

# **Responsibilities of Investigators for Clinical Trials from Consent to Safety Reporting**

**Young-Hak Kim, MD, PhD**

**Department of Medicine, Asan Medical Center,  
University of Ulsan College of Medicine, Seoul, Korea**

# Responsibilities of Investigators

## GUIDELINE FOR GOOD CLINICAL PRACTICE

### ICH Harmonised Tripartite Guideline

Having reached Step 4 of the ICH Process at the ICH Steering Committee meeting on 1 May 1996, this guideline is recommended for adoption to the three regulatory parties to ICH  
(This document includes the Post Step 4 corrections agreed by the Steering Committee on 10 June 1996)

### TABLE OF CONTENTS

INTRODUCTION.....	1
1. GLOSSARY .....	2
2. THE PRINCIPLES OF ICH GCP.....	8
3. INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC).....	9
3.1 Responsibilities.....	9
3.2 Composition, Functions and Operations.....	11
3.3 Procedures .....	11
3.4 Records.....	12
<b>4. INVESTIGATOR .....</b>	<b>12</b>
4.1 Investigator's Qualifications and Agreements.....	12
4.2 Adequate Resources .....	12
4.3 Medical Care of Trial Subjects.....	13
4.4 Communication with IRB/IEC.....	13
4.5 Compliance with Protocol .....	13
4.6 Investigational Product(s).....	14
4.7 Randomization Procedures and Unblinding.....	15
4.8 Informed Consent of Trial Subjects.....	15
4.9 Records and Reports.....	18
4.10 Progress Reports.....	19
4.11 Safety Reporting.....	19
4.12 Premature Termination or Suspension of a Trial .....	19
4.13 Final Report(s) by Investigator.....	20
5. SPONSOR.....	20
5.1 Quality Assurance and Quality Control.....	20
5.2 Contract Research Organization (CRO).....	20
5.3 Medical Expertise.....	21
5.4 Trial Design .....	21
5.5 Trial Management, Data Handling, and Record Keeping.....	21

KGCP.hwp [F:\Clinical trials\WICH\W1 - 한국

**Korean GCP**

의약품 임상시험관리기준

2000.1. 4. 식품의약품안전청 고시 제1999-67호  
2007.1.19. 식품의약품안전청 고시 제2007- 4호

**제4장 시험자**

제10조(시험자의 자격요건 등) ① 시험자는 임상시험을 적정하게 실시할 수 있기 위해 필요한 교육·훈련을 받고 충분한 경험을 갖고 있어야 하며, 의뢰자·심사위원회·식품의약품안전청장의 요청이 있을 경우 최근 이력서나 기타 관련 문서를 통해 이를 입증할 수 있어야 한다.

② 시험자는 계획서, 임상시험자자료집, 의뢰자가 제공한 기타 의약품 관련 정보에 기술된 바와 같이 임상시험에 사용되는 의약품의 적절한 사용에 대해 숙지하고 있어야 한다.

③ 시험자는 이 기준 및 관련규정을 숙지하고 이를 준수하여야 한다.

④ 시험책임자 또는 시험기관의 장은 의뢰자의 모니터링 및 점검, 식품의약품안전청장이 실시하는 실태조사에 응하여야 한다.

⑤ 시험책임자는 중요한 임상시험 관련 업무를 시험담당자들에게 위임한 경우, 이들의 명단을 확보·유지하여야 한다.

제11조(임상시험 실시에 필요한 자원 확보) ① 시험책임자는 과거 진료기록 등에 근거하여 의뢰자와 합의한 피험자 등재 기간 내에 해당 임상시험에서 요구되는 피험자를 등재시킬 수 있음을 타당하게 입증하고, 의뢰자의 요청이 있는 경우 해당 입증자료를 제공하여야 한다.

② 시험책임자는 의뢰자와 합의한 임상시험 기간 동안 해당 임상시험을 적절히 수행하고 완료할 수 있도록 충분한 시간을 할애하여야 한다.

