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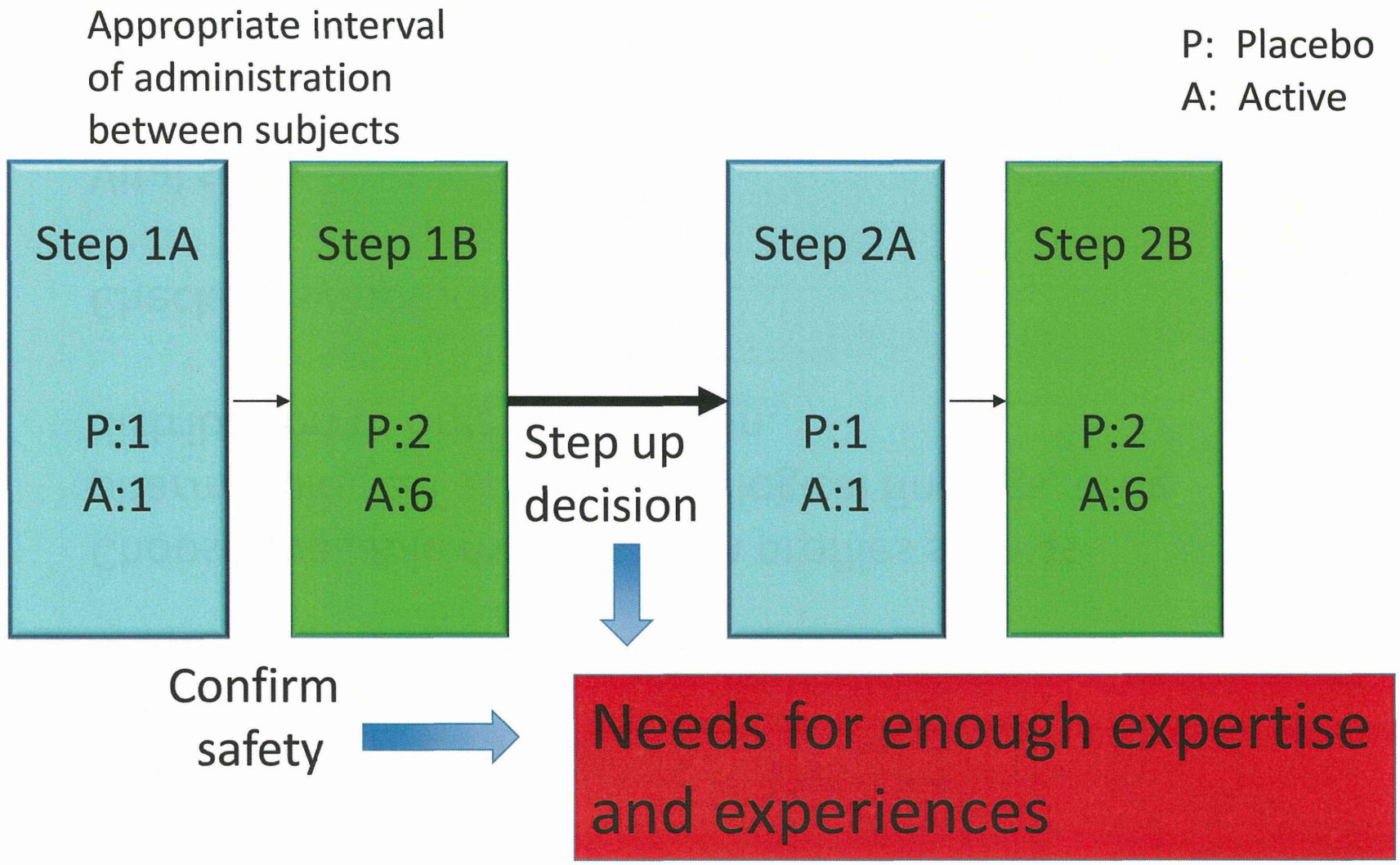
Standard design of FIH



