR. Primary outcome was functional health at 28 days, measured by the Short Form (SF)-12 physical component summary scale score (PCS score), non-inferiority margin was set at 1 point. Secondary outcomes included hospital admission, hospital length of stay (LOS) and patients in follow-up because of incidental findings.

Results 2418 consecutive patients (ULDCT: 1208 and CXR: 1210) were included. Mean SF-12 PCS score at 28 days was 37.0 for ULDCT and 35.9 for CXR (difference 1.1; 95% lower CI: 0.003). After ULDCT, 638/1208 (52.7%) patients were admitted (median LOS of 4.8 days; IQR 2.1–8.8) compared with 659/1210 (54.5%) patients after CXR (median LOS 4.6 days; IQR 2.1–8.8). More ULDCT patients were in follow-up because of incidental findings: 26 (2.2%) versus 4 (0.3%).

Conclusions Short-term functional health was comparable between ULDCT and CXR, as were hospital admissions and LOS, but more incidental findings were found in the ULDCT group. Our trial does not support routine use of ULDCT in the work-up of patients suspected of non-traumatic pulmonary disease at the emergency department.

Trial registration number NTR6163.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Several studies underscore the higher diagnostic accuracy of chest CT as compared with chest X-ray (CXR), but since no patient outcome measures were collected, the effectiveness of both strategies cannot be compared.

WHAT THIS STUDY ADDS

⇒ Our randomised trial is unique in its aim to assess the yield of replacing CXR by ultra-low-dose chest-CT (ULDCT) in the diagnostic work-up of emergency department patients suspected of non-traumatic pulmonary disease in terms of patient outcomes and healthcare efficiency. We showed that ULDCT leads to functional health outcomes at 28 days that are at least similar to those obtained if management is guided by CXR, while resulting in minimal differences in hospital admission rates, length of stay and mortality rates.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE AND/OR POLICY

⇒ The results of our study enforces the current guidelines that adhere to CXR as first-line imaging technique. Future research should focus on subgroups of patients that might benefit of ULDCT.

INTRODUCTION

While chest X-ray (CXR) is a standard diagnostic procedure in patients suspected of non-traumatic pulmonary disease at the emergency department (ED), chest CT highlights chest pathology better than CXR.[1 2] Studies in patients with possible community-acquired pneumonia (CAP) and other non-traumatic pulmonary diseases have demonstrated that the diagnostic accuracy of CXR is limited.[3–6] Three studies showed CT markedly improved diagnostic accuracy, and subsequently changed diagnoses and clinical management.[4 5 7] CT also requires more radiation and increases the risk of radiation-induced cancer.[8 9] Ultra-low-dose chest-CT (ULDCT; dose <1 mSv) has overcome this disadvantage, while preserving diagnostic accuracy for many acute pulmonary diseases that present at the ED, like pneumonia and congestive heart failure.[10 11]

The use of ULDCT reduced false-positive and false-negative CXR findings with consequences for clinical management by 20% in a prospective study in an outpatient setting.[7] Yet ULDCT is still more expensive and less accessible than CXR, and incidental findings are more prevalent.[12 13] While the superior diagnostic accuracy could lead to faster detection of underlying conditions and timely initiation of effective treatment, incidental findings detected on ULDCT could also complicate healthcare processes, potentially prolonging hospital stay.[5]

The value of a diagnostic test is not expressed by its accuracy but depends on how it affects patients health.[14] New tests should only be introduced into clinical practice when they have demonstrated to impact clinical decision-making, resulting in better patient health outcomes or a simplification of the healthcare process.[15] Diagnostic imaging technologies that affect large numbers of patients and hold the potential to substantially increase healthcare costs require more extensive and more robust data on outcomes than those without these attributes.[16]

At present, there is no direct evidence that patient management in the ED guided by chest-(ULD)CT rather than CXR results in better patient outcomes or a more efficient process of care; for example, with fewer or shorter hospital admissions. We designed a multicentre non-inferiority randomised clinical trial in which we randomly allocated consenting ED patients suspected of non-traumatic pulmonary disease to either ULDCT or CXR.

The link between imaging and health outcomes is an indirect one, and superior accuracy is not guaranteed to lead to improved health outcomes.[16] We did not expect ULDCT to lead to better patient outcomes but anticipated that it would result in functional health after 28 days at least as good as obtained with CXR, hence the non-inferiority design. In addition, we hypothesised that improved detection of underlying conditions with ULDCT would lead to a more efficient healthcare process, reflected in fewer hospital admissions and a shorter hospital length of stay, compared with CXR.

METHODS

Study design

In this pragmatic, multicentre, non-inferiority randomised clinical trial we compared patient outcomes and short-term health process parameters after ULDCT to those after CXR in ED patients suspected of non-traumatic pulmonary disease. The protocol and statistical analysis plan for this trial on the OPTimal IMAging strategy in patients suspected of non-traumatic pulmonary disease at the ED: chest X-ray or CT (OPTIMACT) have been published earlier.[17 18] In short, during randomly assigned periods of one calendar month between 31 January 2017 and 31 May 2018, either ULDCT or conventional CXR was used in two participating Dutch hospitals: one university hospital (Amsterdam UMC) and one large teaching hospital (Spaarne Gasthuis).

The trial was performed according to General Data Protection Regulation and Good Clinical Practice standards. Written informed consent was provided by all study participants. This study report was prepared following the CONsolidated Standards Of Reporting Trials (CONSORT) reporting guidelines, using the extension for non-inferiority and equivalence randomised trials.[19]

Setting and participants

Eligible for inclusion were ED patients aged 18 years and older, suspected of non-traumatic pulmonary disease and requiring CXR according to the attending physician. Patients could be either self-referred or referred by a general practitioner or their treating physician at the hospital. Excluded were patients unable to undergo ULDCT or CXR, incapacitated patients, pregnant women and patients with a life expectancy less than 1 month or with other anticipated barriers to 28-days follow-up data collection; subjects could only participate once.

Study procedures

History taking, physical examination and laboratory tests were initiated by the attending physician. After setting the indication for chest imaging and acquiring informed consent, the attending physician provided a working diagnosis on the structured and standardised radiology request form. This was followed by either ULDCT or CXR, according to the imaging method allocated to the month of presentation. If the clinical question was not adequately answered after obtaining the CXR or ULDCT, standard additional imaging (eg, chest CT with intravenous contrast medium, CT pulmonary angiography) was performed. If there was a high suspicion of pulmonary emboli at ED admission, patients directly underwent a CT pulmonary angiography, in accordance with regular clinical practice. The technical aspects of the imaging methods can be found in the study protocol paper and online supplemental text S1.[17]

Radiologists used a structured standardised report to optimise and standardise reading. Reading and reporting was performed or supervised by the radiologist on call at the time of clinical management, also outside office hours. The ULDCT and CXR were read with prior imaging if available. To increase inter-reader consistency, the residents and radiologist less experienced in the field of chest imaging were supervised by a group of seven radiologists with a subspecialty in chest imaging. The attending physician subsequently formulated an ED discharge diagnosis. Decisions on additional imaging, treatment, hospital admission and discharge were at the discretion of the attending physician, according to national guidelines, if applicable.

Data collection

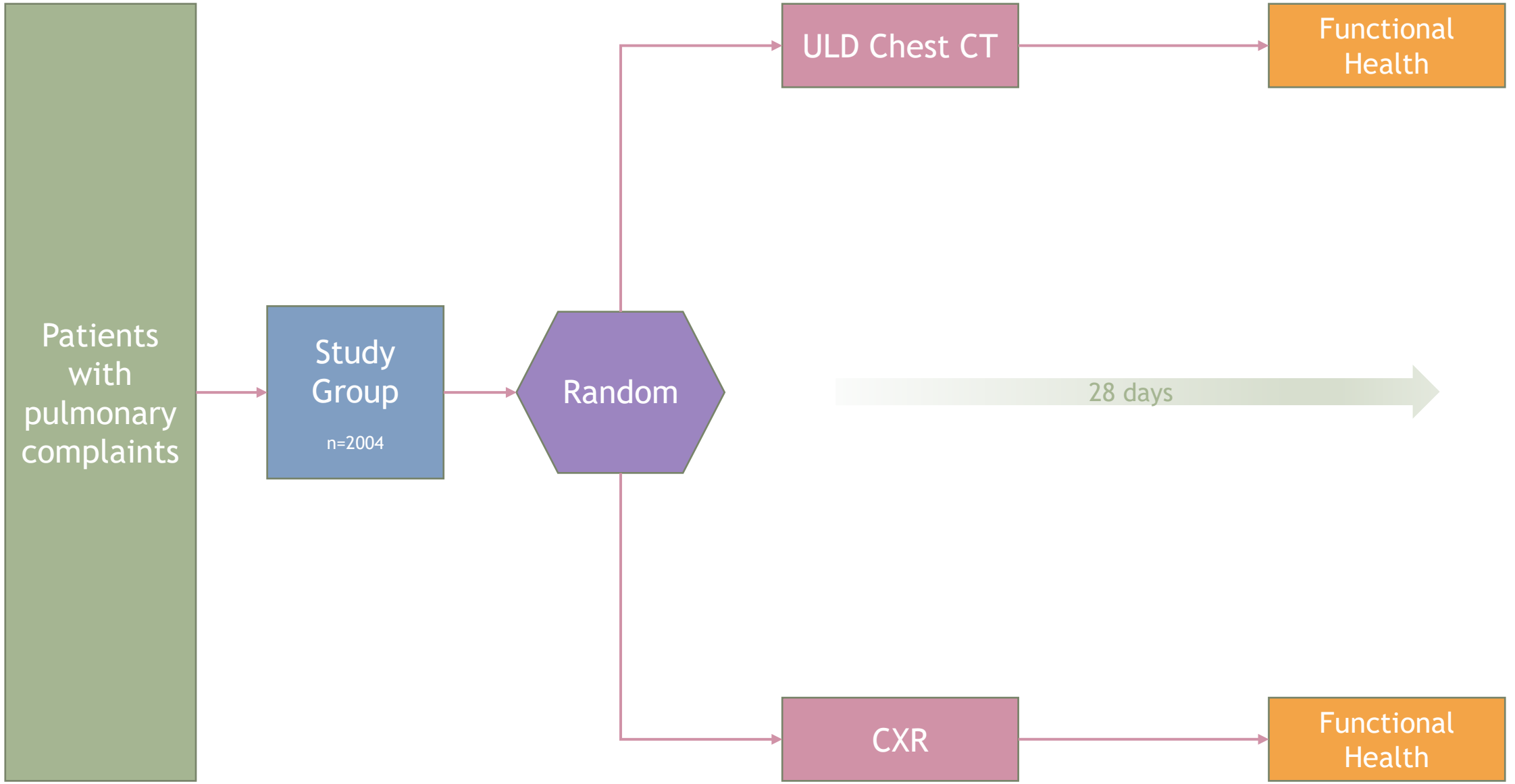
Baseline ED data included medical history and physical examination, laboratory, microbiological and radiological test results, diagnosis at ED discharge, prescription of antibiotics or diuretics and hospital admission. Follow-up data after ED discharge included disease course, treatment outcome, additional imaging, hospital length of stay, mortality up to day 28 and patients in follow-up after day 28 because of incidental findings. All data were obtained from electronic patient records.

Whenever necessary, additional information was obtained from general practitioners, nursing wards, outpatient clinics or hospitals where patients had been transferred or referred to. Twenty-eight days after ED presentation study participants received the Short Form (SF)-12 questionnaire; the questionnaires were available in Dutch and English and in electronic and paper form. We prompted with frequent reminders to ensure maximum response.

