CW-08 Randomized controlled trial in radiology research

16:50-17:20 201

Chairperson(s): Jeong Min Lee *Seoul National University Hospital, Korea*

AMC cardiology – multicenter trial을 중심으로

Young-Hak Kim
Asan Medical Center, Korea. mdyhkim@amc.seoul.kr

Multicenter Clinical Trial

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Department of Cardiology, Asan Medical Center,
University of Ulsan College of Medicine

서울아산병원 Asan Medical Center

Contents

- Definition
- Registration
- Data collection
- Multicenter observational study
- Adjustment
- Authorship

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Defining IIT vs. Industry-Sponsored Trial

Source: Clinical Trial Magnifier Vol. 2:5 May 2009
www.clinicalmagmifier.com

Supporting/Collaborating Party
Clinical study conducted with the support of or in collaboration with outside party(ise), other than governmental, government-affiliated or scientific/academic research grant body(ies)

Yes

Legal Contract
Legal contract between institution and supporting/collaborating party(ies) required.

Yes

Data Ownership
Institution has full and exclusive ownership of and unlimited rights to use the data and results arising form the study

Yes

IPR Ownership
Institution has ownership(whether full or restricted) of any intellectual property right on any invention or discovery arising from the study.

Yes

Investigator-Initiated Clinical Study

Industry-sponsored Clinical Study

**This condition could be waived if the Principal Investigator certifies that will be no or very low possibility of generating commercial from the study.

General principles differentiating ii-clinical studies from industry-sponsored clinical studies.

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다기관 임상시험: KGCP

"다기관임상시험(Multicenter Trial)"이라 함은 하나의 임상시험계획서에 따라 둘 이상의 시험기관에서 수행되는 임상시험을 말한다.

"조정위원회(Coordinating Committee)"라 함은 다기관임상시험의 수행을 조정하기 위하여 의뢰자가 조직하는 위원회를 말한다.

"임상시험조정자(Coordinating Investigator, 이하 "시험조정자"라 한다)"라 함은 각 시험기관의 시험책임자 중에서 다기관임상시험에 참여하는 시험자 사이의 의견을 조정할 책임을 부여받은 자를 말한다.

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DECREASE-PCI Design

(Multicenter, randomized double-blind clinical trial)

The lesion suitable for coronary stenting with drug-eluting stent

1:1 randomization

Stratified by sites (20 centers)

stent implantation (any second-generation limus-family DES)

Aspirin + clopidogrel + cilostazol* (n=1055)

Aspirin + clopidogrel + placebo* (n=1055)

Clinical follow-up at 1 year, follow-up up to 3 years

- Study drug for 12 months (허가범위외 사용)
- Aspirin indefinitely and Clopidogrel for 1 years

Primary endpoint: composite of any death, MI, TVR, ischemic stroke at 1 year

Drug compliance and adverse drug events monitoring: compliance questionnaire
CBC, LFT, hsCRP, HBA1c at baseline, 1, 6, 12 months, 2, 3 years
Verify now (aspirin/P2Y12): postprocedure 24 and hospital discharge

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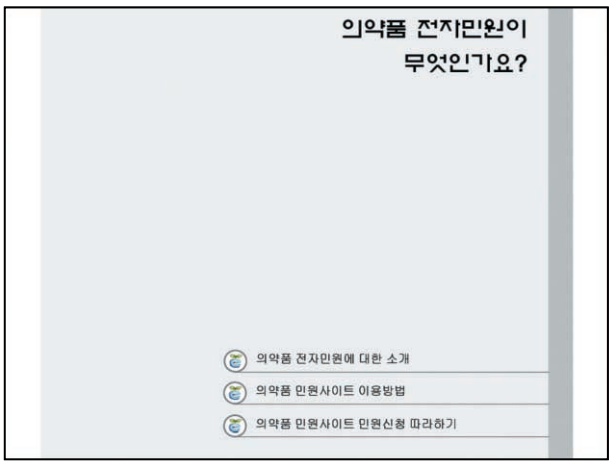
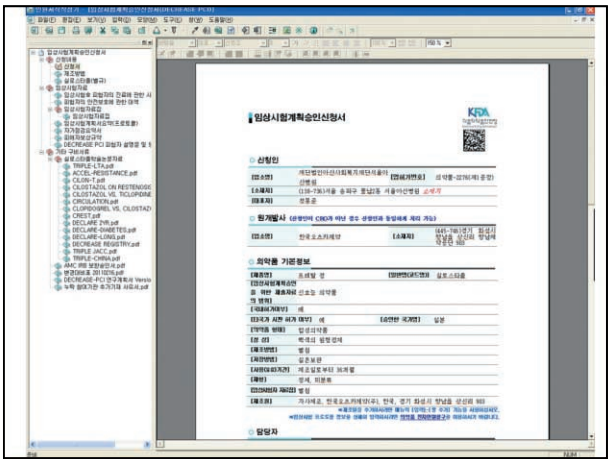
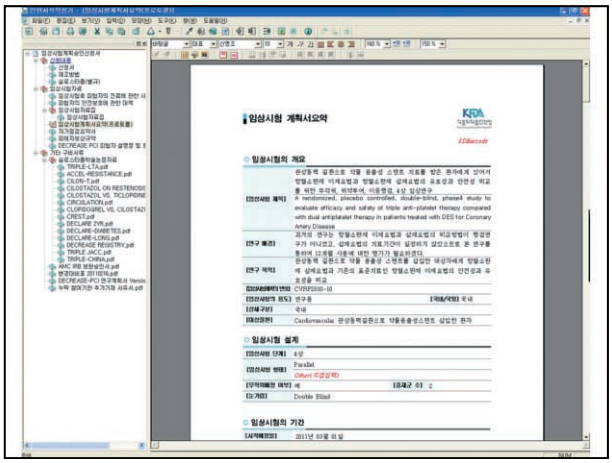
CW (201), Oct 19, Fri