Types of ADR

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Type		Dependent on	
A1	Primary pharmacology	Cmax	Warfarin; bleeding Insulin; hypoglycemia
A2	Secondary pharmacology	Cmax	Terfenadine; TdP
B	Immunology	Subject	Idiosyncracy
C	Organ Toxicity	AUC/Cmax	Acetoaminophen; DILI*
D	Carcinogenicity Tratogenicity	AUC	

*DILI: Drug induced liver injury

Two types of clinically important adverse reactions

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1. Commonly observed ADR — Often predictable

Not so severe, but commonly found in daily practice.

ex. Headache, GI symptoms, palpitation, high blood pressure ….

2. Rare but severe ADR — Prediction by surrogate markers

Even it's very rare, but it may be fatal once occurred.

ex. Hepatitis, rhabdomyosis, TdP, progressive multifocal leukoencephalopathy (PML)

Raptiva® (efalizumab) increased risk of PML.

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Possible Safety Biomarkers

Specific markers for candidates

Direct biomarkers for acute organ damage

- Kim-1

Indirect biomarkers to detect signals of rare and severe ADRs

- QT/QTc, Hy's law, HR

Rediscovery of known biomarkers

- CRP, HR

Early detection of ADR
&
Risk group specification

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Increasing sampling

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New Approach for Renal Injury

- Critical Path Institute's Predictive Safety Testing Consortium (PSTC) consulted PMDA concerning pharmacogenomic biomarkers.

- PSTC's activity was accepted and encouraged for further researches.

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Biomarkers of Renal Injury

- Representative markers are Creatinine, BUN and NAG.
- Serum creatines is always employed in any stage of CTs.

- However, predictability of Cr is not enough in early stage of renal injury owing to little correlation between its serum level and GFR when Cr level is low.

Biomarkers to detect damages in renal tubules

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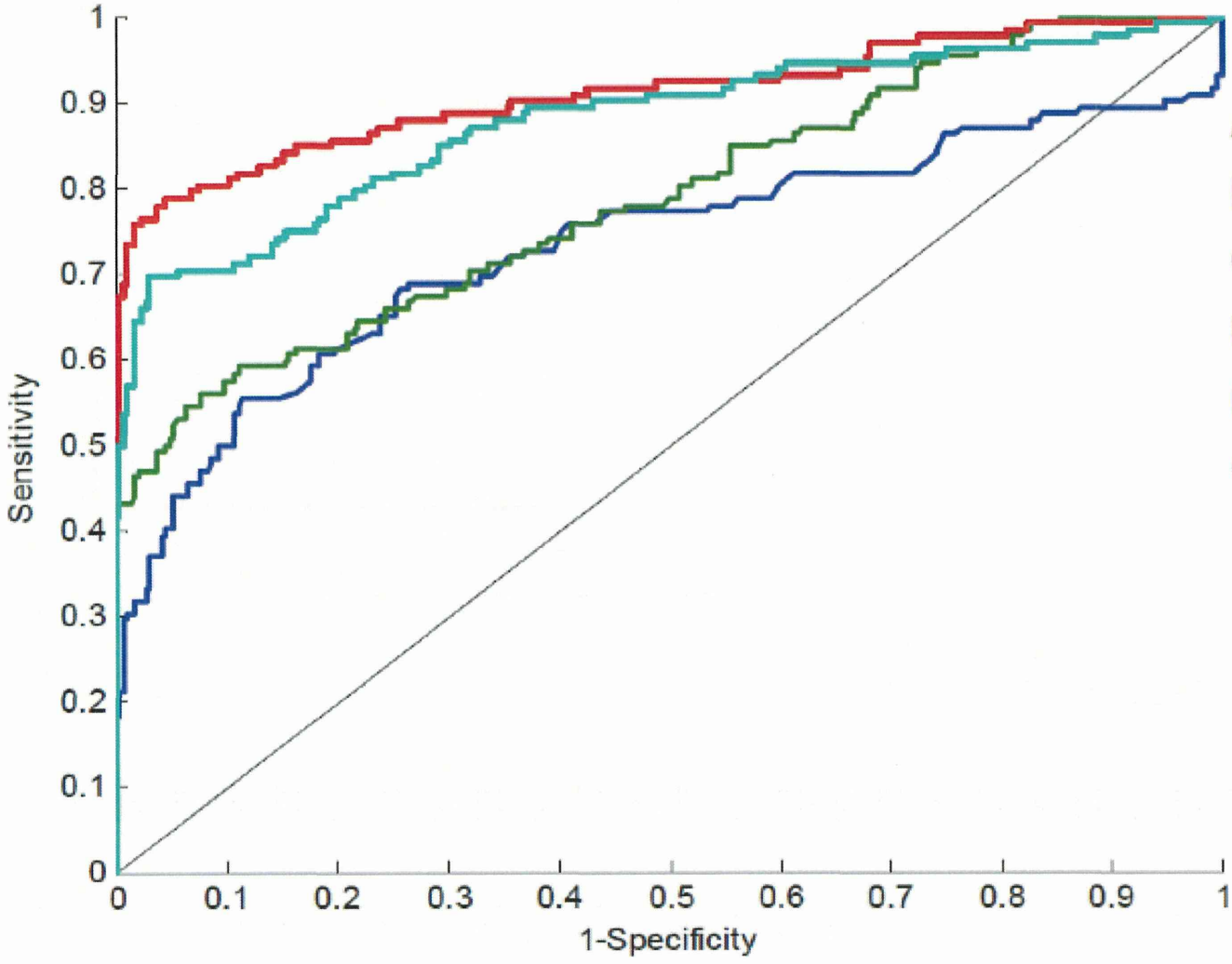