We assigned one or more final diagnoses after 28 days of follow-up, based on a review of all clinical, radiological and microbiological data available. For this purpose, a diagnostic handbook was developed enabling standardised and reproducible categorisation for 32 diagnoses. More details on the methodology of the handbook, its evaluation and validation are

Clinical Question: PICO format

- P: Patients with Non-traumatic Pulmonary Complaints
- I: ULD Chest CT
- C: Chest X-ray
- O: Primary: Functional Health at 28 Days
  Secondary: Process of Care


Patients with pulmonary complaints
Study Group
n=2004
Random
ULD Chest CT
Functional Health
28 days
CXR
Functional Health

Ah, Language….

- Outcome — Functional Health
- Outcome Measure — SF-12 Physical score
- Effect — Better Functional Health
- Effect Measure — Difference in Mean Score SF-12 at 28 days
- Endpoint — Event that marks the end-of-follow up
  (not in this RCT)
  (often used to refer to one of the above)

3.
Observational Studies

Or Clinical Studies

What is a Clinical Trial?

NIH Definition of a Clinical Trial

A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.

National Institutes of Health

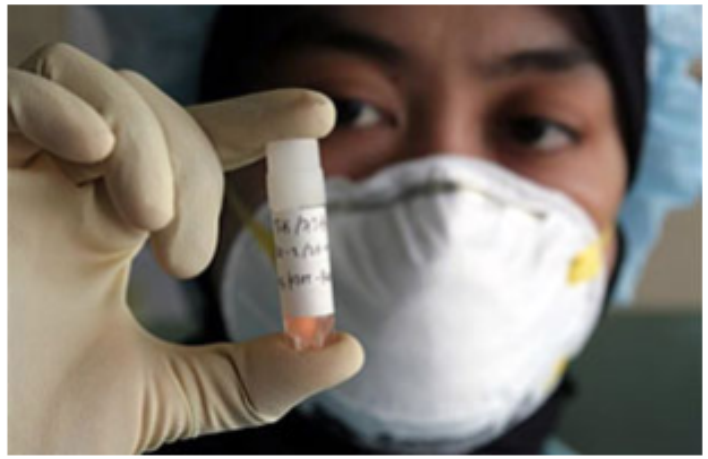
Use the following four questions to determine the difference between a clinical study and a clinical trial:

1. Does the study involve human participants?
2. Are the participants prospectively assigned to an intervention?
3. Is the study designed to evaluate the effect of the intervention on the participants?
4. Is the effect being evaluated a health-related biomedical or behavioral outcome?

World Health Organization

Health topics

Clinical trials



WHO/G. Hampton

For the purposes of registration, a clinical trial is any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes.

Interventions include but are not restricted to drugs, cells and other biological products, surgical procedures, radiological procedures, devices, behavioural treatments, process-of-care changes, preventive care, etc.

Observational Clinical Study

- In an observational study, investigators assess health outcomes in groups of participants according to a research plan or protocol.

- Participants may receive interventions or procedures as part of their routine medical care, but participants are not assigned to specific interventions by the investigator (as in a clinical trial).

NIH U.S. National Library of Medicine
ClinicalTrials.gov

Radiology

Breast MR Imaging before Surgery: Outcomes in Patients with Invasive Lobular Carcinoma by Using Propensity Score Matching[1]

Su Min Ha, MD
Eun Young Chae, PhD
Joo Hee Cha, PhD
Hak Hee Kim, PhD
Hee Jung Shin, PhD
Woo Jung Choi, PhD

Purpose: To investigate the association between preoperative breast magnetic resonance (MR) imaging and surgical outcomes in patients with invasive lobular carcinoma (ILC) to decide whether MR examination is beneficial in the ILC subtype of breast cancer.

Materials and Methods: The authors identified 603 patients with ILC who underwent surgery between January 2005 and December 2016. Of the 603 patients, 369 (61.2%) underwent MR imaging. The authors calculated the MR detection rate of additional lesions that were occult at mammography and ultrasonography and analyzed any alterations in surgical management.

[1] From the Department of Radiology, Research Institute of Radiology, Chung-Ang University Hospital, Seoul, Korea (S.M.H.); and Department of Radiology, Research Institute of Radiology, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic-ro 43 gil, Songpa-gu, Seoul 05505, Korea (E.Y.C., J.H.C., H.H.K., H.J.S., W.J.C.). Received June 23, 2017; revision requested September 7; revision received December 3; final version accepted December 8. **Address correspondence to** E.Y.C. (e-mail: *chaeey@amc.seoul.kr*).

Invasive lobular carcinoma (ILC) is the second most common histopathologic subtype of breast cancer and accounts for approximately 5%–15% of all breast cancer (1). The incidence of ILC is increasing, especially in post-

It is important to identify the subpopulations in which breast MR imaging may be most beneficial. A recent study (11) reported that surgeons often recommend breast MR imaging for patients at higher risk of younger

MR Imaging Technique

Patients underwent dynamic contrast material–enhanced MR imaging with either a 1.5- or 3.0-T imager (MagnetomAvanto or Skyra, Siemens Medical

retrospective design.

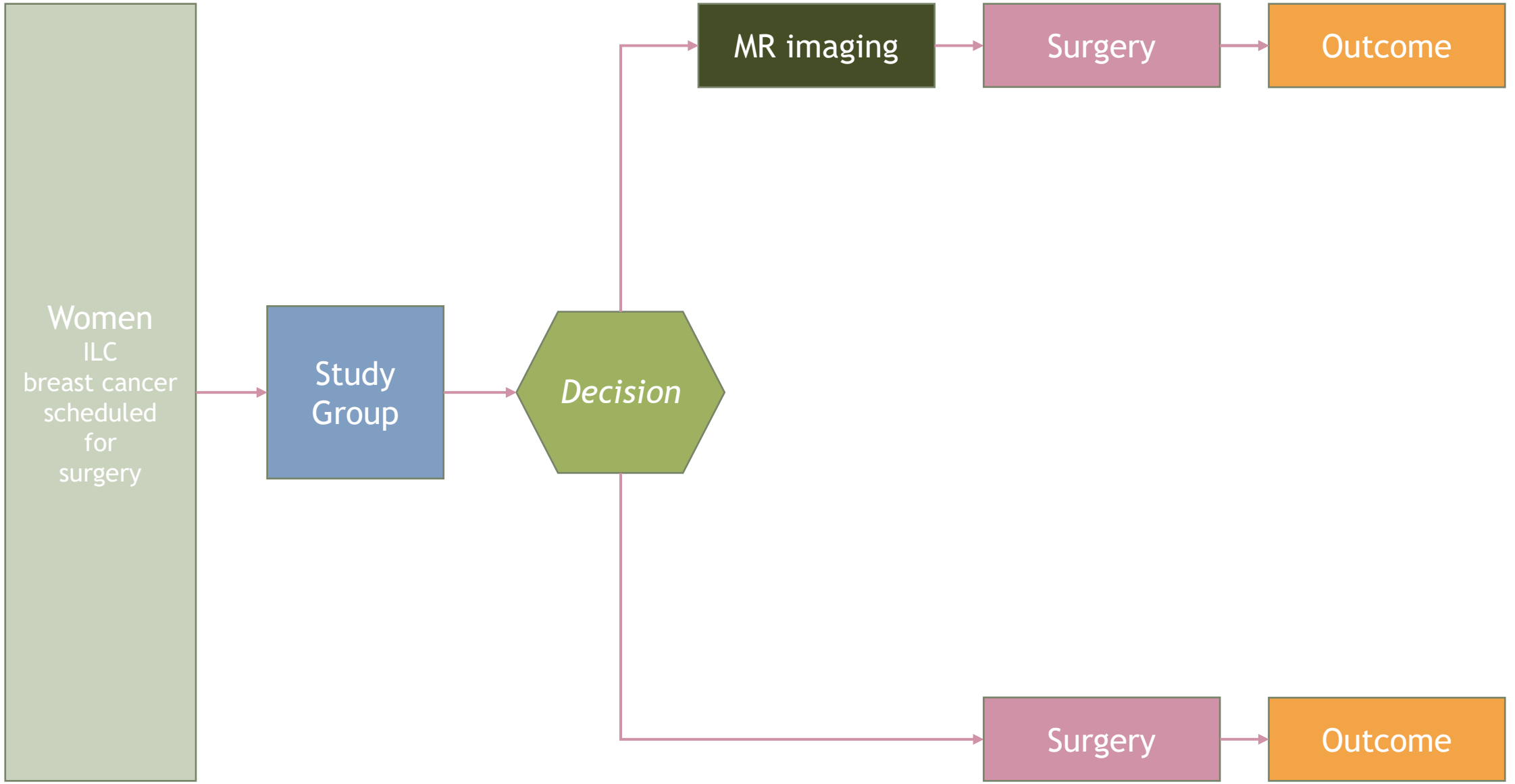
Implication for Patient Care

- Preoperative breast MR imaging depicts additional malignant foci and reduces the chances of repeat surgery, without increasing the rate of mastectomy, in patients with invasive lobular carcinoma.

the cohort to women in whom either breast-conserving surgery or mastectomy was likely to be considered. Ultimately, we analyzed a series of 603 patients with ILC (age range, 31–82 years; mean age, 50.6 years). Of these 603 patients, 369 (61.2%) had undergone preoperative breast MR imaging (MR imaging group) and 234 (38.8%) had not (non–MR imaging group).

concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, S.M.H., E.Y.C., H.H.K.; clinical studies, all authors; experimental studies, S.M.H., W.J.C.; statistical analysis, S.M.H., E.Y.C.; and manuscript editing, S.M.H., E.Y.C., J.H.C., H.H.K., H.J.S.

Conflicts of interest are listed at the end of this article.

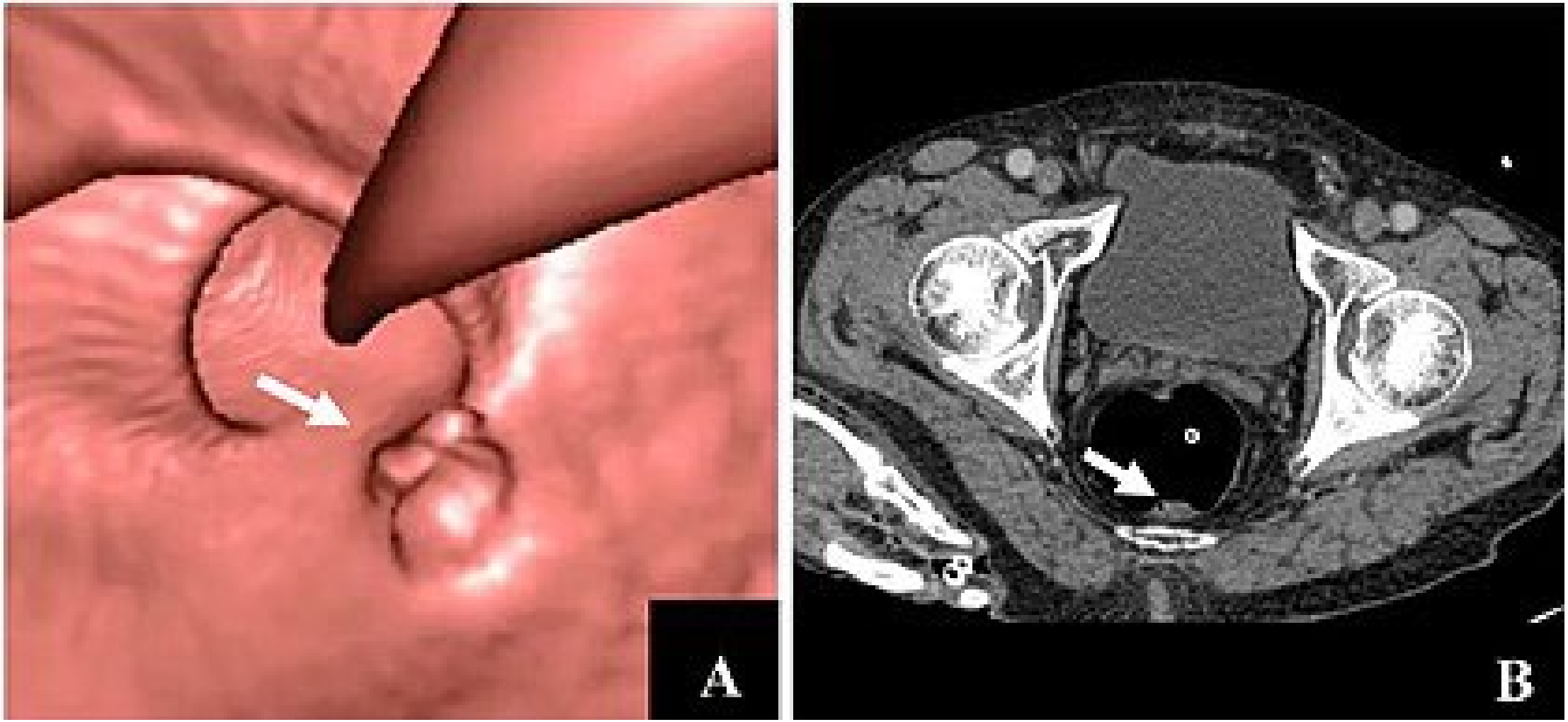

Women
ILC
breast cancer
scheduled
for
surgery
Study
Group
Decision
MR imaging
Surgery
Outcome
Surgery
Outcome