KIFDA ezDrug
WINDOW FOR CIVIL PETITIONS


의약품 전자민원이
무엇인가요?
의약품 전자민원에 대한 소개
의약품 민원사이트 이용방법
의약품 민원사이트 민원신청 따라하기


임상시험계획승인신청서


임상시험 계획서요약


ClinicalTrial.gov
Registrationn of Trials
ClinicalTrials.gov
Protocol Registration System
Login
Organization:
User Name:
Password:
Login
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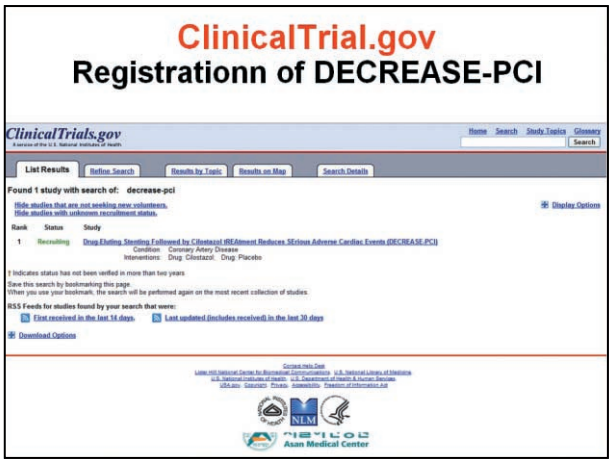
ClinicalTrial.gov
Registrationn of DECREASE-PCI
ClinicalTrials.gov
Found 1 study with search of: decrease-pci
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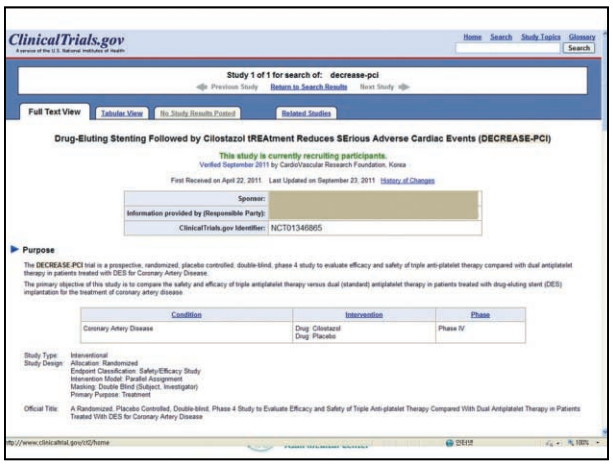
ClinicalTrials.gov
Drug-Eluting Stenting Followed by Cilostazol tREAtment Reduces SErious Adverse Cardiac Events (DECREASE-PCI)


ClinicalTrial.gov
ClinicalTrials.gov
서울아산병원
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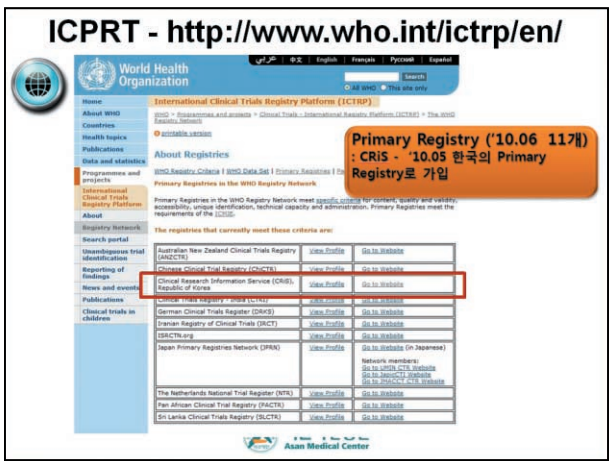
ICPRT - http://www.who.int/ictrp/en/
World Health Organization
Primary Registry ('10.06 117개) : CRiS - '10.05 한국의 Primary Registry로 가입
Asan Medical Center


ICTRP – Search Portal
World Health Organization
INTERNATIONAL CLINICAL TRIALS REGISTRY PLATFORM
SEARCH PORTAL
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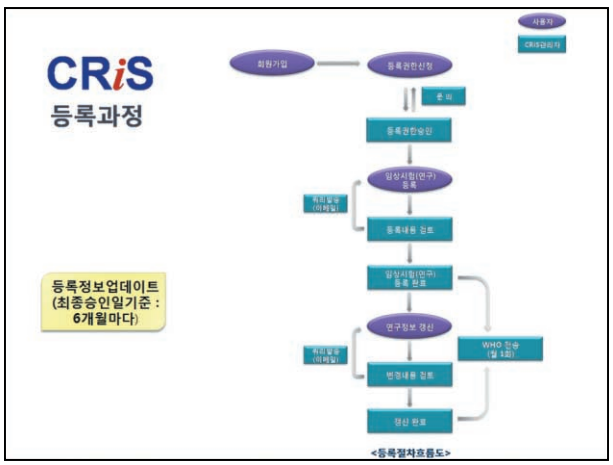
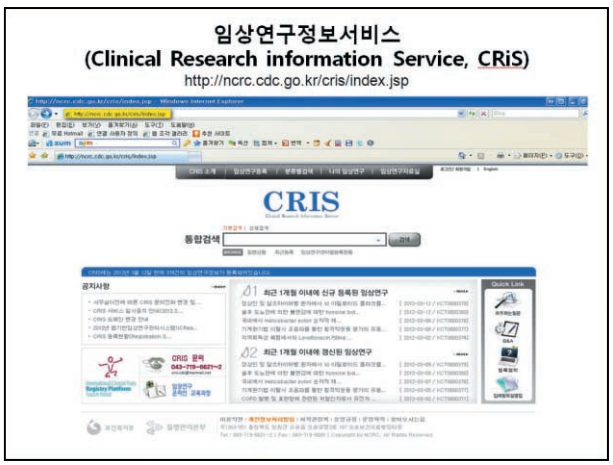