Area Under Curve:

Random = 0.5

Creatinine = 0.73

BUN = 0.79

Kim-1 = 0.91

Clusterin = 0.88

132 Diseased

289 (283) Controls

Biomarkers to detect damages in glomerulus

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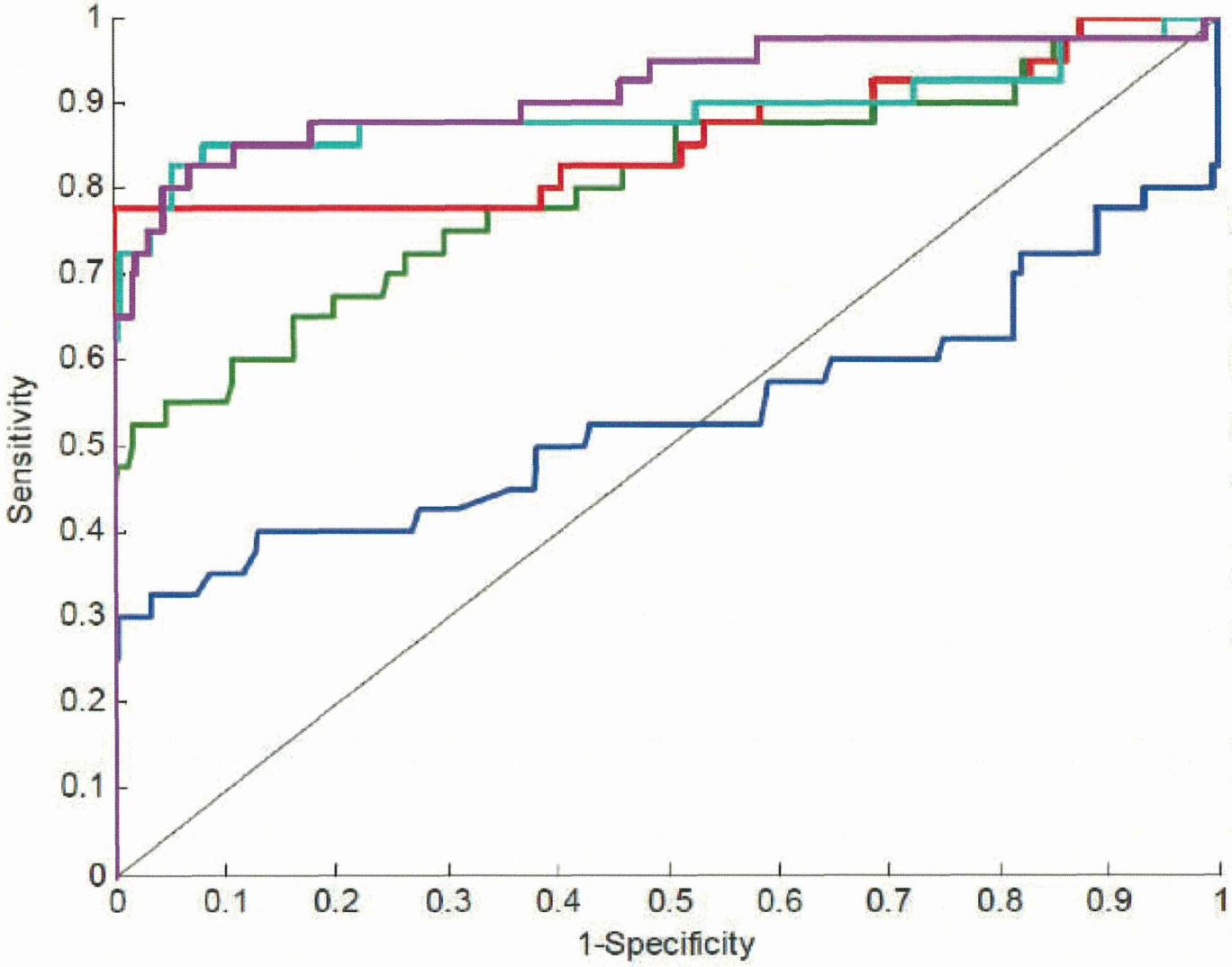

Area Under Curve:

Random = 0.5

Creatinine = 0.53

BUN = 0.80

Tot. Protein = 0.86

B2-Microglob. = 0.89

Cystatin C = 0.91

40 Diseased

291 Controls

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PMDA's attitude for safety biomarkers