Clinical Question: PICO format

- P: Women with Invasive Lobular Carcinoma
- I: Pre-operative Breast MR
- C: Pre-operative Breast MR
- O: Repeat Surgery

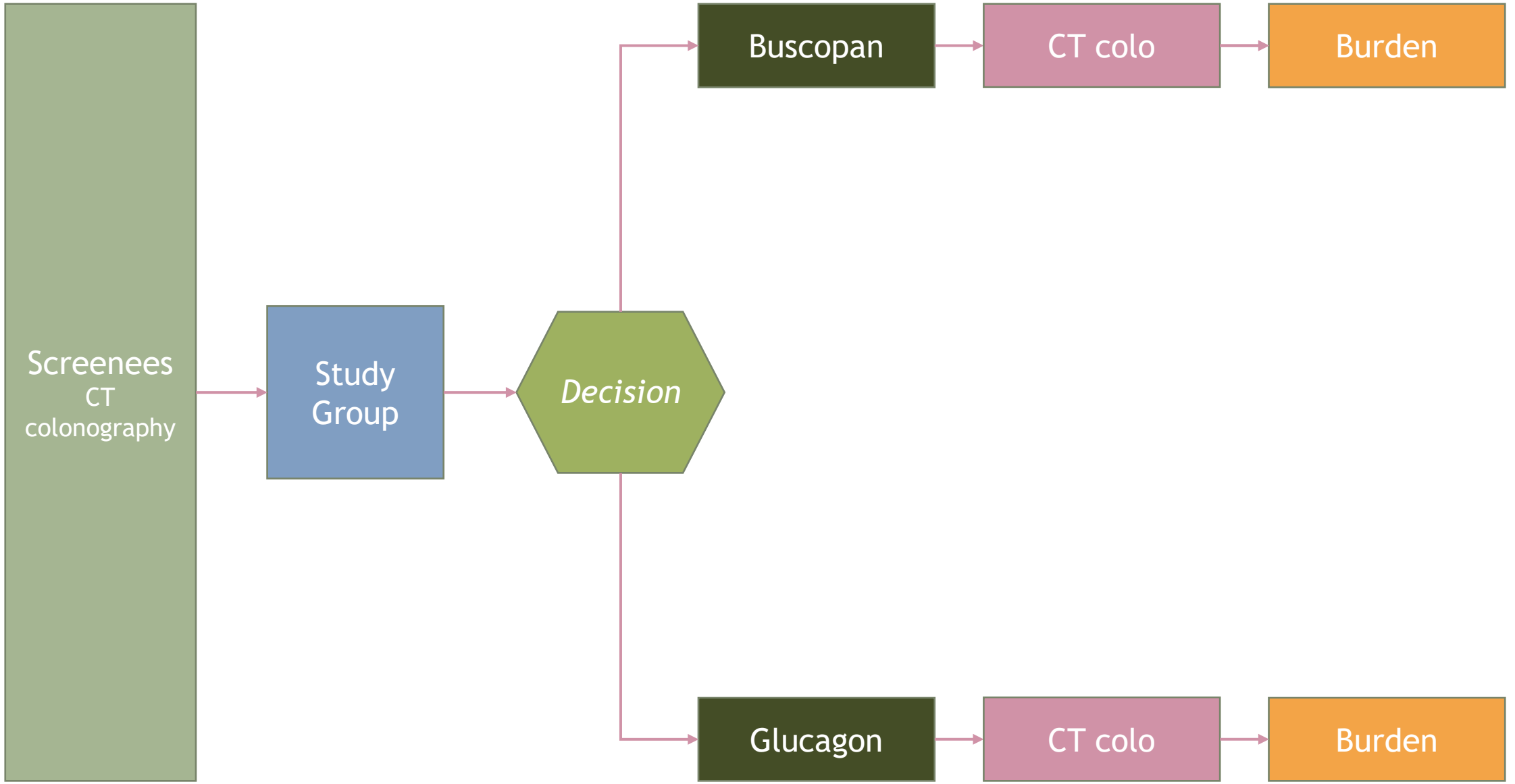
3.
Non-Randomized Clinical Trials (nRCT)

An example:
CT colonography Screening Trial

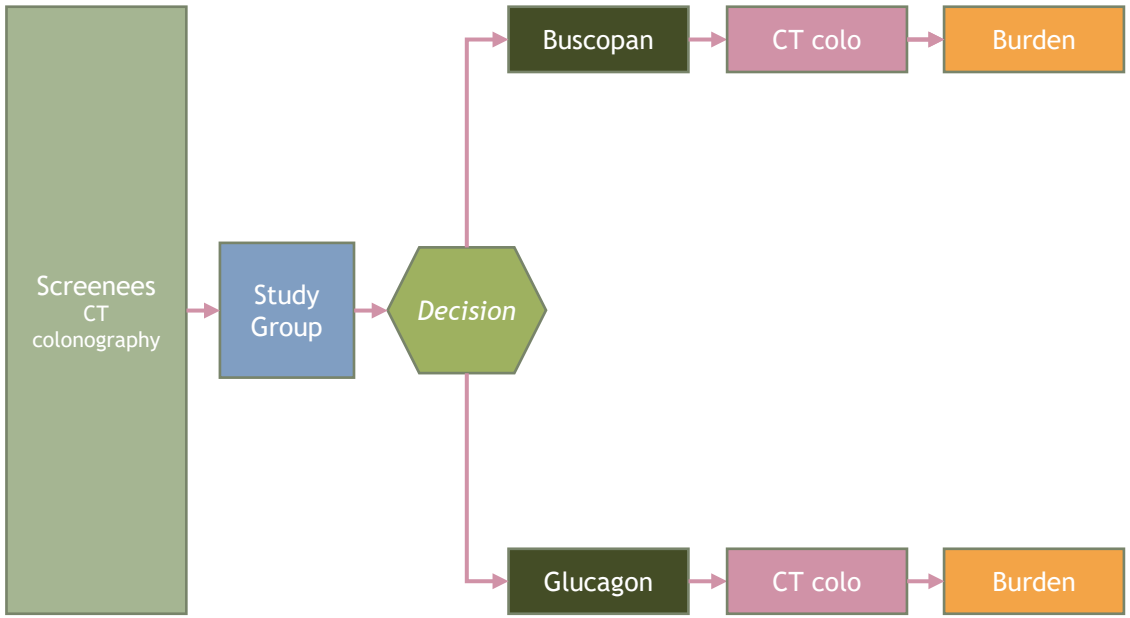


Clinical Question: PICO format

- P: Persons undergoing screening CT colonography
- I: Buscopan as bowel relaxant
- C: Glucagon as bowel relaxant
- O: Experienced burden


Screenees
CT
colonography
Study
Group
Decision
Buscopan
CT colo
Burden
Glucagon
CT colo
Burden

Exchangeability



- If groups had been swapped, outcomes after intervention/comparator would have been as observed
- Key assumption to infer *effect* of the intervention from an observed *difference* in outcomes between groups
- Plausible in large RCT, questionable otherwise

4.
Single-Arm Clinical Trial

Radiology

Diffusion-weighted MRI Findings Predict Pathologic Response in Neoadjuvant Treatment of Breast Cancer: The ACRIN 6698 Multicenter Trial

Savannah C. Partridge, PhD • Zheng Zhang, PhD • David C. Newitt, PhD • Jessica E. Gibbs, BA • Thomas L. Chenevert, PhD • Mark A. Rosen, MD, PhD • Patrick J. Bolan, PhD • Helga S. Marques, MS • Justin Romanoff, MA • Lisa Cimino, RT • Bonnie N. Joe, MD, PhD • Heidi R. Umphrey, MD • Haydee Ojeda-Fournier, MD • Basak Dogan, MD • Karen Oh, MD • Hiroyuki Abe, MD, PhD • Jennifer S. Drukteinis, MD • Laura J. Esserman, MD, MBA • Nola M. Hylton, PhD • For the ACRIN 6698 Trial Team and I-SPY 2 Trial Investigators

From the Department of Radiology, University of Washington, 825 Eastlake Ave E, G2-600, Seattle, WA 98109 (S.C.P.); Department of Biostatistics (Z.Z.) and Center for Statistical Sciences (Z.Z., H.S.M., J.R.), Brown University, Providence, RI; American College of Radiology Imaging Network (ACRIN), Reston, Va (Z.Z., H.S.M., J.R.); Department of Radiology and Biomedical Imaging, University of California, San Francisco, San Francisco, Calif (D.C.N., J.E.G., B.N.J., L.J.E., N.M.H.); Department of Radiology/MRI, University of Michigan, Ann Arbor, Mich (T.L.C.); Department of Radiology, University of Pennsylvania, Philadelphia, Pa (M.A.R.); Department of Radiology, Center for Magnetic Resonance Research, University of Minnesota, Minneapolis, Minn (P.J.B.); American College of Radiology and ECOG-ACRIN Cancer Research Group, Reston, Va (L.C.); Department of Radiology, University of Alabama, Birmingham, Birmingham, Ala (H.R.U.); Department of Radiology, University of California, San Diego, San Diego, Calif (H.O.); Department of Radiology, University of Texas MD Anderson Cancer Center, Houston, Tex and the University of Texas Southwestern Medical Center, Dallas, Tex (B.D.); Department of Radiology, Oregon Health and Science University, Portland, Ore (K.O.); Department of Radiology, University of Chicago, Chicago, Ill (H.A.); and Department of Diagnostic Radiology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, Fla and Department of Women's Imaging, St Joseph's Women's Hospital, Tampa, Fla (J.S.D.).
Received February 8, 2018; revision requested March 28; final revision received July 12; accepted July 18. **Address correspondence to** S.C.P. (e-mail: *scp3@uw.edu*).

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Conflicts of interest are listed at the end of this article.

See also the editorial by deSouza in this issue.

Radiology 2018; 289:618–627 • https://doi.org/10.1148/radiol.2018180273 • Content codes: BR MR OI

Purpose: To determine if the change in tumor apparent diffusion coefficient (ADC) at diffusion-weighted (DW) MRI is predictive of pathologic complete response (pCR) to neoadjuvant chemotherapy for breast cancer.