CRiS
등록과정
등록정보업데이트 (최종승인일기준 : 6개월마다)
<등록절차흐름도>


임상연구정보서비스
(Clinical Research information Service, CRiS)
http://ncrc.cdc.go.kr/cris/index.jsp
CRIS

Limitations of IIT

- Less structured and organized
- No SOPs
- Limited experience
- Lower priority level
- Low budget
- Less qualified and regulated

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Study Designs for Clinical Research

Weakest evidence

- Single case report (anecdote)
- Consecutive case series
- Retrospective case-control or cohort study
- Prospective cohort with historical controls
- Prospective cohort with contemporary controls
- Single randomized clinical trial (RCT)
- Multiple large, randomized clinical trials

Strongest evidence

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Limitations of RCTs

- Often underpowered for modest treatment effects
  - Still relevant from public health standpoint if affected population is large
- Surrogate endpoints→ ? Clinical relevance
- Generalizability?
  - Tend to study generally healthy patients
  - Treated with standardized protocols
  - By experienced providers
- Certain questions not easily subject to RCT
  - Unethical, impractical, no business case, or
  - Studies of harmful effects

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'all-comer' RCT pt vs. Excluded pt

Evaluating the 'all-comers' design: a comparison of participants in two 'all-comers' PCI trials with non-participants

Sanneke P.M. de Boer, Mattie J. Lenzen, Rohit M. Oemrawsingh, Cihan Simsek, Henricus J. Duckers, Willem J. van der Giessen, Patrick W. Serruys, and Eric Boersma*

Department of Cardiology, Erasmus MC, Thoraxcenter, 's Gravendijkwal 230, 3015 CE Rotterdam, The Netherlands

Revised 27 September 2010; revised 24 January 2011; accepted 30 March 2011

Aims We aimed to asses the generalizability of two 'all-comers' randomized clinical trials (AC-RCTs) in patients undergoing percutaneous coronary intervention (PCI).

Methods and results Recently two large AC-RCT's comparing drug-eluting stents were performed in our institution (LEADERS and RESO-LUTE-III). During the inclusion period of these trials 1242 consecutive PCI patients were treated of whom 579 (48%) were actually included. The most important reasons for non-participation were inability to provide informed consent (33.5%), refused to participate (19%), or patient met one of the other exclusion criteria (26.9%). Trial participants more frequently had stable angina (42.5 vs. 34.4%) and less frequently acute myocardial infarction as indication for PCI (31.4 vs. 42.4%) than non-participants. Hypertension (52.8 vs. 49.1%) and hypercholesterolaemia (56.3 vs. 49.1%) were seen more frequently in trial participants; heart failure was less common (2.1 vs. 4.4%). A significant difference in 30-day mortality was observed between AC-RCT participants and non-participants [0.7 vs. 4.5% events; adjusted hazard ratio (aHR) 0.18 and 95% confidence interval (CI) 0.06–0.52]. One-year mortality was also lower (3.1 vs. 6.9% events; aHR: 0.51 and 95% CI: 0.29–0.91, but 1-year mortality in 48 h survivors was similar (3.1 vs. 4.3% events; aHR: 0.74 and 95% CI: 0.41–1.34).

Conclusion Applying the all-comers design did not result in inclusion of all consecutive patients, as only half of the target population was enrolled. It should be noted, however, that this design included more patients than observed in classical RCTs. AC-RCT participants and non-participants were different in terms of baseline characteristics and outcome.

Keywords Randomized controlled trials • All-comers • Percutaneous coronary intervention

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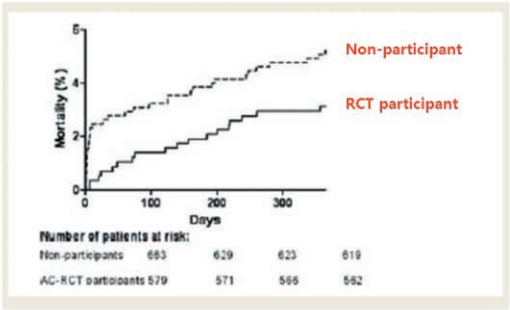
'all-comer' RCT pt vs. Excluded pt

1-year mortality



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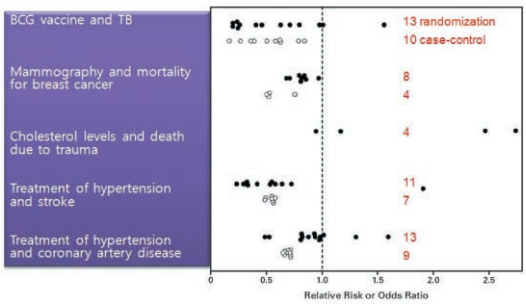
RCT vs. Case control

Point of estimate between randomized vs. case control study



서울아산병원 Asan Medical Center Concato J et al. NEJM 2000;342:1887

Registry Studies: Key Advantages

- Allows for rapid enrollment of large numbers of patients → accomodates changes in practice over time
- Broad inclusion criteria ensure that study's findings may be applicable to most patients
- Ideal for determining optimal procedural technique as well as for identifying appropriate patient subsets for treatment

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Registry Studies: Key Disadvantages

Data quality and completeness

- Analysis results only as solid as the data ("Bad data in...")
- Particularly challenging with administrative datasets
- Incomplete data
- Not necessarily related to registry design, but more related to degree of rigor employed in data collection

Treatment selection bias

- Pt Level: risk factors, disease severity, comorbidity
- MD level: those selecting a specific treatment may differ in care process and quality
- Site-level: structural and quality of care differences