PMDA will accept use of safety biomarkers even they are not validated, but general markers should be used together.

PMDA will request an evidence whether the safety markers are sensitive or specific enough.

It is encouraged to include novel safety biomarkers together with traditional markers for future utility.

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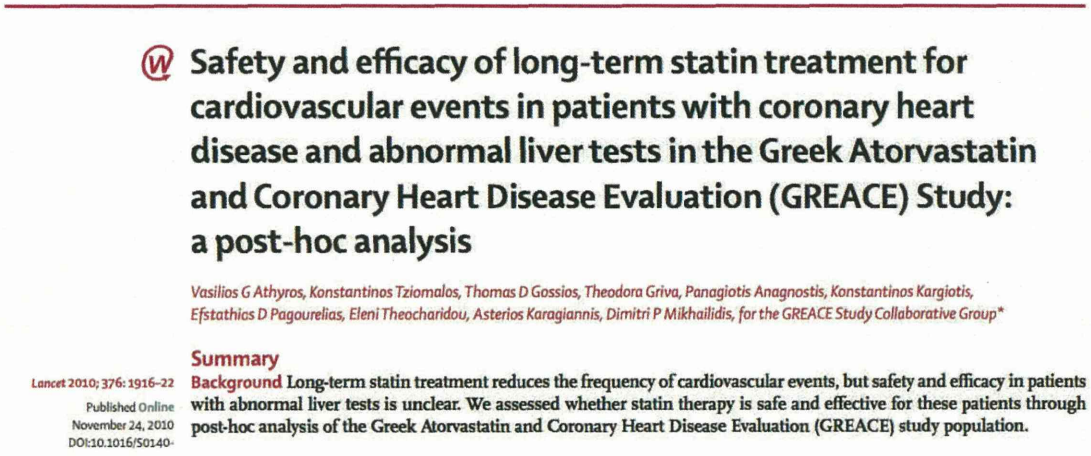
Markers for DILI

Trans-aminase such as AST and ALT are generally used, however they are not specific to DILI.