③ 시험책임자는 예상되는 임상시험 기간 동안 해당 임상시험을 적절하고 안전하게 실시할 수 있도록 자격요건을 갖춘 적절한 수의 시험담당자와 적합한 장비나 시설을 확보하여야 한다.

④ 시험책임자는 시험담당자들이 계획서, 임상시험에 사용되는 의약품, 임상시험과 관련된 의무 및 업무 등을 숙지하고 있음을 확인하여야 한다.

14쪽 1단 1줄 30칸 1/ 1구역 삽입

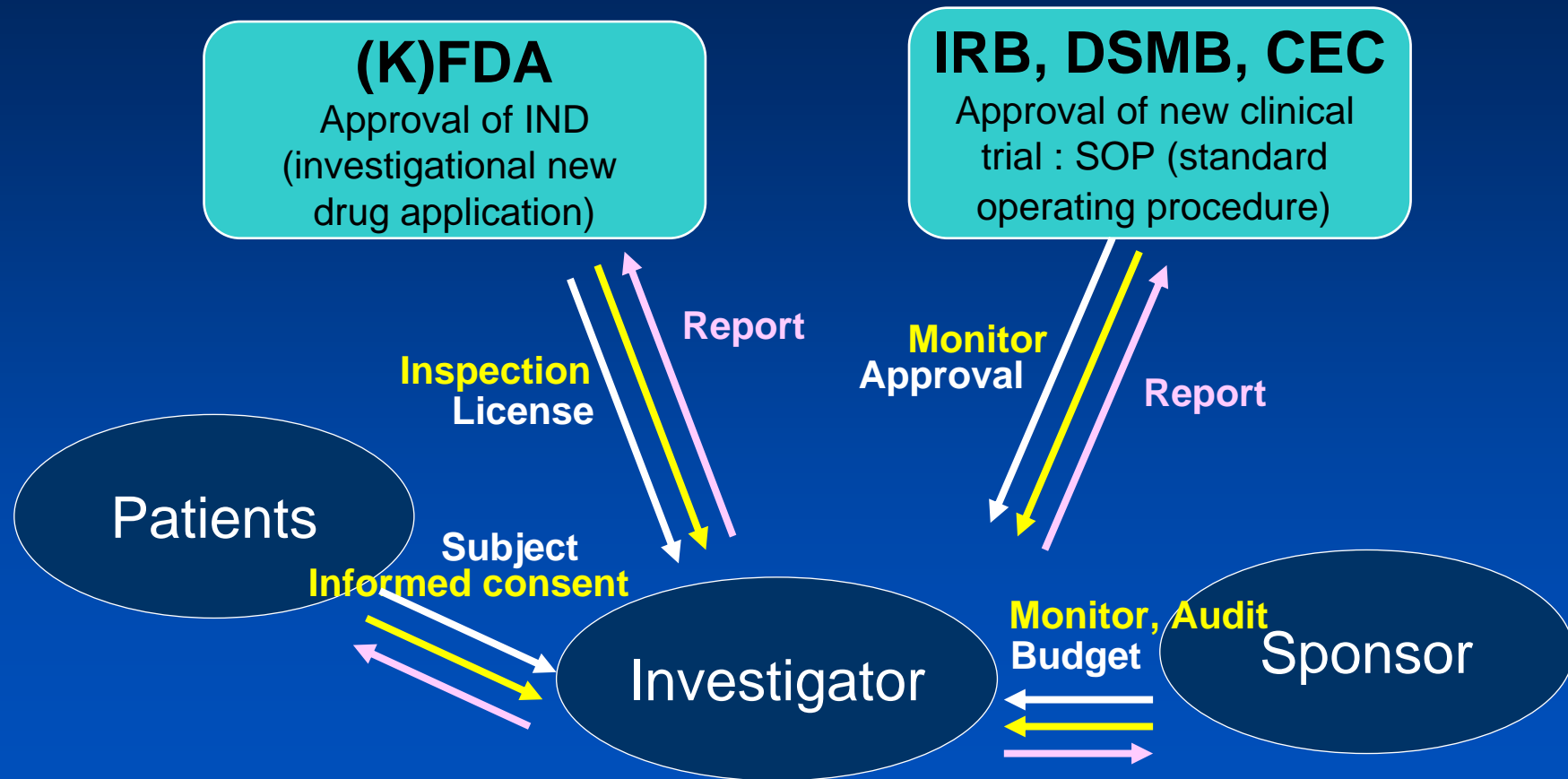


# Investigator's Responsibility

The investigator is responsible for insuring that an investigation is conducted according to the signed agreement, the investigational plan and applicable regulations for protecting the rights, safety and welfare of human subjects in the studies she/he conducts (*21 CFR 320-60, 21 CFR parts 50 and 56, 21 CFR 812-100, ISO 14155, ICH E6*)

# Investigator :

## A Core in the Process of Clinical Trial



# Example

## My Role in the BEST Trial

Randomized Comparison of Coronary Artery Bypass Surgery and Everolimus-Eluting Stent Implantation in the Treatment of Patients with Multivessel Coronary Artery Disease

**Patients with Multivessel CAD**  
Without LM disease

Stratified by

- DM
- Site

Randomize 1,776 (1:1)

**PCI with  
Everolimus-Eluting  
Stent**

**CABG**

- **PRIMARY Endpoint: mean 2-year clinical MACE (all death, MI, clinically-driven TVR)**
- **SECONDARY Endpoints: 2, 5 and 10-year MACE, MACCE, others**