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Good Observational Study
Registry Controlled Trial vs. Simple Registry

- Primary end point vs. primary objective
- Power calculation vs. no sample size estimation
- Good controlled registry
  - Clinical primary end point with long follow-up (more than 6 months)
  - Reached primary end point
  - Adequate power calculation
  - Blinded analysis (including physician)
  - Clinical event committee and DSMB
  - Follow-up > 80% for surrogate end point, > 95% for clinical primary end point

서울아산병원 Asan Medical Center Silber S et al. J Interven Cardiol 2006;19:485

2011

Observation Study: PROSPECT study

ORIGINAL ARTICLE

A Prospective Natural-History Study of Coronary Atherosclerosis

Gregg W. Stone, M.D., Akiko Maehara, M.D., Alexandra J. Lansky, M.D., Bernard de Bruyne, M.D., Ecaterina Cristea, M.D., Gary S. Mintz, M.D., Roxana Mehran, M.D., John McPherson, M.D., Naim Farhat, M.D., Steven P. Marso, M.D., Helen Parise, Sc.D., Barry Templin, M.B.A., Roseann White, M.A., Zhen Zhang, Ph.D., and Patrick W. Serruys, M.D., Ph.D., for the PROSPECT Investigators*

From Columbia University Medical Center/New York–Presbyterian Hospital and the Cardiovascular Research Foundation, New York (G.W.S., A.M., A.J.L., E.C., G.S.M., R.M., H.P.); Cardiovascular Center, Onze-Lieve-Vrouwziekenhuis, Aalst, Belgium (B.B.); Vanderbilt University Medical Center, Nashville (J.M.); North Ohio Heart Center/Elyria Memorial Hospital Regional Medical Center, Elyria, OH (N.F.); Mid America Heart Institute, St. Luke's Hospital, Kansas City, MO (S.P.M.); Abbott Vascular, Santa Clara, CA (B.T., R.W., Z.Z.); and Erasmus University, Thoraxcentrum, Rotterdam, the Netherlands (P.W.S.). Address reprint requests to Dr.

ABSTRACT

BACKGROUND

Atherosclerotic plaques that lead to acute coronary syndromes often occur at sites of angiographically mild coronary-artery stenosis. Lesion-related risk factors for such events are poorly understood.

METHODS

In a prospective study, 697 patients with acute coronary syndromes underwent three-vessel coronary angiography and gray-scale and radiofrequency intravascular ultrasonographic imaging after percutaneous coronary intervention. Subsequent major adverse cardiovascular events (death from cardiac causes, cardiac arrest, myocardial infarction, or rehospitalization due to unstable or progressive angina) were adjudicated to be related to either originally treated (culprit) lesions or untreated (nonculprit) lesions. The median follow-up period was 3.4 years.

2011

Controlled Prospective Registry

Study Number	04-800
Title	Providing Regional Observations to Study Predictors of Events in the Coronary Tree (PROSPECT) An Imaging Study in Patients with Unstable Atherosclerotic Lesions.
Purpose	To identify in patients presenting with Acute Coronary Syndromes (ACS) imaging modalities and/or serologic markers of inflammation which may aid in the identification of non-flow obstructing lesions with an increased risk for future acute coronary events. This study will ascertain the prevalence and clinical significance of non-flow obstructing lesions, which subsequently result in acute coronary events - defined as vulnerable plaque. The safety of regional imaging of non-culprit lesions in ACS patients will also be assessed.
Study Design	This is a multi-center prospective registry of ACS patients with single or double vessel coronary artery disease. Approximately 700 patients with ACS will be enrolled into the study at sites in the United States and European Union.
Geography and Sites	Up to 40 sites in the Unites States and the European Union.

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2011

Primary Outcome Variable

Outcome Variables	1. The primary outcome variable is Non-Culprit Lesion Related Major Adverse Cardiac Events (NC-MACE) defined as the composite of cardiac death, cardiac arrest, MI, ACS, revascularization by CABG or PCI, or rehospitalization for angina, adjudicated to a non-culprit lesion secondary to significant fixed, non-reversible (no-spasm-related) lesion progression of more than 20% from the baseline study (confirmed either by serial angiography or by necropsy). Event rates will be determined at: in

	hospital, 30, 180 days, 1 year, and then yearly for up to 5 years. 2. Serologic markers of inflammation and lesion characteristics will be evaluated for predictive value relative to recurrent events. 3. Procedural success (ability to complete the imaging procedures as specified in the Investigational Plan without imaging device or procedure related complication).

2011

Power Calculation

A Cox proportional hazards regression model is utilized in the power calculation. The Cox model assumes that the hazard function $\lambda(t)$ for time to NC-MACE given a single predictor X_i has the following regression formulation: $\log[\lambda(t|X_i)/\lambda_0(t)] = \beta_0 + \beta_1 X_i$, where $\lambda_0(t)$ is the baseline hazard, and X_i is the imaging measure or VP indicator variable. The null and alternative hypotheses in Cox regression model are:

H_0: $\beta_1 = 0$
H_a: $\beta_1 = B \neq 0$,

where β_1 is the slope coefficient for X_i, which is the log hazard ratio of the two groups (patients with and without positive observations for VP).

Various assumptions have to be made in the power calculations including the percentage of patients with VP at baseline, hazard ratio, and overall NC-MACE rate. Notice that these percentages and rates are exactly what will be estimated from the trial as stated in the first two research questions. Reflecting the uncertainties in making these assumptions, several scenarios of power calculations are presented below, each with different assumptions of the above three parameters: % of patients with positive observations for VP (a positive observation is defined as the patient has at least one detectable VP), overall NC-MACE rate, and hazard ratio between patients with and without positive observation for VP.