They often increase in early CTs due to relative increase of oral intake.

Several drugs do have pharmacologic action of increasing AST and ALT.



Safety and efficacy of long-term statin treatment for cardiovascular events in patients with coronary heart disease and abnormal liver tests in the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) Study: a post-hoc analysis

*Vasilios G Athyros, Konstantinos Tziomalos, Thomas D Gossios, Theodora Griva, Panagiotis Anagnostis, Konstantinos Kargiotis, Efstathios D Pagourelias, Eleni Theocharidou, Asterios Karagiannis, Dimitri P Mikhailidis, for the GREACE Study Collaborative Group**

Lancet 2010; 376: 1916–22
Published Online November 24, 2010
DOI:10.1016/S0140-

Summary

Background Long-term statin treatment reduces the frequency of cardiovascular events, but safety and efficacy in patients with abnormal liver tests is unclear. We assessed whether statin therapy is safe and effective for these patients through post-hoc analysis of the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) study population.

Athyros VG et al,
Lancet 2010;376:1916-1922

Present situation of DILI

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Main reason of withdrawal is idiopathic liver injury.

In US, 58% of liver damage are drug-induced, and 46% are induced by acetoaminophen.

In Japan 15% of liver damage are drug-induced, and among them, 18% are induced by NSAIDs.

Dose of 44 drugs with evidence or risk of idiopathic DILI

Daily Dose (mg/man)	<10	< 100	≥100
Number of Drugs	1	5	38

(Pfizer, Walgren et al., 2005)

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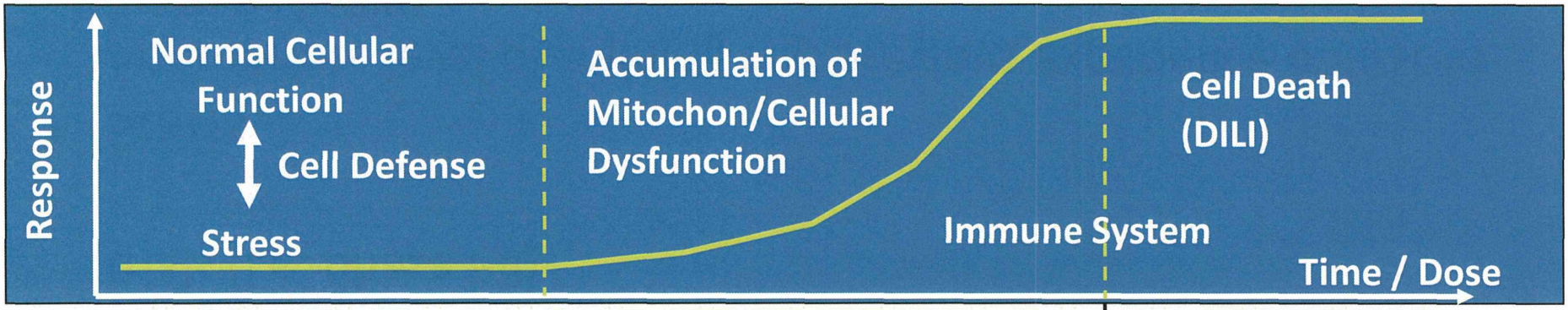
Hy's law (Temple 2001; Reuben 2004).