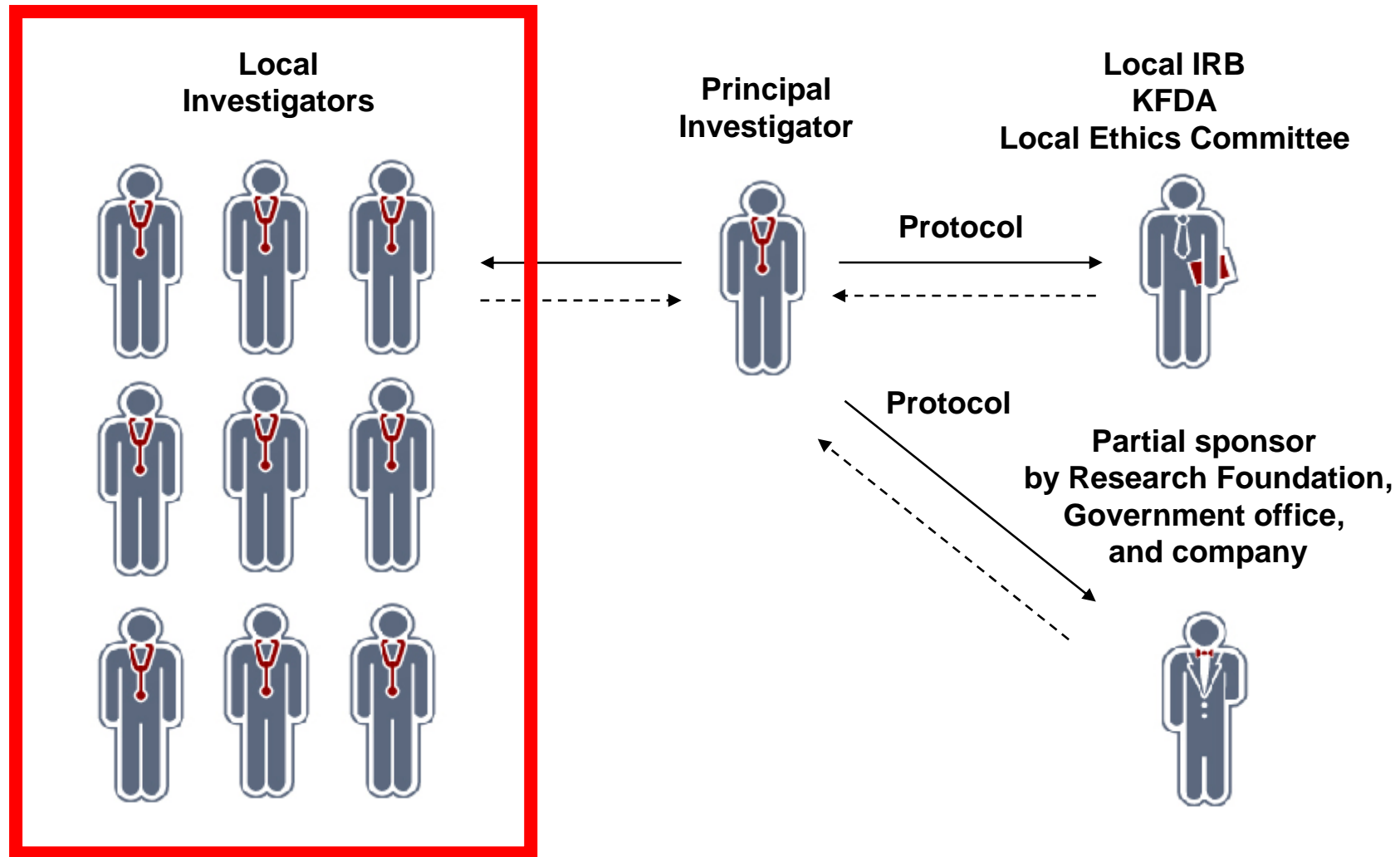
PI: Seung-Jung Park, MD, PhD

# Organization

- **Sponsor**
  - CardioVascular Research Foundation (CVRF), Seoul
- **Funding** : CVRF, Abbott Corp
- **PI**: Seung-Jung Park, MD, PhD
- **Executive Committee**
- **Steering Committee**
- **Data Safety Monitoring Board**
- **Clinical Event Committee**
- **Angiographic Core Lab** :
- **Data Management** :
- **Thallium Study Core Lab** : Asan Medical Center
- **Sites**: Korea, China, Malaysia, Hong Kong, Taiwan

CVRF

# Process of the BEST Trial Study Initiation



# Before Initiation

## Qualification

- The investigator must have qualifications recognized within his/her country of practice and be competent in the field of study as evidenced by **a written curriculum vitae**
- Be competent and experienced in research or receive scientific support from an **experienced colleague**
- Have **good knowledge of and experience** in the field of study defined by the protocol
- Have the **necessary resources** to participate in and take full responsibility for the proper conduct of the study
- Is not listed on the debarment list



# Before Initiation

## Investigational Product

- The investigator must have a knowledge of the properties, effects and side effects of the investigational product
- Must be familiar with the pre-study data, as described by the sponsor in the investigator's brochure, and
- Must be satisfied that the possible advantage to be gained from the study justifies any discomfort or risks involved for the participant

# Before Initiation Protocol

- The investigator must have a good knowledge of the protocol, protocol related documents and the requirements of the local participant code of rights and privacy legislation
- The protocol and related documents should be approved and signed by the principal investigator and a representative of the sponsor
- A budget in the form of a written contract should be established and documented in the investigator's information package for each study

# Before Initiation Protocol

- Data ownership should be stated clearly in the protocol or contract
- The protocol related documents should clearly describe a process for resolving problems concerning any investigator who has failed to adhere to any aspect of the agreement contained within the protocol

# BEST Trial

# Investigator's Brochure

BEST Trial



Randomized Comparison of Coronary Artery Bypass Surgery and Everolimus-Eluting Stent Implantation In the Treatment of Patients with Multivessel Coronary Artery Disease

## The BEST Trial

### Principle investigator:

Seung-Jung Park, MD, PhD.