Materials and Methods: In this prospective multicenter study, 272 consecutive women with breast cancer were enrolled at 10 institutions (from August 2012 to January 2015) and were randomized to treatment with 12 weekly doses of paclitaxel (with or without an experimental agent), followed by 12 weeks of treatment with four cycles of anthracycline. Each woman underwent breast DW MRI before treatment, at early treatment (3 weeks), at midtreatment (12 weeks), and after treatment. Percentage change in tumor ADC from that before treatment (ΔADC) was measured at each time point. Performance for predicting pCR was assessed by using the area under the receiver operating characteristic curve (AUC) for the overall cohort and according to tumor hormone receptor (HR)/human epidermal growth factor receptor 2 (HER2) disease subtype.

Results: The final analysis included 242 patients with evaluable serial imaging data, with a mean age of 48 years ± 10 (standard deviation); 99 patients had HR-positive (hereafter, HR+)/HER2-negative (hereafter, HER2-) disease, 77 patients had HR-/HER2- disease, 42 patients had HR+/HER2+ disease, and 24 patients had HR-/HER2+ disease. Eighty (33%) of 242 patients experienced pCR. Overall, ΔADC was moderately predictive of pCR at midtreatment/12 weeks (AUC = 0.60; 95% confidence interval [CI]: 0.52, 0.68; $P = .017$) and after treatment (AUC = 0.61; 95% CI: 0.52, 0.69; $P = .013$). Across the four disease subtypes, midtreatment ΔADC was predictive only for HR+/HER2- tumors (AUC = 0.76; 95% CI: 0.62, 0.89; $P < .001$). In a test subset, a model combining tumor subtype and midtreatment ΔADC improved predictive performance (AUC = 0.72; 95% CI: 0.61, 0.83) over ΔADC alone (AUC = 0.57; 95% CI: 0.44, 0.70; $P = .032$.).

Conclusion: After 12 weeks of therapy, change in breast tumor apparent diffusion coefficient at MRI predicts complete pathologic response to neoadjuvant chemotherapy.

Online supplemental material is available for this article.

Diffusion-weighted (DW) MRI, a functional imaging technique reflecting water diffusion properties in tissue, holds strong potential to reveal early pathologic changes in tumors responding to therapy. Specifically, the apparent diffusion coefficient (ADC) measured at DW MRI, which reflects cellularity and interstitial water mobility, has shown promise as an imaging biomarker to measure early tumor response to treatment (1). Cytotoxic effects of chemotherapy cause cell lysis, alterations in cell membrane permeability, and increases in extracellular space, which lead to a less restrictive environment for water to diffuse. Therefore, it has been hypothesized that an increase in tumor ADCs may reflect favorable treatment response earlier than detectable changes in tumor size.

Change in tumor ADC with treatment has been investigated in a variety of malignancies, including breast cancer (2). Results of prior studies have demonstrated that breast tumor ADCs can significantly differentiate patients who respond to treatment from those who do not (3–5) and predict pathologic response (6–9). However, reports have been variable as to the utility of DW MRI for monitoring therapy (10–12), and authors of a recent meta-analysis identified wide heterogeneity in approach and findings across 15 studies, concluding that further investigation in the form of well-designed large-scale multicenter clinical trials is needed to validate ADC as a predictive biomarker of therapeutic efficacy in breast cancer (13).

The American College of Radiology Imaging Network (ACRIN) trial 6698, Diffusion Weighted MR Imaging Biomarkers for Assessment of Breast Cancer Response to Neoadjuvant Treatment (14), is a multicenter study to evaluate the effectiveness of quantitative DW MRI for assessing breast cancer response to chemotherapy, performed as a substudy to the ongoing I-SPY 2 (Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging and Molecular analysis 2) trial to identify more effective breast cancer treatments (15–17).

Although there have been numerous promising single-center studies, DW MRI has not previously been validated as a reliable biomarker of breast cancer response to therapy in a prospective multicenter clinical trial. Therefore, the primary objective of ACRIN 6698 was to test the hypothesis that change in tumor ADC at DW MRI is predictive of pathologic complete response (pCR) in women undergoing neoadjuvant chemotherapy for breast cancer. A secondary aim was to investigate the combined predictive value of ADC and dynamic contrast material–enhanced (DCE) MRI-derived functional tumor volume (FTV) measures.

Abbreviations

ACRIN = American College of Radiology Imaging Network, ADC = apparent diffusion coefficient, AUC = area under the receiver operating characteristic curve, CI = confidence interval, DCE = dynamic contrast enhanced, DW = diffusion weighted, FDA = Food and Drug Administration, FTV = functional tumor volume, HER2 = human epidermal growth factor receptor 2, HR = hormone receptor, I-SPY 2 = Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging and Molecular Analysis 2, pCR = pathologic complete response, ROI = region of interest

Summary

Change in apparent diffusion coefficient at diffusion-weighted MRI after 12 weeks of therapy is a noninvasive and quantitative imaging biomarker of response in women undergoing neoadjuvant chemotherapy for breast cancer.

Implications for Patient Care

- Diffusion-weighted MRI depicts the cytotoxic effects of chemotherapy in breast tumors.
- Greater increases in tumor apparent diffusion coefficient after 12 weeks of chemotherapy predict pathologic response and higher likelihood of pathologic complete response.
- Diffusion-weighted MRI may enable objective assessment of therapeutic efficacy, particularly for hormone receptor–positive, human epidermal growth factor receptor 2–negative disease.

Materials and Methods

Subject Eligibility and Enrollment

In this prospective Health Insurance Portability and Accountability Act–compliant multi-institution study, consecutive subjects who were enrolled in I-SPY 2 at sites that met DW MRI qualification requirements were also co-enrolled in the ACRIN 6698 imaging trial (*ClinicalTrials.gov:* NCT01564368 [14]). Patients eligible for I-SPY 2 included women 18 years of age or older with invasive breast tumors 2.5 cm or larger at clinical examination or imaging who were planning to undergo neoadjuvant chemotherapy. Patients with evidence of distant metastasis were excluded, and those found to have low-risk disease did not proceed to the treatment arm of I-SPY 2. Low-risk disease was defined as hormone receptor (HR)-positive (hereafter, HR+)/human epidermal growth factor receptor 2 (HER2)-negative (hereafter, HER2-) disease or disease with a low-risk profile at MammaPrint testing (Agendia; Irvine, Calif). Both the I-SPY 2 and ACRIN 6698 protocols were approved by institutional review boards at all participating sites, and all subjects gave written informed consent by using a single combined consent form. Six patients in our study overlapped with those of two prior I-SPY 2 trial publications reporting promising efficacy of supplemental neratinib and veliparib-carboplatin treatments in select cancer subtypes (15,16).

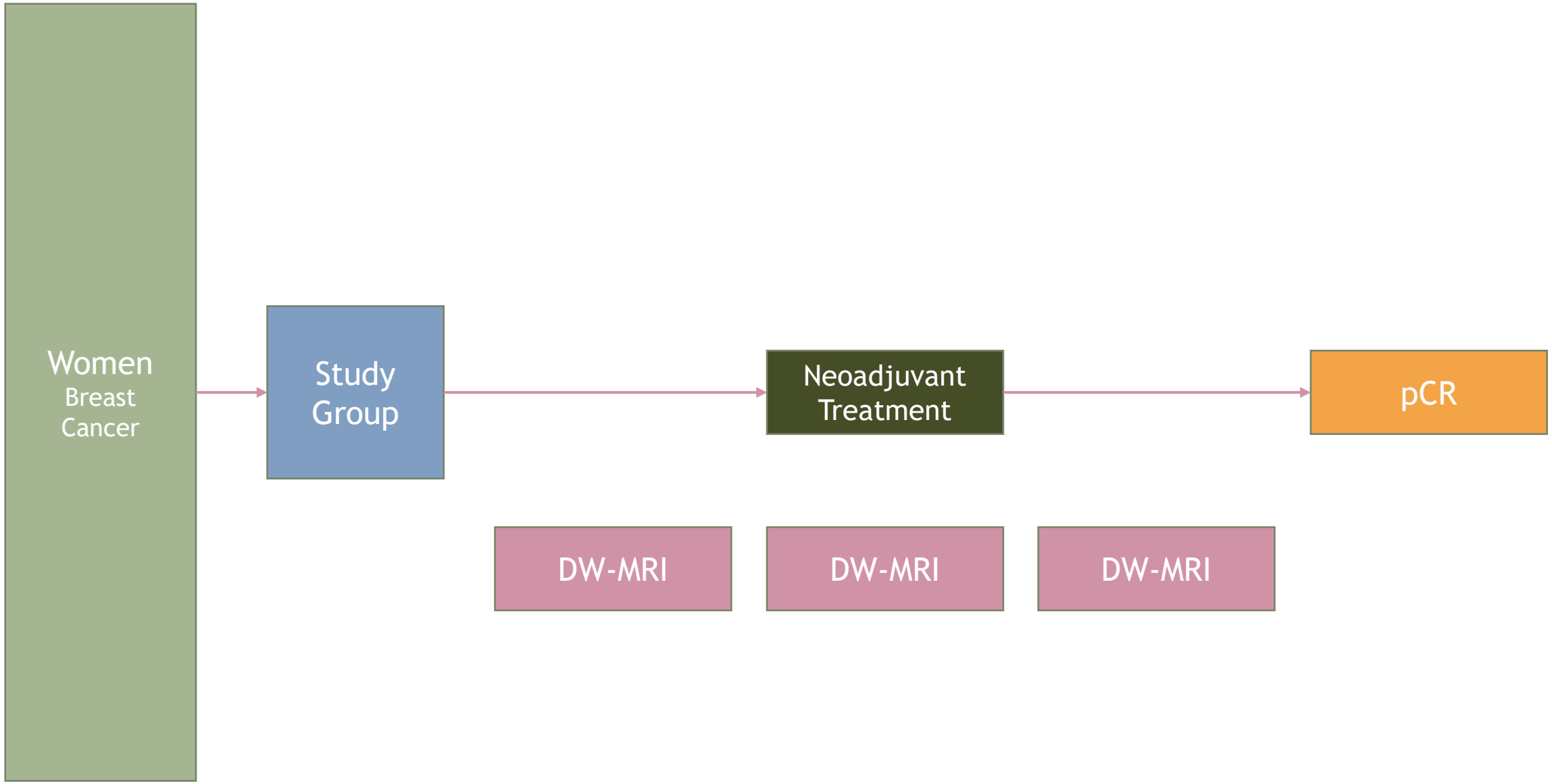
MRI examinations with DW MRI were performed before treatment, during early treatment (after three weekly doses of paclitaxel/taxane-based therapy), at midtreatment (12 weeks, between taxane and anthracycline regimens), and after treatment after all chemotherapy, prior to surgery. Our study schema is shown in Figure 1a.

Site Qualification

Each MRI system used in the ACRIN 6698 study was required to pass a DW MRI qualification process incorporating assessment of both phantom and patient studies, as described in detail in Appendix E1 (online).