Scenario 1: % Patients with Positive Observation at Baseline = 71%, Overall NC-MACE Rate = 10%, and Hazard Ratio = 2

The assumptions used in the power calculations are as follows:

- One-tailed test
- $\alpha = 0.025$

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Single Center vs. Multicenter

- Single center is ideal. If
  - Adequate number of homogenous population
  - Good for optimal condition of study
  - But, needs sufficient capacity, staff, stuff...
- But, lack of resources and representative of real world practice
- Thus, multicenter trial is the standard for clinical trials

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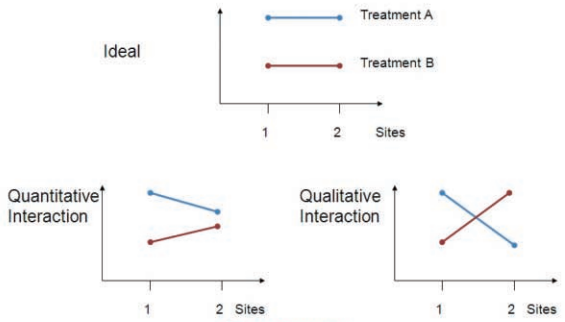
Limitation of Multicener
Treatment-By-Center Interaction



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Heterogeneity !

- CK-MB level : interval of test after coronary stenting, side branch protection, qualified lab...
- Blood pressure : experience of physician, stuff, education of personnel...
- Experience of operators
- Different definitions
- Patients risk profile
- Different quality control
- ...

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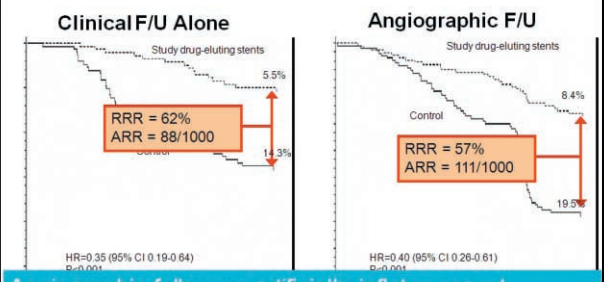
Standardized Protocol and Education
Impact of Angiographic Follow-up on Clinical Outcomes



Angiographic follow-up artificially inflates repeat revascularization rates by ~40% and tends to overestimate the absolute clinical benefit of stents.

Clinical Event Committee (CEC)

- An organization formed to review specific information obtained from research subjects.
- Making judgments regarding this information and to draw conclusions about pre-specified events.
- May or may not agree with conclusions drawn by the investigator from a specific site; in this case the committee's conclusion will serve as the final decision for submission to regulatory authorities and/or for the purposes of reporting and publication.

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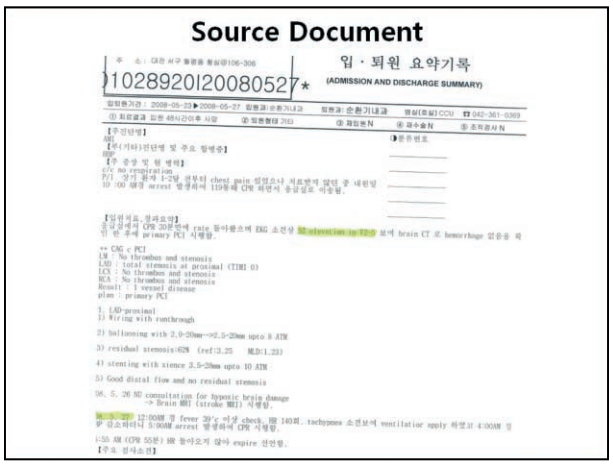
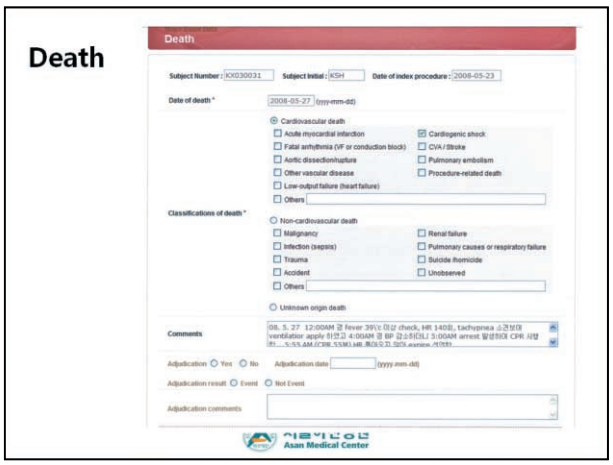

Source Document
입·퇴원 요약기록
(ADMISSION AND DISCHARGE SUMMARY)