Asan Medical Center, University of Ulsan College of Medicine

### Organization and Sponsor:

CardioVascular Research Foundation, Seoul

### Address of principle Investigator:

Seung-Jung Park, MD, PhD.  
Department of Medicine, Asan Medical Center,  
University of Ulsan College of Medicine,  
388-1 Pongnap-dong, Songpa-gu, Seoul, 138-736, Korea.  
Fax: (82-2)-475-6898, Tel: (82-2)-3010-4812, E-mail: sjpark@amc.seoul.kr

Version 2.3  
May 30, 2008

CardioVascular Research Foundation  
Page 1 of 43



# Before Initiation

## Facilities and Staff

- The safety of the participants in a study should be of the highest concern
- The study site must have the necessary facilities, including emergency equipment and appropriate medical, paramedical and clerical staff to support the study

# BEST Trial

# Questionnaire for Feasibility Test



## Site Recruitment Questionnaire

### Part A: Contact Information (Please complete or correct)

Investigator				
First Name		Last Name		
Mailing Address				
Phone		Fax		e-mail

### Part B: Ethics Committee

B.1. Which type of IRB or Ethic committee do you use at your Clinical Site able to use a Central Ethics Committee?	<input type="checkbox"/> Central IRB	<input type="checkbox"/> Local IRB
B2. If No (your site cannot use a Central Ethics Committee), how often does the local IRB at your clinical site meet?	<input type="checkbox"/> Once per week <input type="checkbox"/> Twice a month <input type="checkbox"/> Once per month <input type="checkbox"/> Other (specify: _____ )	
B3. How many weeks are typically required to receive IRB approval following the IRB meeting?	<input type="checkbox"/> One week <input type="checkbox"/> Two weeks <input type="checkbox"/> Three weeks <input type="checkbox"/> Other _____	



### Part C: Center Feasibility

C. 1. Do you have previous experience of clinical trials (in this indication)?	<input type="checkbox"/> Yes	<input type="checkbox"/> No
C. 2. Do you have clinical research staff resources at your site to support conduct of this study?	<input type="checkbox"/> Yes	<input type="checkbox"/> No
a) If yes, please specify the position of the staff:	<input type="checkbox"/> Physicians <input type="checkbox"/> Study Coordinators <input type="checkbox"/> Research Nurses <input type="checkbox"/> Other research staff (specify: _____ )	
b) Please provide the contact information of the clinical research staff :		
Name:		
Phone No:		
Fax No:		
Email:		
C. 3. Do you have experience of using electronic case reports forms?(e-CRF)	<input type="checkbox"/> Yes	<input type="checkbox"/> No
If yes, please provide the contact in formation of the best person in this regard:		
Name:		
Phone No:		
Fax No:		
Email:		

Please return this questionnaire by e-mail to Jay Jang ([jay0025@amc.seoul.kr](mailto:jay0025@amc.seoul.kr))

Thank you for taking the time to complete this questionnaire.

We are very much looking forward to collaborating with you on this exciting protocol.



# Before Initiation

## Study Participants

- The principal investigator (PI) is responsible for ensuring the selection of participants for the study and should have access to an adequate number of individuals who could fulfill the entry criteria
- The investigator is responsible for ensuring that an adequate information package is available for use in the process of seeking informed consent to participate in the study (IRB/MEC approved documents)

# Before Initiation

## Study Participants

- Once consent to participate in the study has been obtained, a copy of the signed consent form and a source document identifying the study and recording the dates of participation should be placed in the participant's medical record
- The investigator must ensure that participants are provided with high quality medical care during and after the study, including care to the participants should they suffer an adverse event and be withdrawn from the study



# During the Study

## Adherence to the Protocol

- The PI is responsible for ensuring that **the protocol and appendices** are strictly followed
- The investigator must not omit, delete, or add any procedures to those detailed in the protocol nor can the investigator make any changes to the investigational product use, or the product
- **Written approval** of any protocol amendments from the IRB / ethics committee must be received prior to the investigator instituting any changes to the protocol

# During the Study

## Handling of investigational products

- Responsible for
  - the safe handling, storage and use of the investigational product(s)
  - the safe handling, storage and use of the reference product(s) and placebo used in the study, and
  - the keeping of records

# During the Study

## Data Management

- The PI is responsible for the collection, quality, recording, maintenance and retrieval of **source data** arising from the clinical study
- Each CRF case book (and selected pages) must be signed and dated by the investigator, or designated person, then stored securely
- The investigator should make the data available to the sponsor on a timely basis
- The investigator must be available for **agreed visits** by the monitor during the study and also cooperate in the data editing, quality control and audit