MRI Acquisition

MRI was performed by using a 1.5- or 3.0-T field strength magnet and a dedicated breast radiofrequency coil. The standardized image acquisition protocol included T2-weighted, DW, and DCE MRI sequences performed bilaterally in the axial orientation (18); imaging parameters for each sequence are provided in Table E1 (online). DW MRI was performed before DCE MRI by using a DW single-shot echo planar imaging sequence with parallel imaging (reduction factor, two or greater); fat suppression; a repetition time of greater than 4000 msec; echo time minimum; flip angle, 90°; field of view, 300–360 mm; acquired matrix, 128 × 128 to 192 × 192; in-plane resolution, 1.7–2.8 mm; section thickness, 4–5 mm; and imaging time, 5 or fewer minutes. Diffusion gradients were applied in three orthogonal directions by using diffusion weightings (b values) of 0, 100, 600, and 800 sec/mm^2. No respiratory triggering or other motion compensation methods were used. T2-weighted imaging was performed by using a two-dimensional fast spin-echo or a short inversion time inversion recovery sequence (repetition time msec/echo time msec, 2000–10 000/70–140; flip angle, 90°; in-plane resolution, ≤1.4 mm; section thickness, ≤4 mm; gap, ≤1 mm; and imaging time, ≤7 minutes). DCE MRI was performed by using a three-dimensional fat-suppressed T1-weighted gradient-echo sequence with the following parameters: repetition time,


Women
Breast
Cancer
Study
Group
Neoadjuvant
Treatment
pCR
DW-MRI
DW-MRI
DW-MRI

Single-Arm Trial Also Comparative

Compare participants with large change versus no or small change
DW-MRI assigned, but changes are not: observed

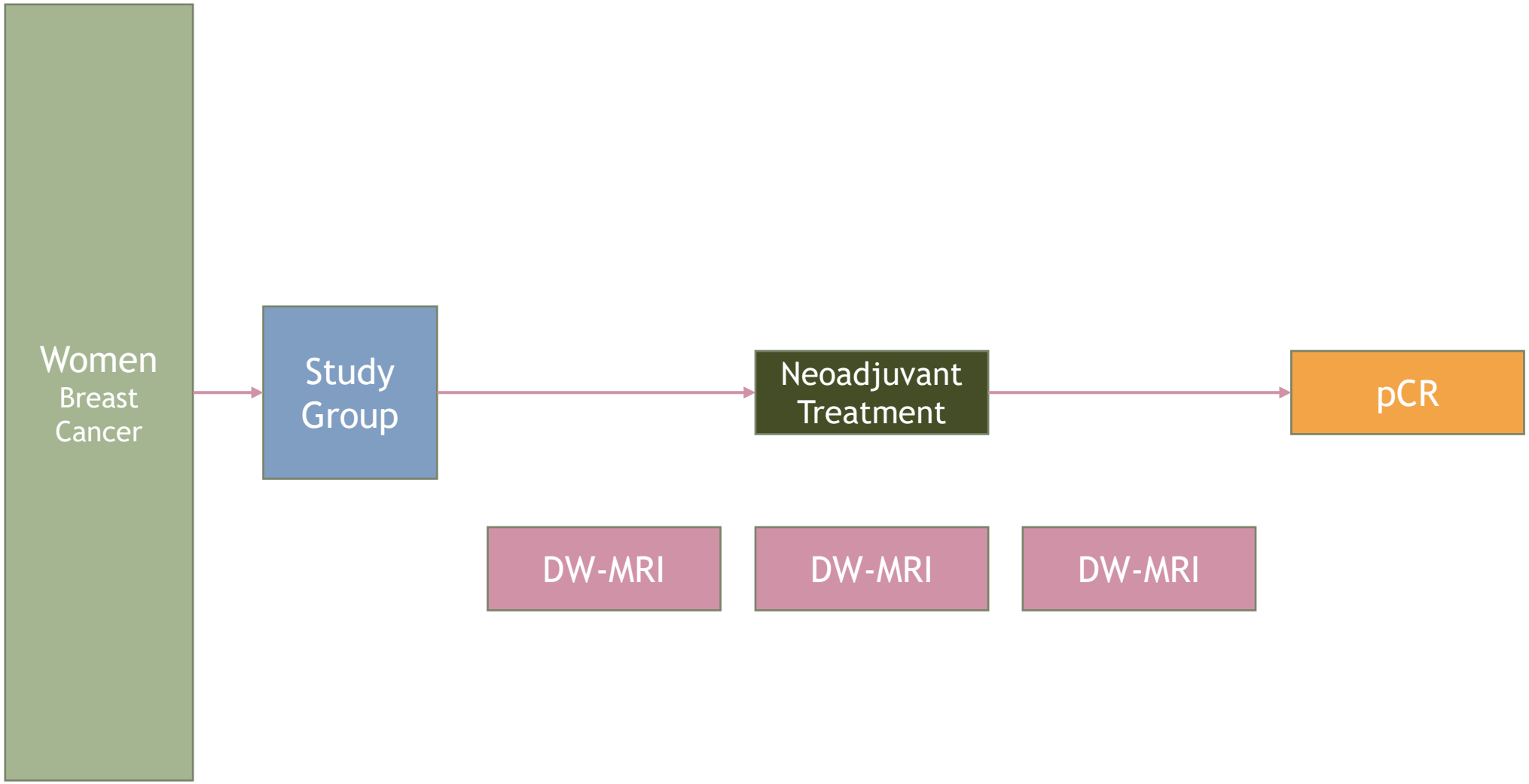
Almost All Clinical Trials and Studies Comparative

Compare Outcomes in Patients With/Without Feature

Almost All Clinical Trials and Studies Comparative

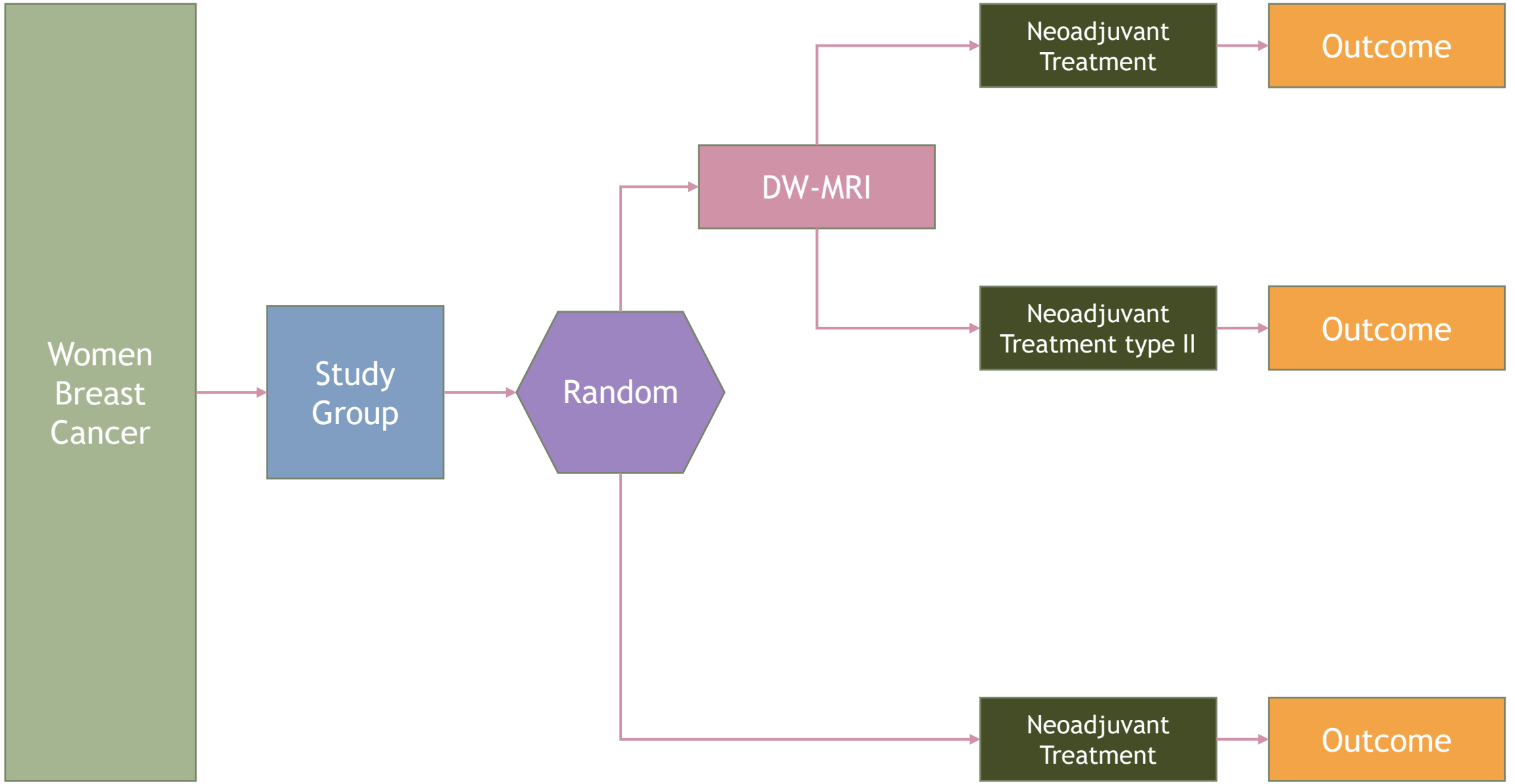
Compare Outcomes in Patients With/Without Feature

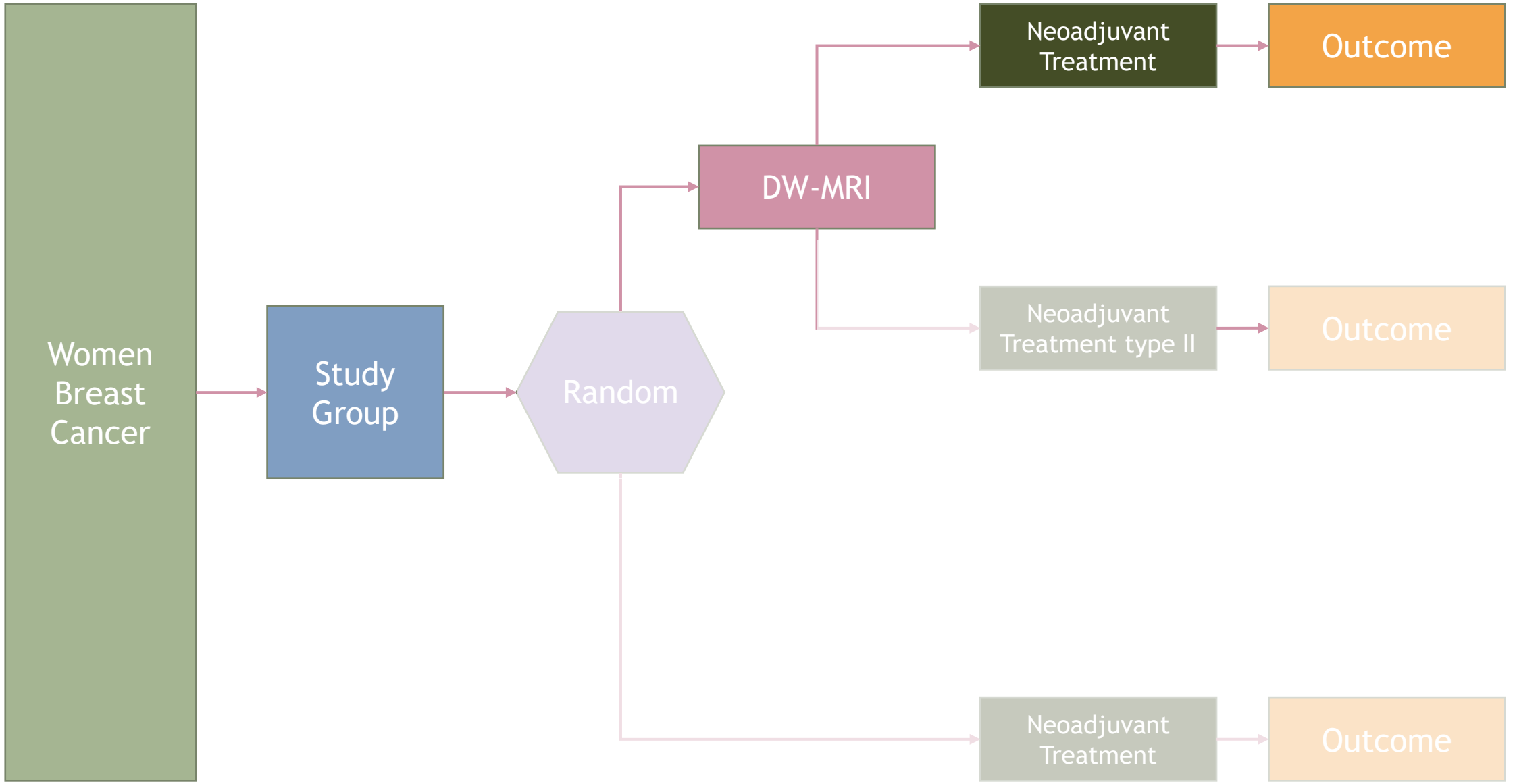
How Would Single-arm Trial Help Decisions?



