# Inventory Guide of Biomarker based Clinical Study Design

- PHuse Japan 3rd. SDE -

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# Agenda

1. Introduction

2. Inventory for Biomarker based Clinical Study Design

3. Pharmacometricians' Perspective

# Definition for BMs

'A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention'

- ***Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: Preferred definitions and conceptual framework. Clin. Pharmacol. Ther. 2001, 69, 89–95.***

# Classification for BMs (1/2)

| Classification | Examples |
|---|---|
| Pharmacodynamic Biomarker | CRP, IL-6, TNF-α, FDG-PET, |
| Prognostic Biomarker | Amyloid β peptide (AB) 1-42 , Mamma Print, BNP, |
| Predictive Biomarker | HER2, EGFR, KRAS mutation, BCR-ABL, CYP2D6, CYP2C9, CYP2C19, ER and PR, PML/RARα, UGT1A1, TMPT, HLA-B*5701, DPYD, Oncotype, MammaPrint, |
| Surrogate Biomarker | LDL cholesterol, HbA1c, PSA, Carcinoembryonic antigen (CEA) |

# Classification for BMs (2/2)

| Classification | Examples |
|---|---|
| Pharmacodynamic Biomarker | CRP, IL-6, TNF-α, FDG-PET, |
| Prognostic Biomarker | Amyloid β peptide (AB) 1-42 , Mamma Print, BNP, |
| Predictive Biomarker | HER2, EGFR, KRAS mutation, BCR-ABL, CYP2D6, CYP2C9, CYP2C19, ER and PR, PML/RARα, UGT1A1, TMPT, HLA-B*5701, DPYD, Oncotype, Mamma Print, |
| Surrogate Biomarker | LDL cholesterol, HbA1c, PSA, Carcinoembryonic antigen (CEA) |

# Prognostic/Predictive BMs

- **Prognostic**

| | Positive | Negative |
|---|---|---|
| Reference | + | - |
| Test | + | - |

- **Predictive**

| | Positive | Negative |
|---|---|---|
| Reference | - | - |
| Test | + | - |

- **Predictive & Prognostic**

| | Positive | Negative |
|---|---|---|
| Reference | + | - |
| Test | ++ | - |

# Clinical qualification

- Co-development ~ Companion Biomarkers
  - What is objective to qualify  Clinical Biomarkers ?
  - Clinical validity
    - Intended to use for Clinical Study
  - Clinical utility
    - Intended to use for actual  patient-treatment
  - Retrospective ~ Prospective –Retrospective ~ Prospective analysis

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# Randomized Clinical Trial (RCT) design

No objective for Clinical qualification of biomarkers

May be used to Initially identify candidate biomarkers by Retrospective analysis for RCTs (ex. KRAS and Cetzuximab).