1. The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST than the (nonhepatotoxic) control drug or placebo

2. Among trial subjects showing such AT elevations, often with ATs much greater than 3xULN, one or more also show elevation of serum TBL to >2xULN, without initial findings of cholestasis (elevated serum ALP)

3. No other reason can be found to explain the combination of increased AT and TBL, such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury

Possible Biomarkers for DILI



Novel Biomarkers

Mechanism Specific → **Function Related** → **Cell-Lysis**

Potential Reactive Met
- -Drug Mercapturate (U)

Oxidative Stress
- -Ophthalmic Acid (B/U)
- -Taurine (U)
- -Aconitase 2 (B/U?)

Metabolomics

Mitochondrial Damage
- -GLDH (B)
- -Cytochrome C (B/U)
- -Malate Dehydrogenase (B)
- -OCT (B)
- -Acyl-carnitine/Acyl glycine (B/U)

Liver Function
- -PON 1 (B)

Leakage
- -SDH (B)
- -Serum F Protein (B)
- -Arginase (B)
- -PNP (B)
- -mi RNA (B)

Apoptosis Specific
- - Keratin 18 frag.(B)

Necrosis / Inflammation
- - Keratin 19 full leng.(B)
- - HMBG1 (B)

Immune System
- -Sensitized T cells (B)
- -Cytokines (B/U)

(U): Urine; (B): Blood

Abb. HMGB1: High Mobility Group Box Protein 1;
OCT: Ornitinecarbamoyl Transferase;
PNP: Purine nucleoside phosphorylase; PON1: Paraoxonase 1

4.4.3 Investigator site facilities and personnel

- Appropriate clinical facilities

  Immediate access to equipment and staff of Intensive Care Unit.

  Ready availability of Intensive Care Unit facilities

  Established procedures for responsibility and transfer

- Investigators

  Enough expertise and experience in conducting early phase trials (i.e. phase I-II)

- Staffs

  Appropriate level of training and previous experience of first-in-human studies

Study Ward and Unit

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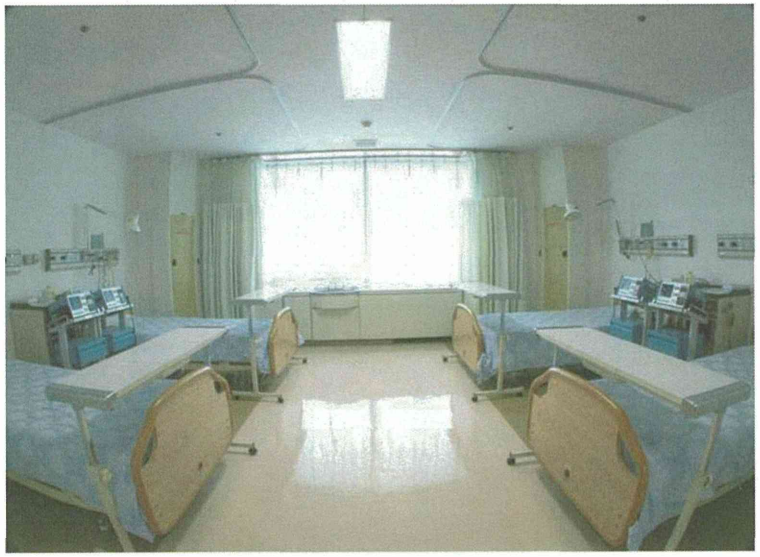

Unit (4 beds)