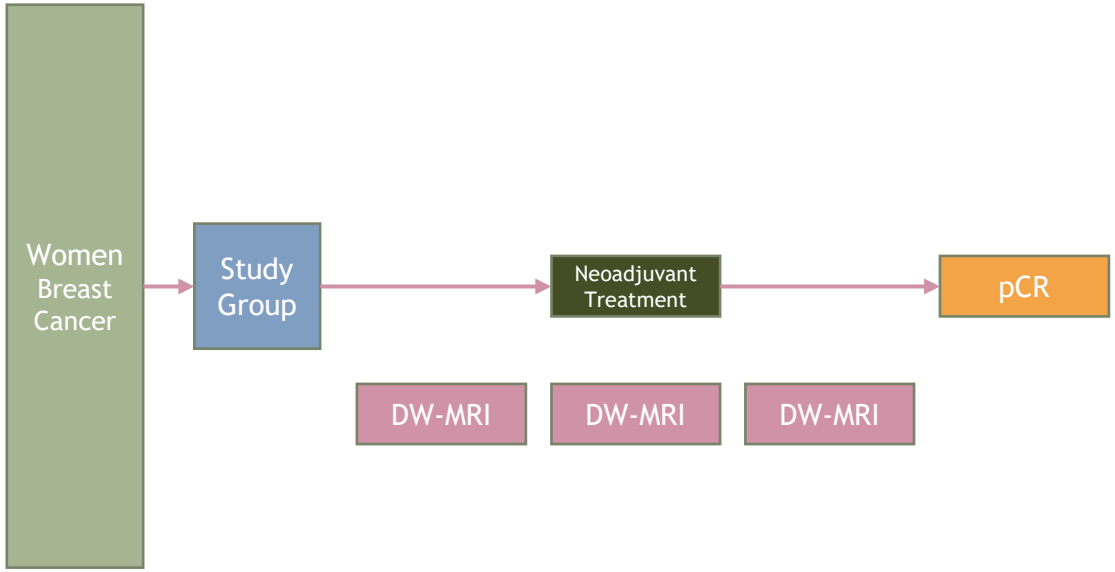
Clinical Question: PICO format

- P: Women with Breast Cancer undergoing neoadjuvant chemotherapy
- I: Mid-Treatment Diffusion-Weighted MRI
- C: No Mid-Treatment Diffusion-Weighted MRI
- O: Patient Outcome


Women Breast Cancer
Study Group
Random
DW-MRI
Neoadjuvant Treatment
Outcome
Neoadjuvant Treatment type II
Outcome
Neoadjuvant Treatment
Outcome


Women Breast Cancer
Study Group
Random
DW-MRI
Neoadjuvant Treatment
Outcome
Neoadjuvant Treatment type II
Outcome
Neoadjuvant Treatment
Outcome

Single-Arm Imaging Trial



- Can explore necessary conditions for an effect
- In example:
  ability of DW-MRI to predict complete pathologic response could guide decisions about neoadjuvant treatment

6.
Trial and Study Qualifiers

Retrospective versus Prospective Studies

- *Prospective*
  - Data collection planned after protocol development
- *Retrospective*
  - Data already collected at protocol development

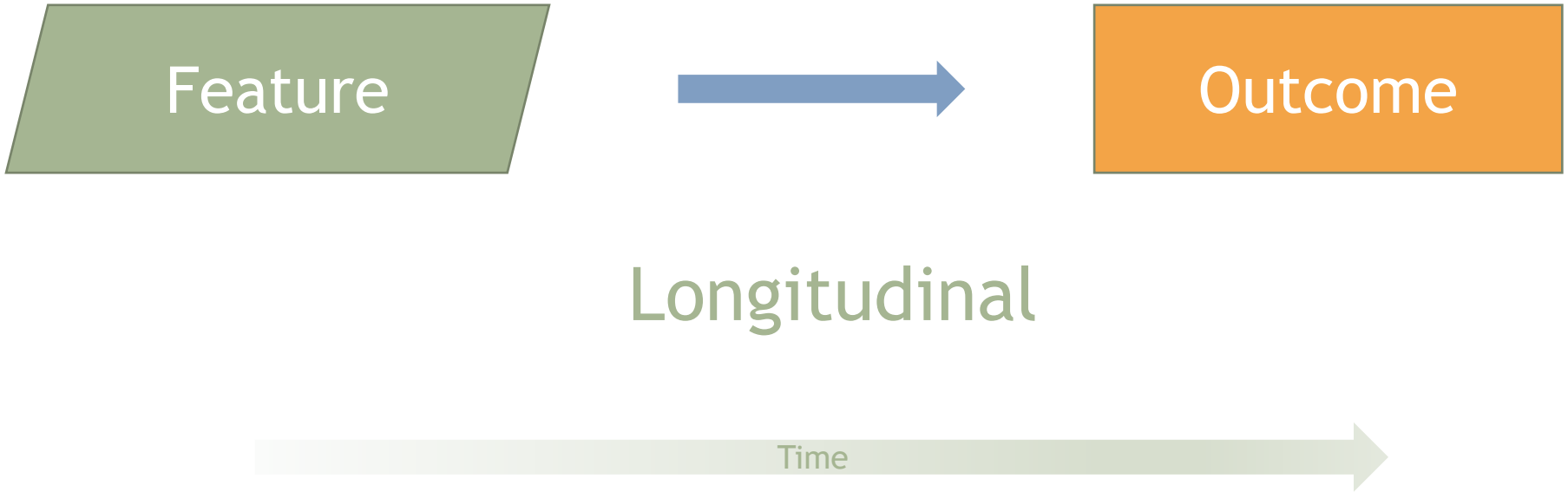
Blinded versus Open-Label

- *Blinding: Allocation Unknown*
  - Single-blind, double-blind, triple-blind
- *Open-Label: Allocation Known*
  - Everybody fully aware of intervention

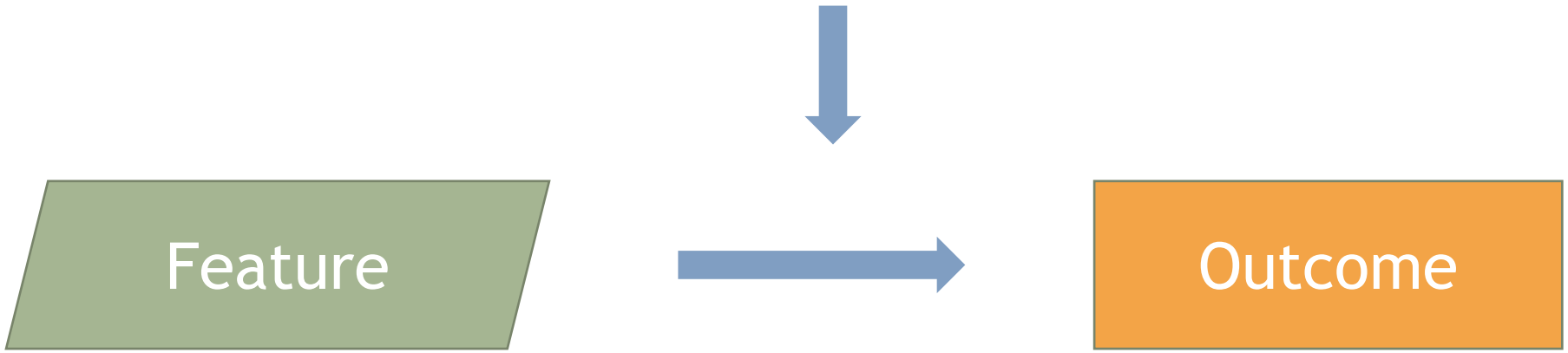
Pragmatic versus Explanatory Trials

- *Pragmatic Trials*
  - Aim at supporting decision making
- *Explanatory Trials*
  - Proof-of-principle / Hypothesis Testing