Death
Death
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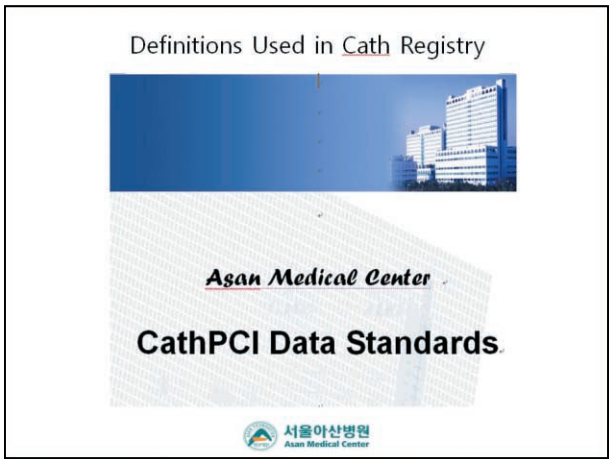
Definitions Used in Cath Registry
Asan Medical Center
CathPCI Data Standards
서울아산병원
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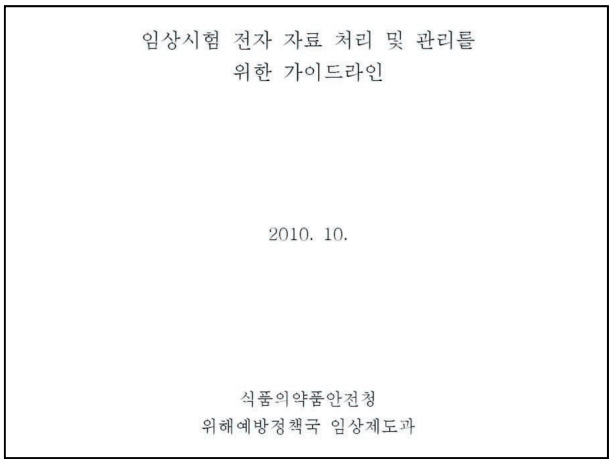
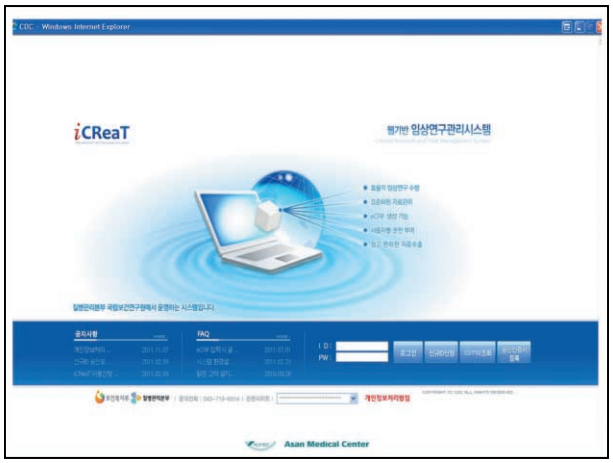
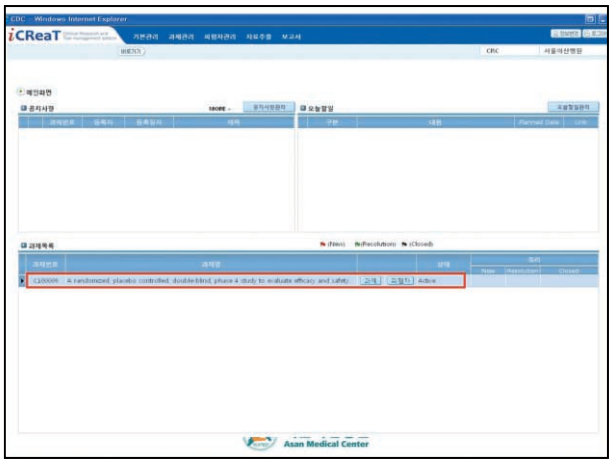
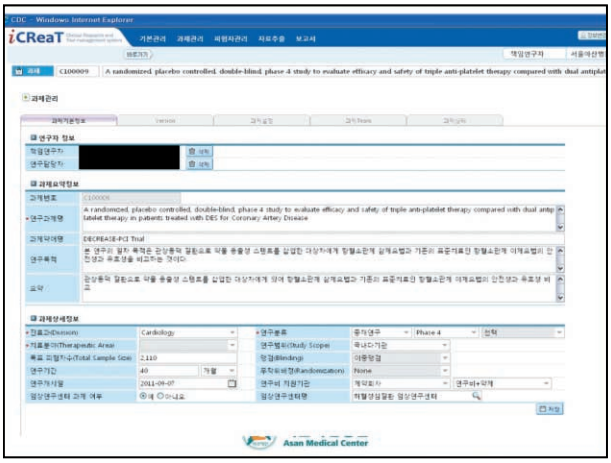
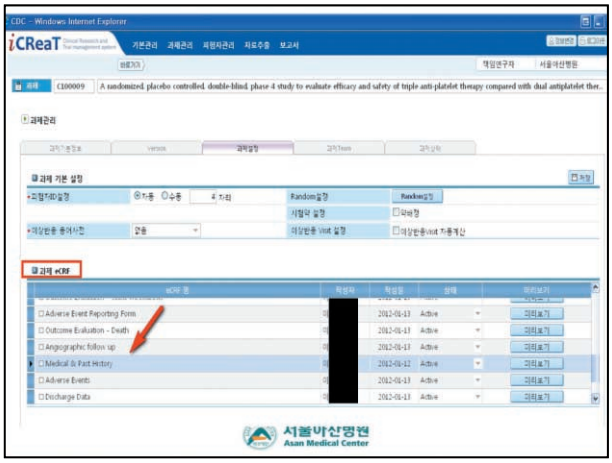
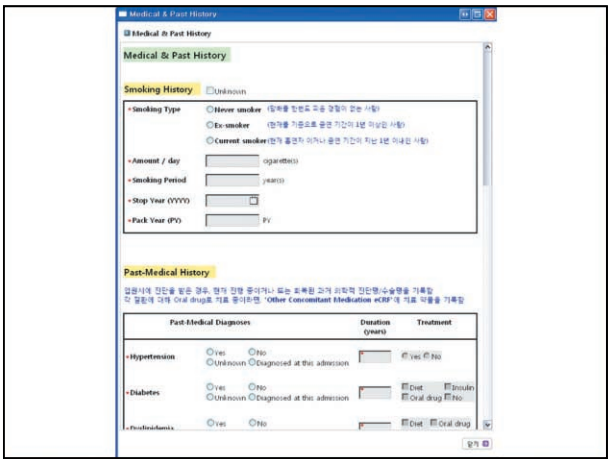