# BEST Trial

## Electronic Data Capturing

### BEST

010005  
HGD  
2007-04-24

[Home](#) / 
 [New Case](#) / 
 [Subject List](#) / 
 [Adjudication](#) / 
 노진석(서울마산병원)
 로그아웃
관리자
문의하기

- > Index Hospitalization Data
  - Demographic Data
  - Admission Data
  - Risk Factor & History
  - Non-Invasive Test
- > Angiographic & Procedural Data
  - Angiographic Lesion Data
  - Index Procedure Data
- > Medications Data
  - Antiplatelete\_Inhospital
  - Antiplatelete\_Follow Up
  - Other Concomitant
- > Pre-Discharge Inhospital Data
  - Discharge Data
  - Laboratory Data
- > Follow Up Data
  - 30days Clinical FU Data
  - 6Month Clinical FU Data
  - 9Month Clinical FU Data
  - 12Month Clinical FU Data
  - Angiographic / Functional Test Follow Up Data
- > Major Event Data
  - Death
  - Myocardial Infarction
  - Repeat Revascularization
  - Stent Thrombosis
  - CVA / Stroke
  - Bleeding

Index Hospitalization Data  
**ADMISSION DATA**

**Admission date \***  (yyyy-mm-dd)

**Admission status \***  Via ER  Via OPD

• Type of ER visit  Direct visit to ER  Transfer to ER

• Arrival Date at ER visit  (yyyy-mm-dd) Time  hr  min

**First medical contact \***  Primary physician  Other hospital  Others

**Treatment at transferred hospital \***  Yes  No

- Antiplatelet agent

Aspirin - Loading Dose  mg Maintenance Dose  mg

Plavix - Loading Dose  mg Maintenance Dose  mg

Thrombolysis  Unfractionated Heparin  LMWH

- Thrombolysis Date  (yyyy-mm-dd) Time  hr  min

- Thrombolysis Drug  UK  U  TNK t-PA  mg  Others

- Thrombolysis Dose  Full dose  Half dose

**Chief complaint on admission \***  Typical chest pain  Atypical chest pain

**✕ Typical chest pain**

Stable angina  Unstable angina  NSTEMI  STEMI

• Stable angina  CCS I  CCS II  CCS III  CCS IV

- Severity  Class I  Class II  Class III

• Unstable angina

# During the Study

## Safety Issues

- Decisions and actions relevant to the clinical management and safety of the participant in acute situations are the responsibility of the investigator.
- The investigator must also know the requirements for reporting serious adverse events to the IRB / ethics committee and to the regulatory authority

# BEST Trial

## Reporting of SAE

**BEST**    Home    New Case    Subject List    Adjudication    노진석(서울아산병원)    로그인    관리자    문의하기

010005  
HGD  
2007-04-24

**Major Adverse Event**  
**Death**

**Death**    Subject Number :     Subject Initial :

**Date of death**     (yyy-mm-dd)

**Date of Index Procedure**     (yyy-mm-dd)

Cardiovascular Death

- Acute myocardial infarction     Cardiogenic shock
- Fatal arrhythmia (VF or conduction block)     CVA / Stroke
- Aortic dissection/rupture     Pulmonary embolism
- Other vascular disease     Procedure-related death
- Low-output failure (heart failure)
- Others