Longitudinal versus Cross-sectional



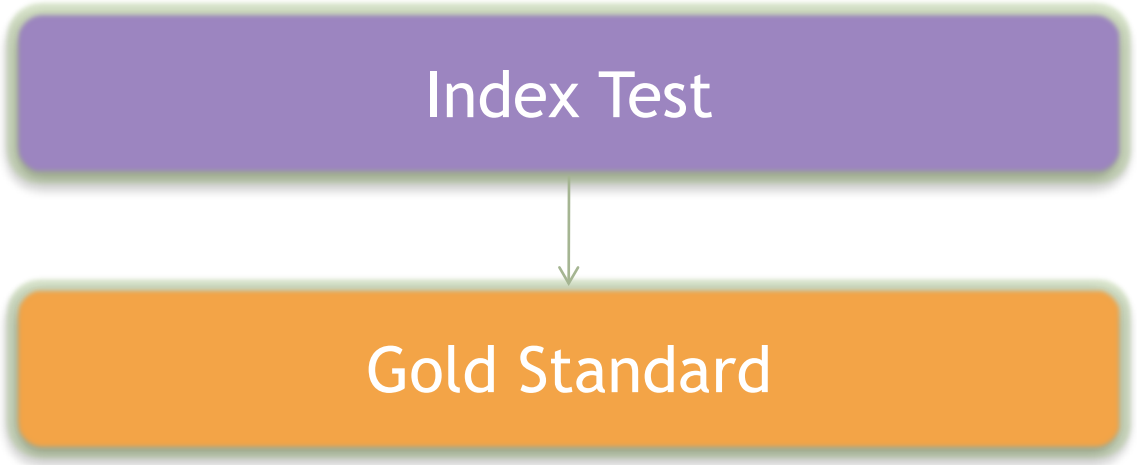
Longitudinal versus Cross-sectional



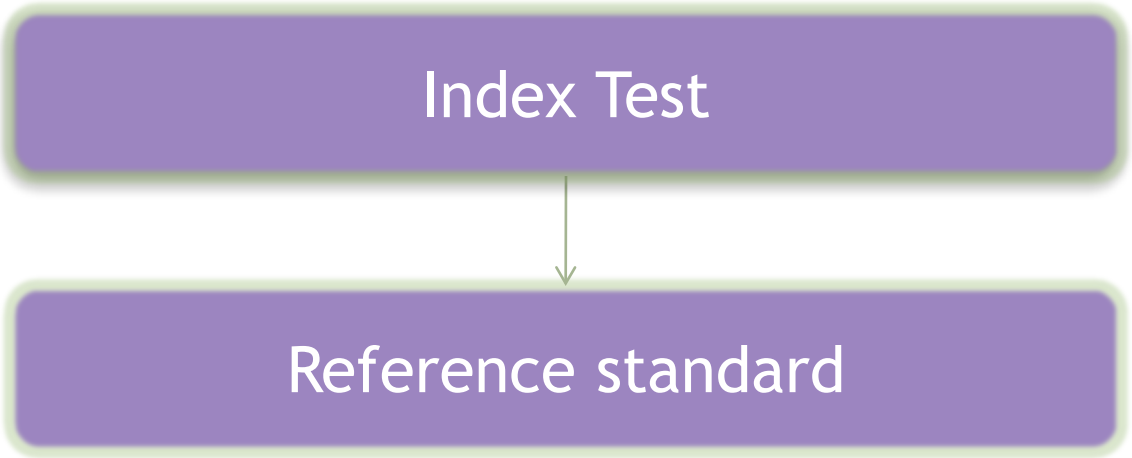
Cross-sectional

7.
Diagnostic Accuracy Trial

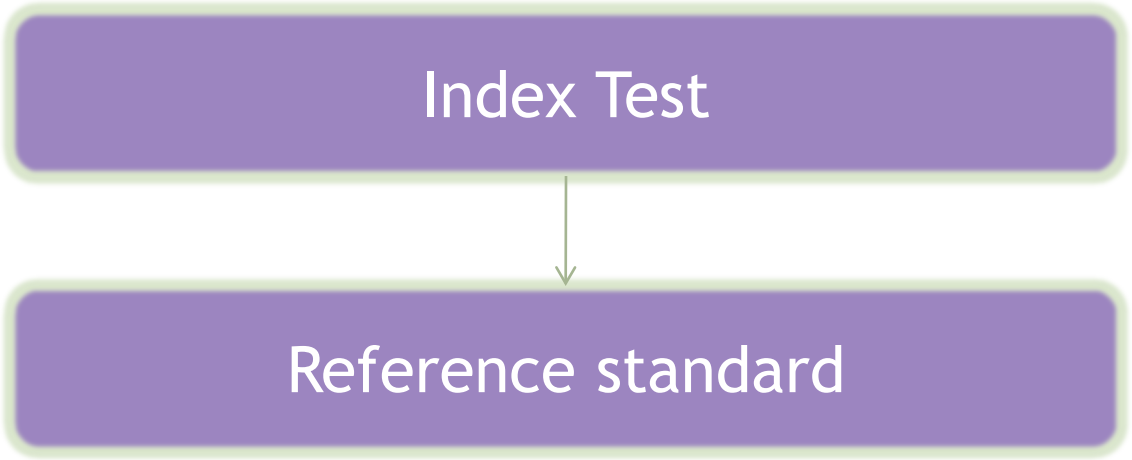
Diagnostic Accuracy



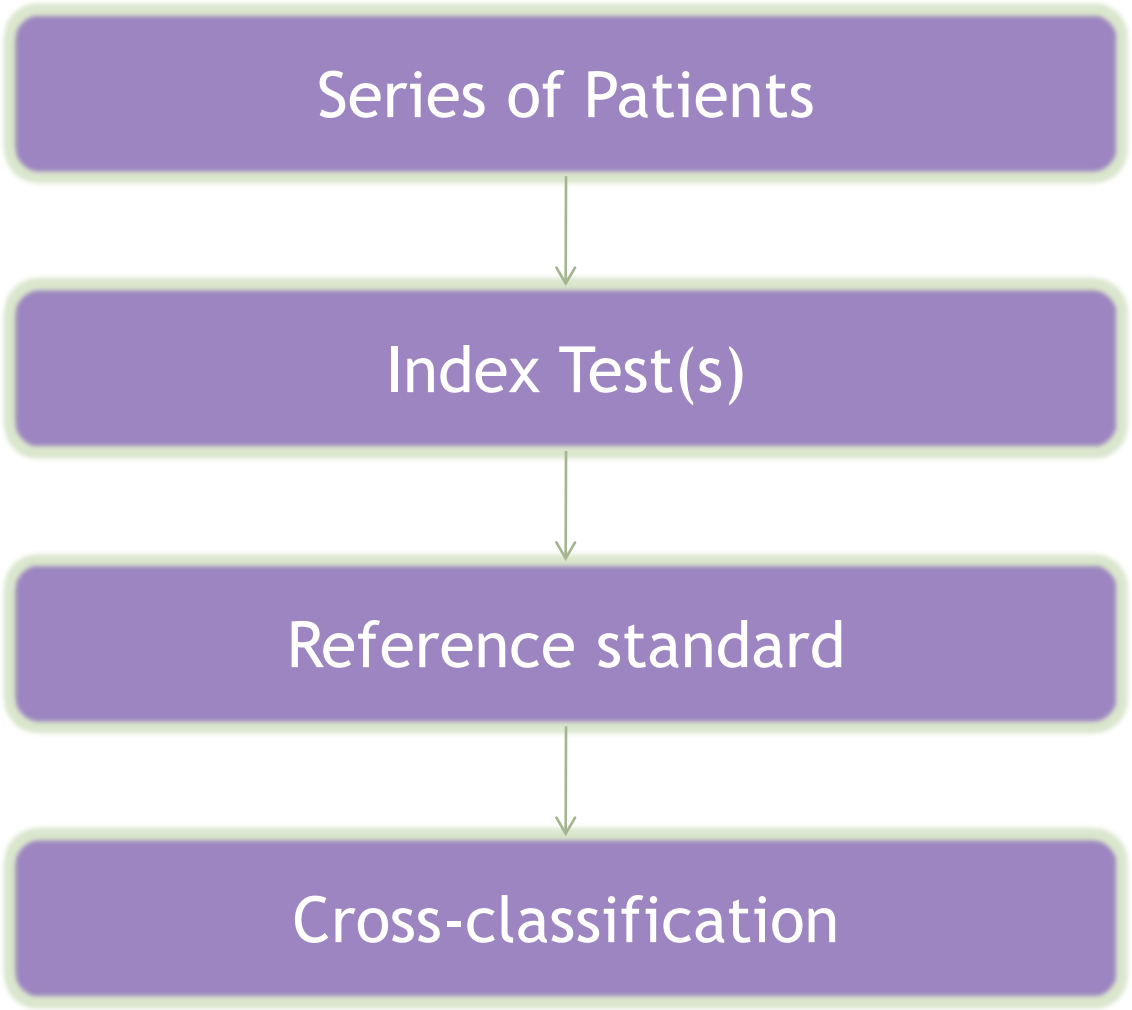
Diagnostic Accuracy



Diagnostic Accuracy



Diagnostic Accuracy Trial



ORIGINAL RESEARCH • GASTROINTESTINAL IMAGING

Radiology

Contrast-enhanced US with Perfluorobutane for Hepatocellular Carcinoma Surveillance: A Multicenter Diagnostic Trial (SCAN)

Ji Hoon Park, MD, PhD • Mi-Suk Park, MD, PhD • So Jung Lee, MD, PhD • Woo Kyoung Jeong, MD, PhD • Jae Young Lee, MD, PhD • Min Jung Park, MD, PhD • Sung Soo Lee, MS • Kyunghwa Han, PhD • Chung Mo Nam, PhD • Seong Ho Park, MD, PhD • Kyoung Ho Lee, MD, PhD

From the Department of Radiology, Seoul National University Bundang Hospital, Gyeonggi-do, Republic of Korea (J.H.P., S.S.L.); Department of Radiology and Research Institute of Radiological Science, Severance Hospital, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Republic of Korea (M.S.P., M.J.P.); Department of Radiology and Research Institute of Radiology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea (S.J.L., S.H.P.); Department of Radiology and Center for Imaging Science, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea (W.K.J.); Department of Radiology and Institute of Radiation Medicine, Seoul National University Hospital, Seoul, Republic of Korea (J.Y.L.); Department of Radiology, Health Promotion Center, Samsung Medical Center, Seoul, Republic of Korea (M.J.P.); Yonsei Biomedical Research Institute, Department of Radiology, Research Institute of Radiological Science (K.H.) and Department of Preventive Medicine (C.M.N.), Yonsei University College of Medicine, Seoul, Republic of Korea; Department of Radiology, Seoul National University College of Medicine, Seoul National University Bundang Hospital, Gyeonggi-do, Republic of Korea (K.H.L.); and Program in Biomedical Radiation Sciences, Department of Transdisciplinary Studies, Graduate School of Convergence Science and Technology, Interdisciplinary Program in Bioengineering, Seoul National University, Seoul, Republic of Korea (K.H.L.). Received January 23, 2019; revision requested March 15; final revision received April 22; accepted May 13. **Address correspondence to** M.S.P. (e-mail: *radpms@yuhs.ac*).

Supported by GE Healthcare (SON-14-01).

Conflicts of interest are listed at the end of this article.

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Background: US has served as a standard surveillance tool for hepatocellular carcinoma (HCC); however, the detection rate and false referral rate with this modality are suboptimal.

Purpose: To evaluate the added value of perfluorobutane-enhanced US when combined with conventional B-mode US as an HCC surveillance tool in participants with liver cirrhosis.

Materials and Methods: This prospective multi-institution diagnostic trial (*https://ClinicalTrials.gov*, NCT02188901) used an intra-individual comparison design in a single arm of study participants and was conducted at five referral hospitals. Eligible participants who had liver cirrhosis related to viral hepatitis and were undergoing US for HCC surveillance were enrolled from October 2014 to August 2016. Immediately after completion of B-mode US but before performance of perfluorobutane-enhanced US, operating radiologists entered the results of B-mode US. After completion of subsequent perfluorobutane-enhanced US (Kupffer phase with or without vascular-phase US), the radiologists recorded the results. The presence of HCC was confirmed either with pathologic analysis or radiologically by using dynamic contrast material–enhanced CT or gadoxetic acid–enhanced MRI. The primary end points were the detection rate of early-stage HCC (Barcelona Clinic Liver Cancer staging system stage 0 or A) and false referral rate. The primary end points were compared in a per-participant manner by using the McNemar test.

with liver-specific contrast material resulted in a higher HCC detection rate and a lower false-positive rate when compared with those attained with US screening (2). Still, lance setting because they can be used only for vascular phase (arterial and portal venous phases) imaging, the duration of which might not be sufficient to examine the

Abbreviations

BCLC = Barcelona Clinic Liver Cancer, CI = confidence interval, CTCAE = Common Terminology Criteria for Adverse Events, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, LI-RADS = Liver Imaging Reporting and Data System

Summary

The detection rate of early-stage hepatocellular carcinoma (HCC) was not improved by adding perfluorobutane-enhanced US to conventional B-mode US; however, the rate of false referrals was reduced when perfluorobutane-enhanced US was used for surveillance of HCC.

Key Points

- The detection rate of early-stage hepatocellular carcinoma (HCC) was not improved by adding perfluorobutane-enhanced US to conventional B-mode US (difference, 0.4%; $P = .16$).
- The false referral rate of HCC was significantly reduced by adding perfluorobutane-enhanced US (difference, −3.2%; $P < .001$).

entire liver (5,6). Meanwhile, the US contrast agent based on perfluorobutane gas–containing microbubbles allows very stable Kupffer phase imaging for at least 60 minutes in addition to

publication. Data generated or analyzed during the study are available from the corresponding author by request.