South wing

5 rooms

North wing

4 rooms

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Emergency Cart

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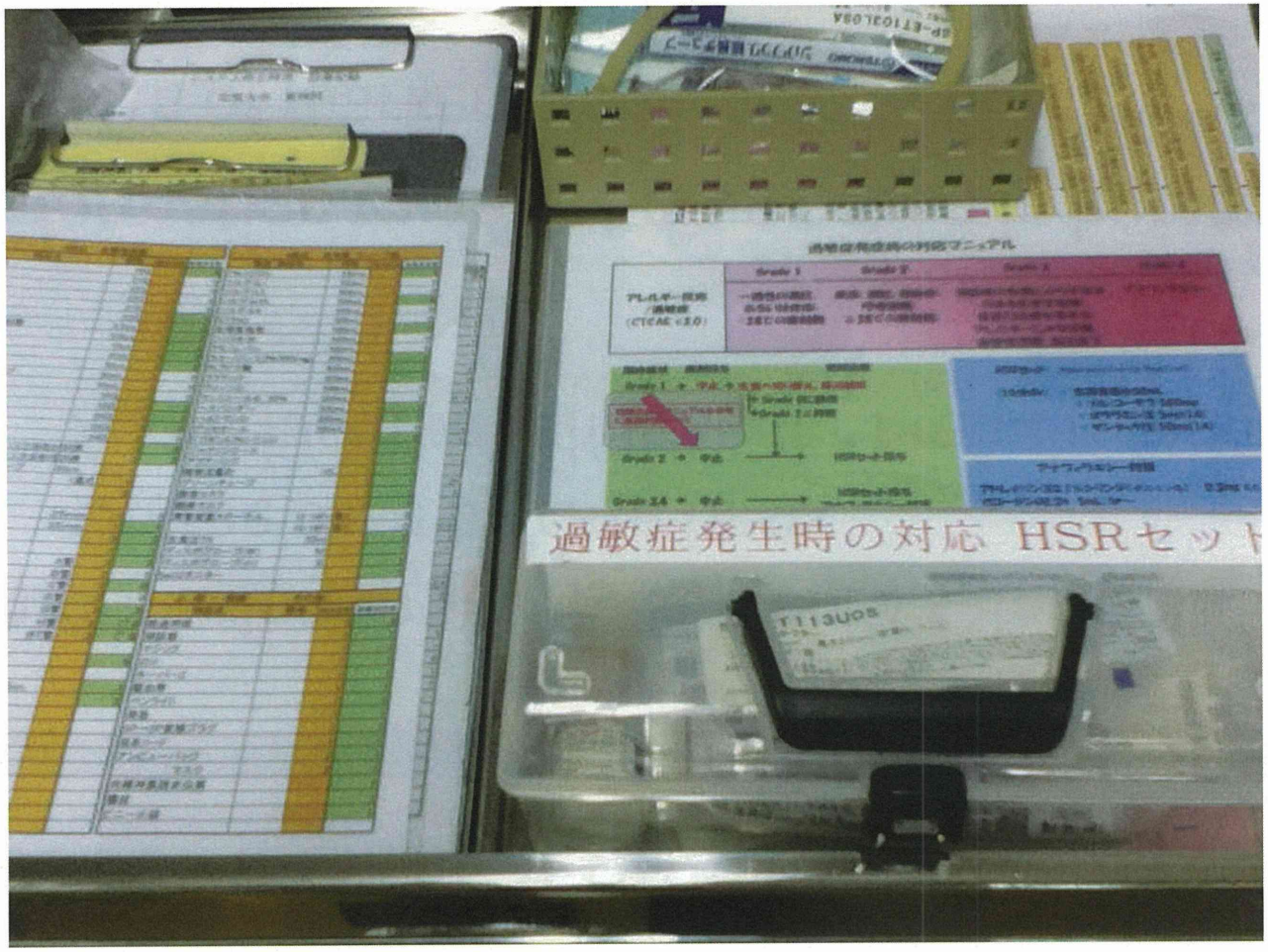
Prepare for Possible Events



Desirable Information from nonclinical studies for a clinical pharmacologist

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Information to secure subject's safety

- On the case by case basis
- Avoid just the fulfillment of requirements

Information to detect drug action in human

- Use of markers applicable to human

Let's aim at global development even at the stage of nonclinical studies

Backup