**Classifications of Death**

Non-cardiovascular Death

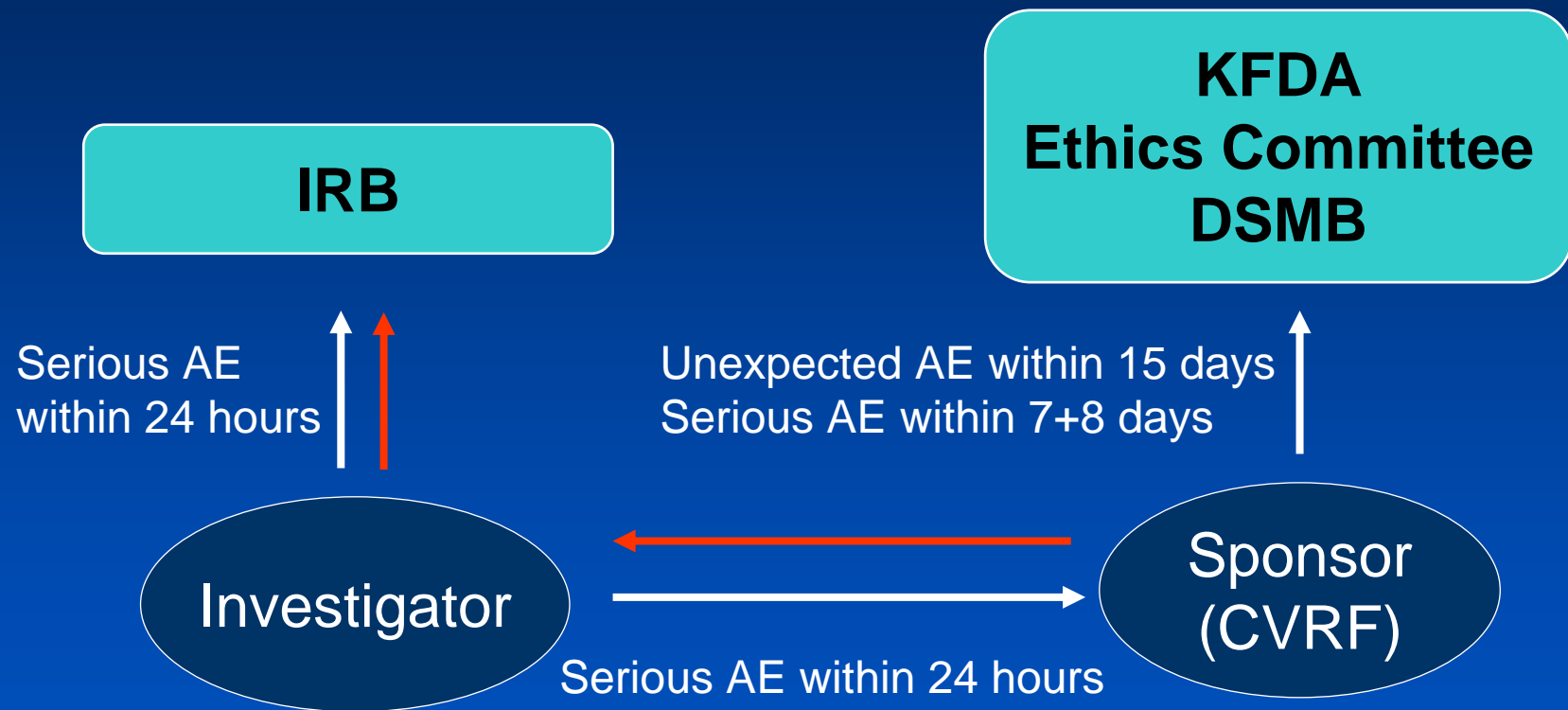
- Malignancy     Renal failure
- Infection (sepsis)     Pulmonary causes or respiratory failure
- Trauma     Suicide /homicide
- Accident     Unobserved
- Others

Unknown Origin Death

**Comments**

**Adjudication**     Yes     No    **Adjudication Date**  (yyy-mm-dd)

# Reporting of Adverse Event by Investigators



# During the Study

## Progress Report

- The investigator is obliged to submit progress reports as required by the sponsor, the regulatory authority and/or the relevant IRB / Medical Ethics Committee (MEC)
- These reports should contain information on how the study is progressing (including safety updates at the time of the report), the number of participants included in relation to the number expected, the number of dropouts and withdrawals



# After the Study

- After the study has ended the investigator is obliged to notify the study participants, IRB/MEC and, if required, regulatory authorities that the study has finished
- Following completion of the study all source documents should be available to the sponsor to review the CRFs for accuracy, completeness and legibility as well as use in independent adjudication of adverse events

# Responsibility of Investigators

- We appreciate your tremendous contributions to our study....