임상시험 전자 자료 처리 및 관리를
위한 가이드라인
2010. 10.
식품의약품안전청
위해예방정책국 임상제도과

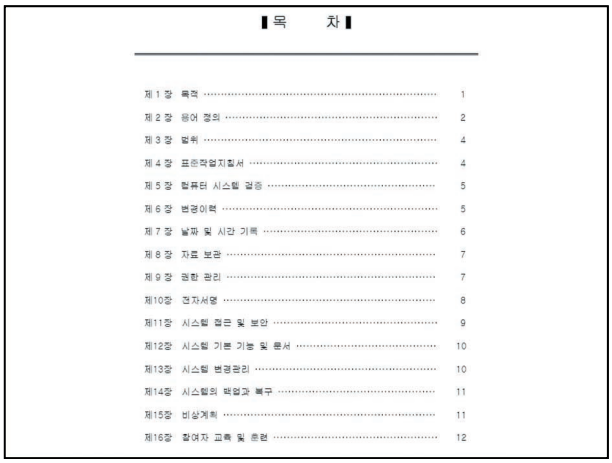

iCReaT
Asan Medical Center


iCReaT
Asan Medical Center


iCReaT
Asan Medical Center


iCReaT
서울아산병원
Asan Medical Center


Medical & Past History
Smoking History
Past-Medical History


▌목 차▐
제 1 장 목적 1
제 2 장 용어 정의 2
제 3 장 범위 4
제 4 장 표준작업지침서 4
제 5 장 컴퓨터 시스템 검증 5
제 6 장 변경이력 5
제 7 장 날짜 및 시간 기록 6
제 8 장 자료 보관 7
제 9 장 권한 관리 7
제10장 전자서명 8
제11장 시스템 접근 및 보안 9
제12장 시스템 기본 기능 및 문서 10
제13장 시스템 변경관리 10
제14장 시스템의 백업과 복구 11
제15장 비상계획 11
제16장 참여자 교육 및 훈련 12


STABLE
ID
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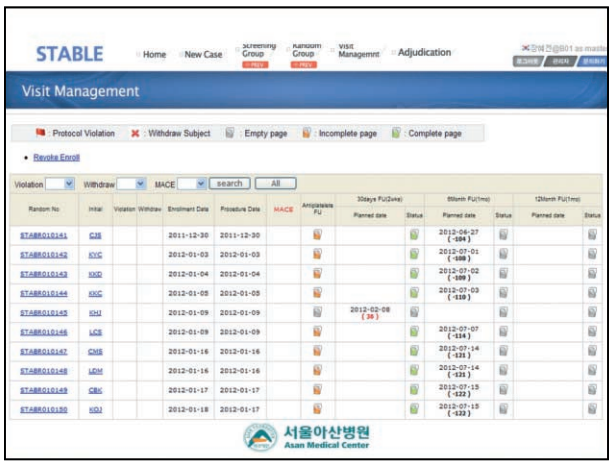
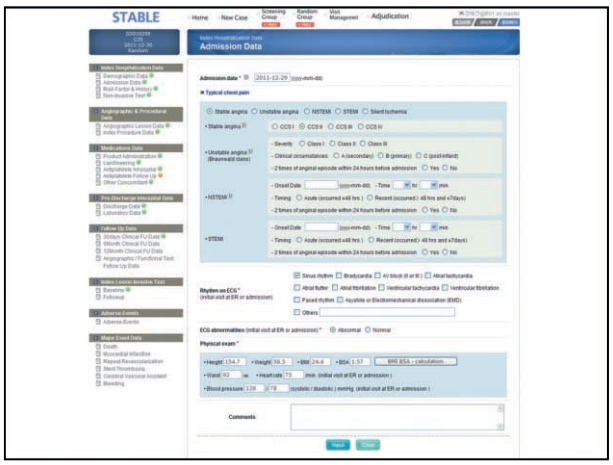
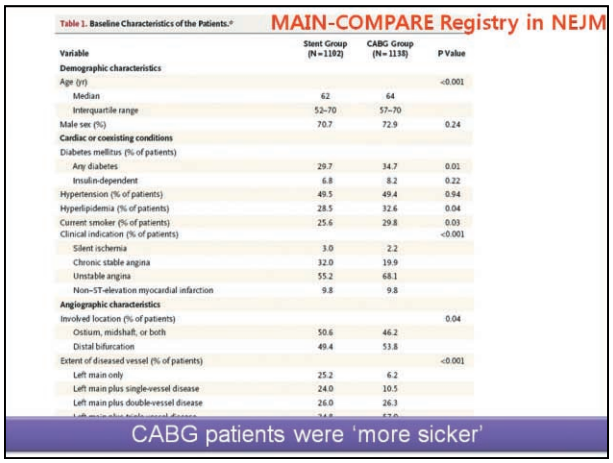
New Case







Classical Adjustments for Covariates

- Three common methods of adjusting for confounding covariates:
  - Matching : large control group
  - Subclassification (stratification) : not valid in many covariates
  - Regression (Covariate) adjustment : not appropriate in many covariates of small group and low incidence

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Techniques for Regression Analysis

- **Regression modeling**
  - Adjust results directly for 'confounding factors' associated with treatment and outcome
- **Propensity adjustment**
  - Identify factors associated with treatment selection
  - Then adjust for the probability of treatment (propensity score) or match patients for this factor
- **Newer approaches**
  - Instrumental variables analysis

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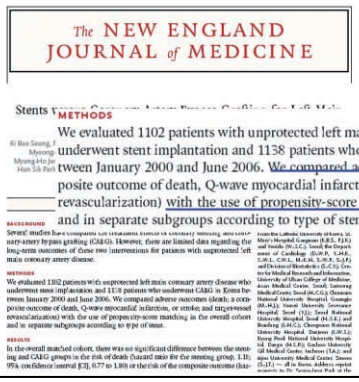
Propensity-Score Matching
MAIN-COMPARE Registry