Design and Setting

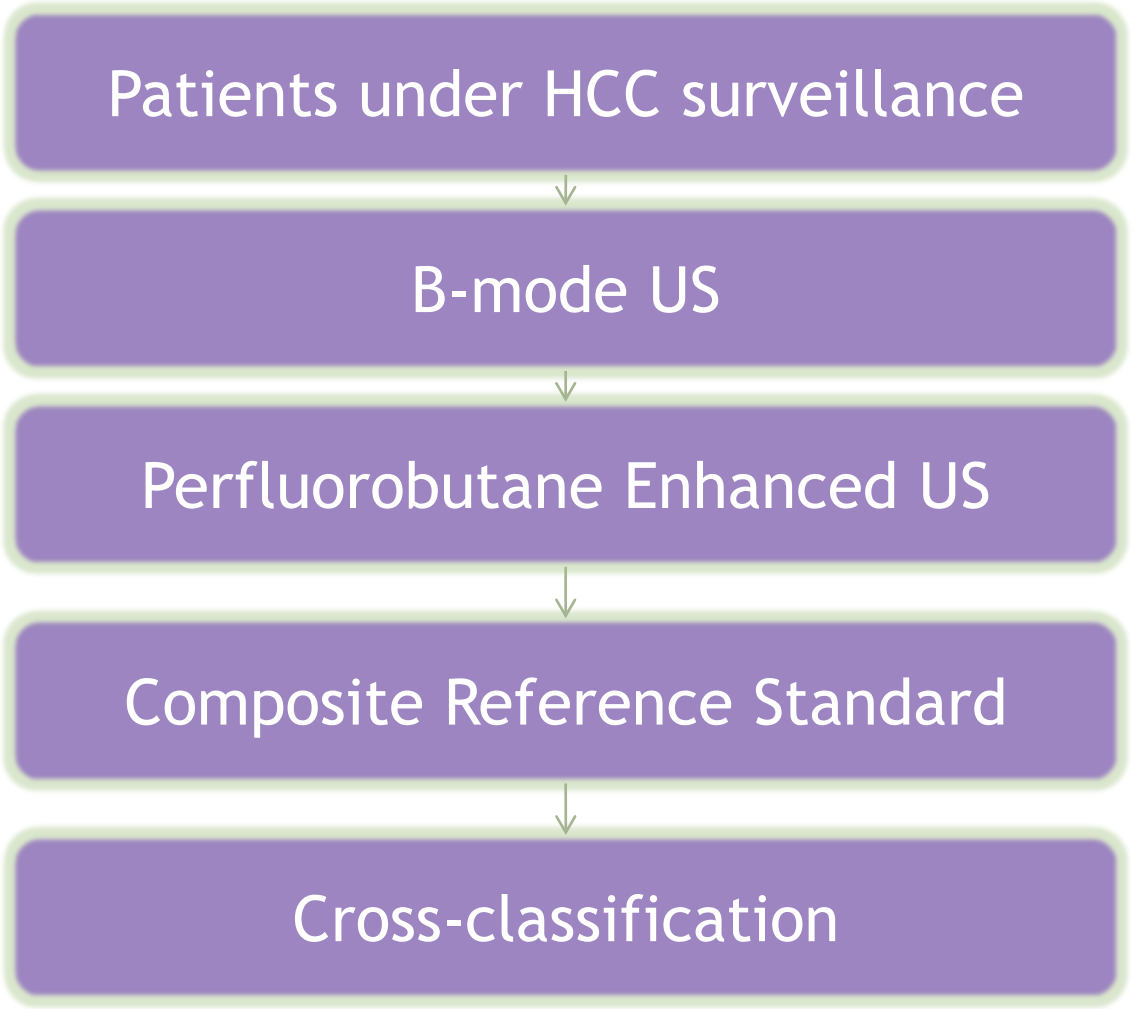
The study was a prospective multi-institutional diagnostic trial that used an intraindividual comparison design in a single-arm of participants. Patient enrollment was conducted from October 2014 to August 2016 at five tertiary referral hospitals in Korea (Asan Medical Center, Samsung Medical Center, Seoul National University Hospital, Severance Hospital, Seoul National University Bundang Hospital). The participating institutions were chosen based on their potential to recruit a high number of participants currently undergoing HCC surveillance. The primary end points were the detection rate of early-stage HCC and the false referral rate.

Eligibility Criteria

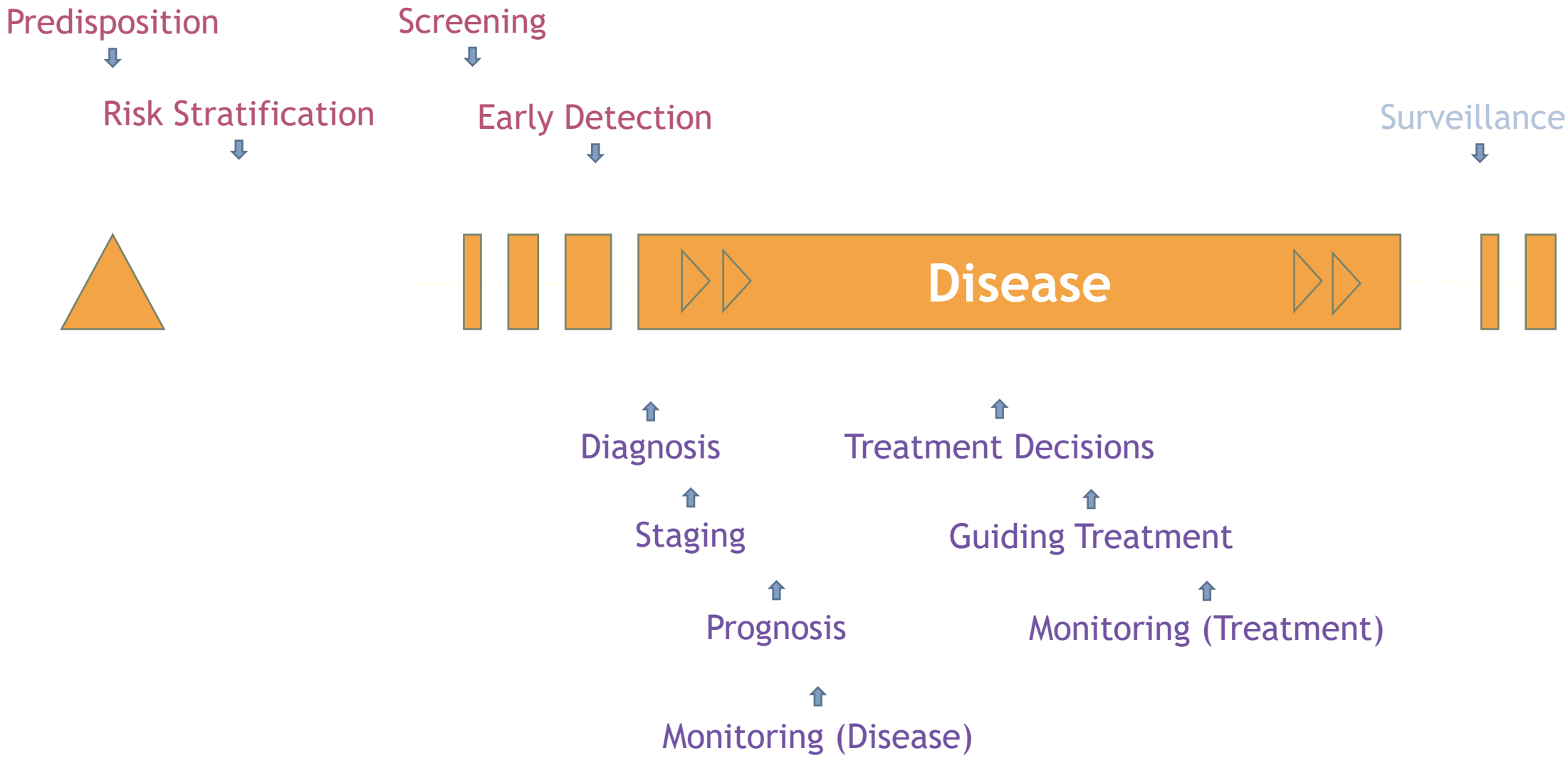
This study was conducted in a convenience sample of participants. Participants aged 20–80 years who had liver cirrhosis related to the hepatitis B virus (HBV) or hepatitis C virus (HCV) and who were undergoing US for HCC surveillance were eligible for this study. Investigators in participating institutions

final responsibility for the decision to submit the results for case report form. In case there was a lesion suspicious for HCC

Diagnostic Accuracy Trial



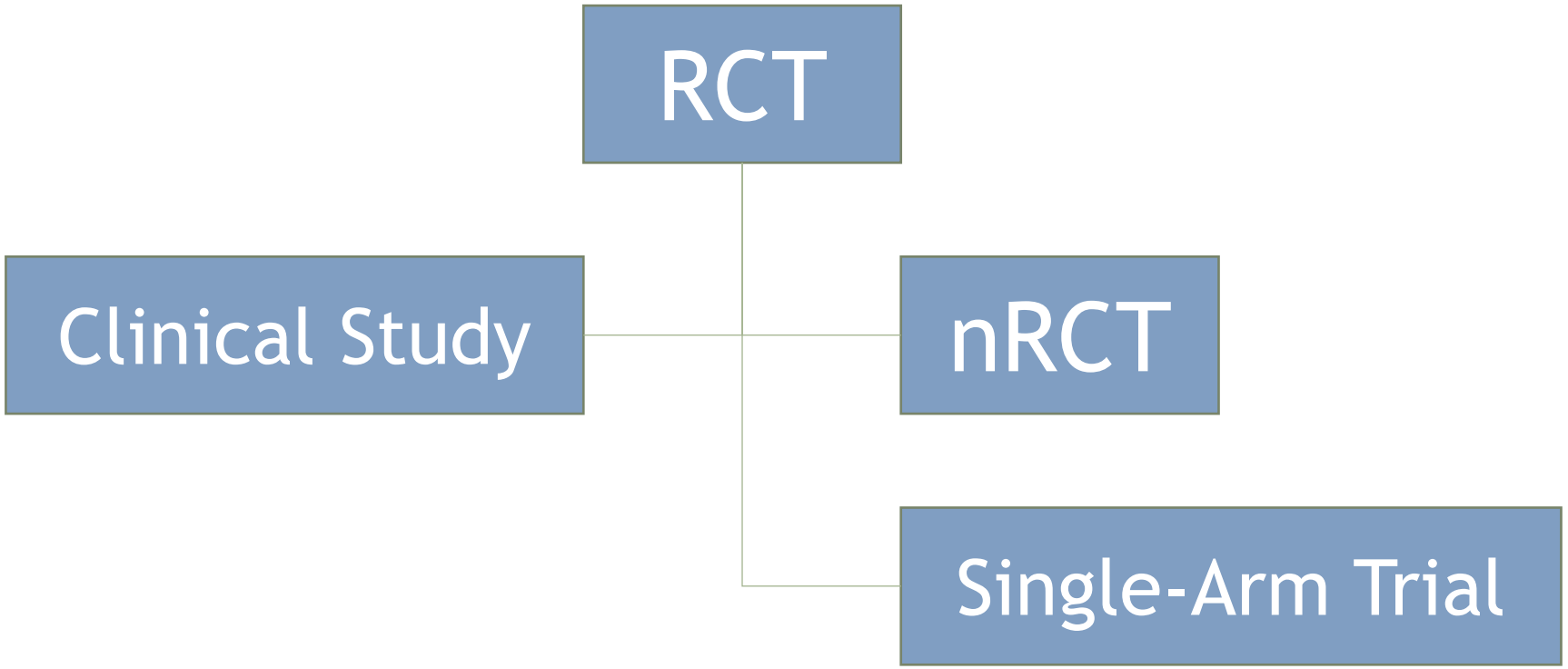
Testing Purposes



Session Outline

1. Randomized Clinical Trial (RCT)
2. RCT components
3. Observational Clinical Studies
4. Non-Randomized Clinical Trial (nRCT)
5. Single-Arm Trial
6. Trial and Study Qualifiers
7. Diagnostic Accuracy Trial

Taxonomy Imaging Trials



A Taxonomy of Imaging Trials

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