Limitation of Statistical Adjustment

Complete Database

- Dependent variable : Stent/CABG
- Independent variable : Demographic characteristics, Cardiac or coexisting conditions and Angiographic characteristics
  → logistic regression

```
proc logistic data=sun;
class sex clin_inx ecgrhyth ext_dis;
model group1=age sex dm dm_insu htn hyperlip smoking prepci premi precht cld cvd pvd crf
      mind mivef ecgrhyth clin_inx ext_dis rca_disresten
      age*sex age*dm age*dm_insu age*htn age*hyperlip age*smoking age*prepci age*premi
      age*prechtage*cld age*cvd age*pvd age*crf age*mind age*mivef age*ecgrhyth age*clin_inx
      age*ext_dis age*rca_dis age*resten
      sex*dm sex*dm_insu htn sex *hyperlip sex *smoking sex *prepci sex *premi sex *precht sex*cld
      sex*cvd sex*pvd sex*crf sex*mind sex*mivef sex*ecgrhyth sex*clin_inx sex*ext_dis sex*rca_dis sex*resten
      /selection=s lackfit
output out=pred pprob;
run;
```

In logistic regression analysis, the patient with missing is excluded in the propensity-score model. Moreover, unmeasured confounder cannot be considered in creating propensity score.

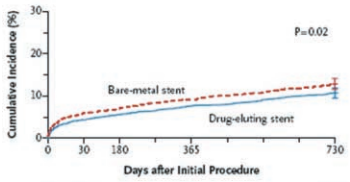
How Long Follow-up

- ≤ 5% of loss (attrition) is little concern
- ≥ 20% of loss posses threat to validity, cutoff to classify 'high or low quality'
- High loss will (1) lose study power, (2) have follow-up bias, and lose (3) generalisability.

Fewtrell M et al. Arch Dis Child 2008;93:458

Complete Follow-up of NY State PCI

$Pt_{start\ (2570)} - Pt_{event\ (195)} - Pt_{end\ (2375)} = Pt_{loss\ (0)}$

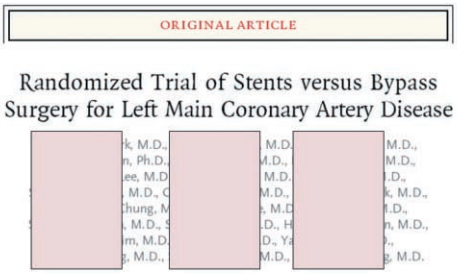


Drug-Eluting Stent					
No. at risk	2570	2560	2492	2427	2375
Cumulative no. of events	10	78	143	195	276
Cumulative incidence (%)	0.4	3.0	5.6	7.6	10.7
Bare-Metal Stent					
No. at risk	2570	2557	2465	2392	2334
Cumulative no. of events	13	105	178	236	330
Cumulative incidence (%)	0.5	4.1	6.9	9.2	12.8

Laura M et al. N Engl J Med 2008;359:1330

Authors

Who are satisfied?



Publication

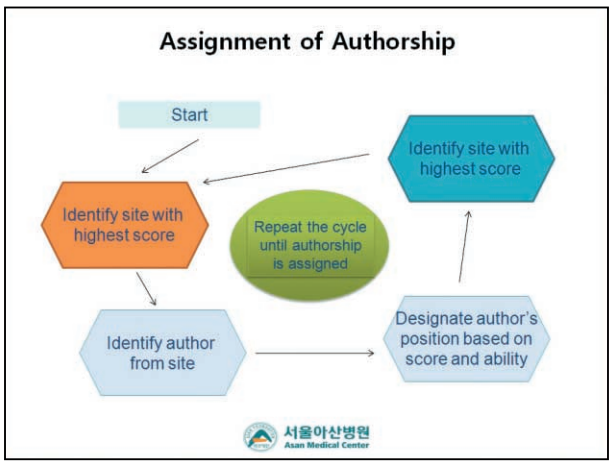
- Principal investigator and executive committee (or publication committee) play a major role to identify important manuscript topics.
- The authors of the design manuscript are designated based on the consensus in the publication committee and PI.
- All analyses should be centrally controlled in the independent analysis department.

Ann Intern Med. 2009;151:414

Authorship

- Author distribution will be decided based on the score calculating :
  1) enrollment (x 1.7)
  2) adherence to the exercise regimen (x 1.3)
  3) data completion (x 1.5)
  4) other trial efforts, such as serving on active trial committees or overseeing operations of 1 of the core laboratories.

Ann Intern Med. 2009;151:414


Assignment of Authorship
Start
Identify site with highest score
Identify site with highest score
Repeat the cycle until authorship is assigned
Identify author from site
Designate author's position based on score and ability
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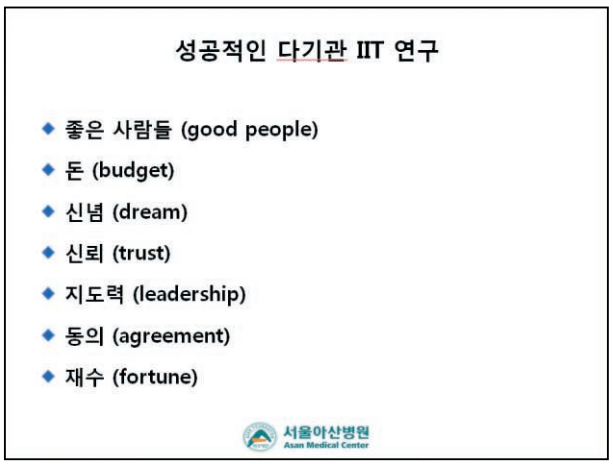
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좋은 사람들 (good people)
돈 (budget)
신념 (dream)
신뢰 (trust)
지도력 (leadership)
동의 (agreement)
재수 (fortune)
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