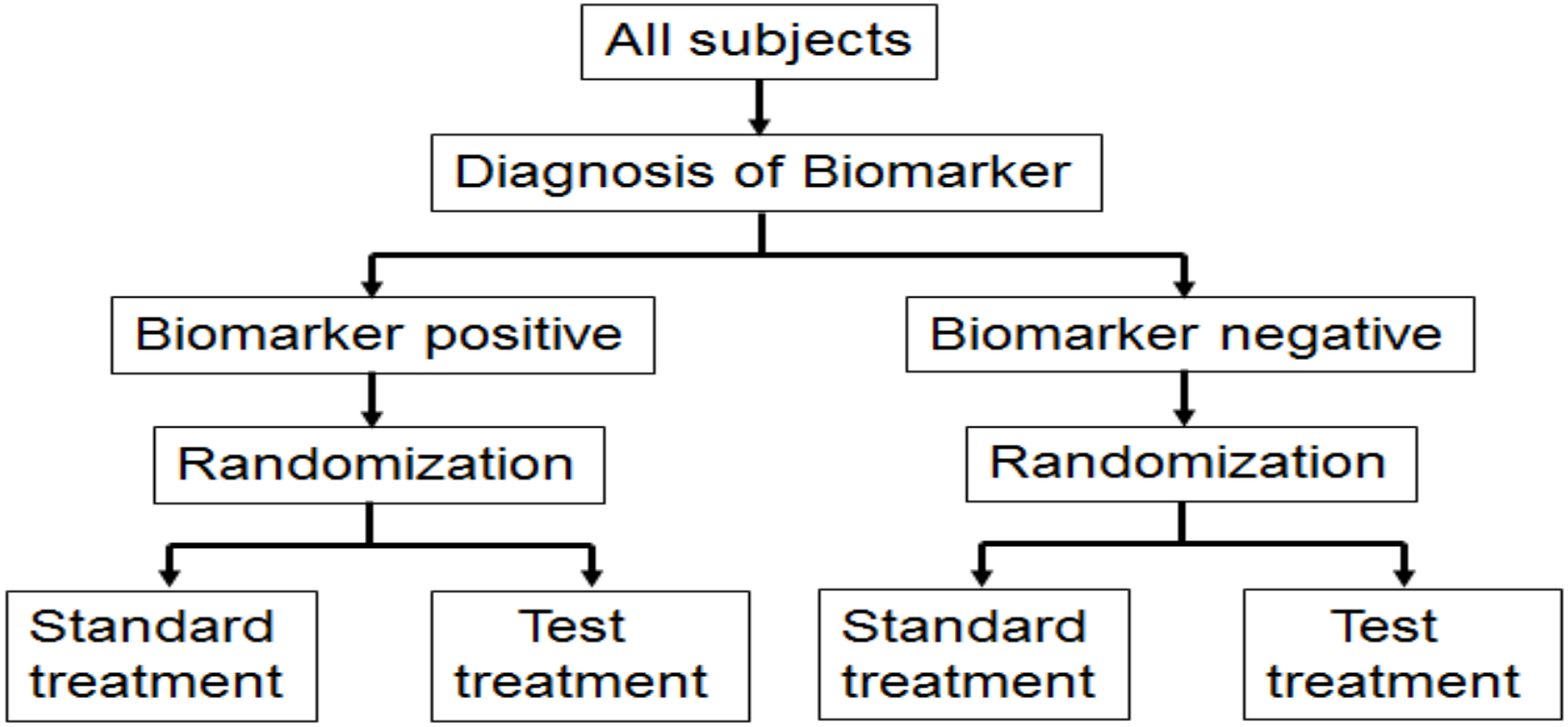
- For a prognostic biomarker

  The clinical utility or validity of the biomarkers may need to be confirmed in prospective studies.

- For a predictive biomarker

  The clinical utility or validity of the biomarkers may be lack thereof and the clinical utility or validity of the biomarkers may be required to validate in prospective studies.

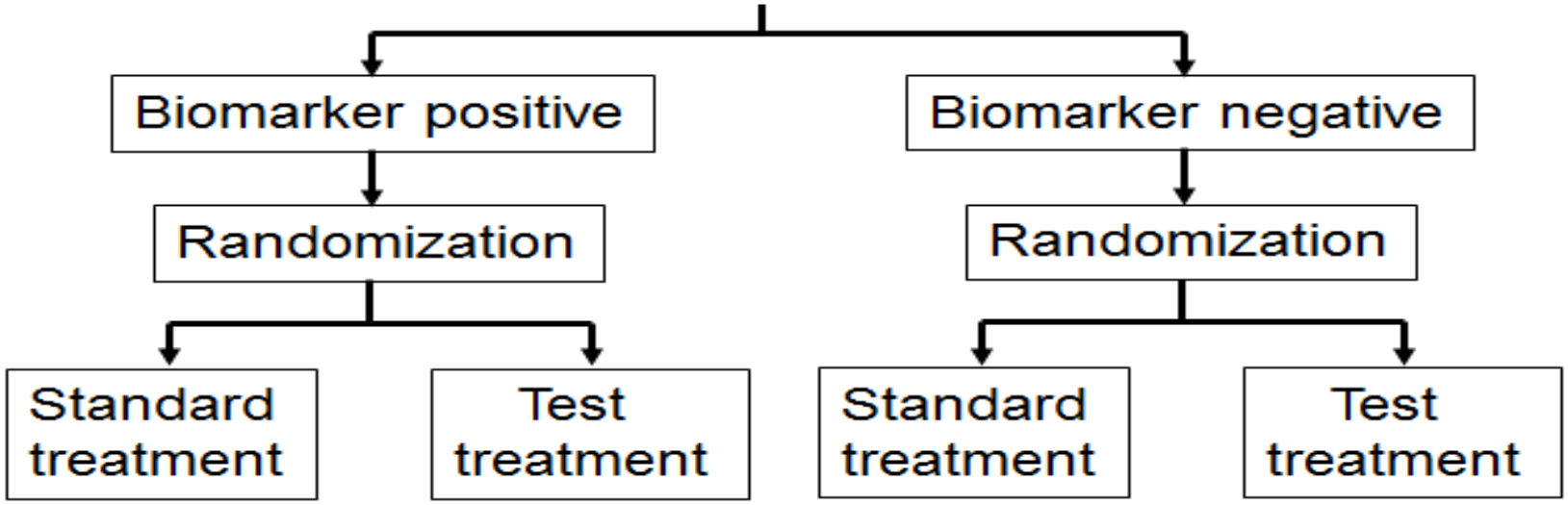
# *Biomarker by Treatment Interaction Design*




a Cancer and Leukemia Group B trial to investigate benefit of adjuvant chemotherapy in stage NSCLC patients http://www.cancer.gov/clinical trials/CALGB-30506 (accessed on 31 May 2012

# *Biomarker by Treatment Interaction Design*

Could be used to confirm the Clinical validity of the biomarker previously qualified

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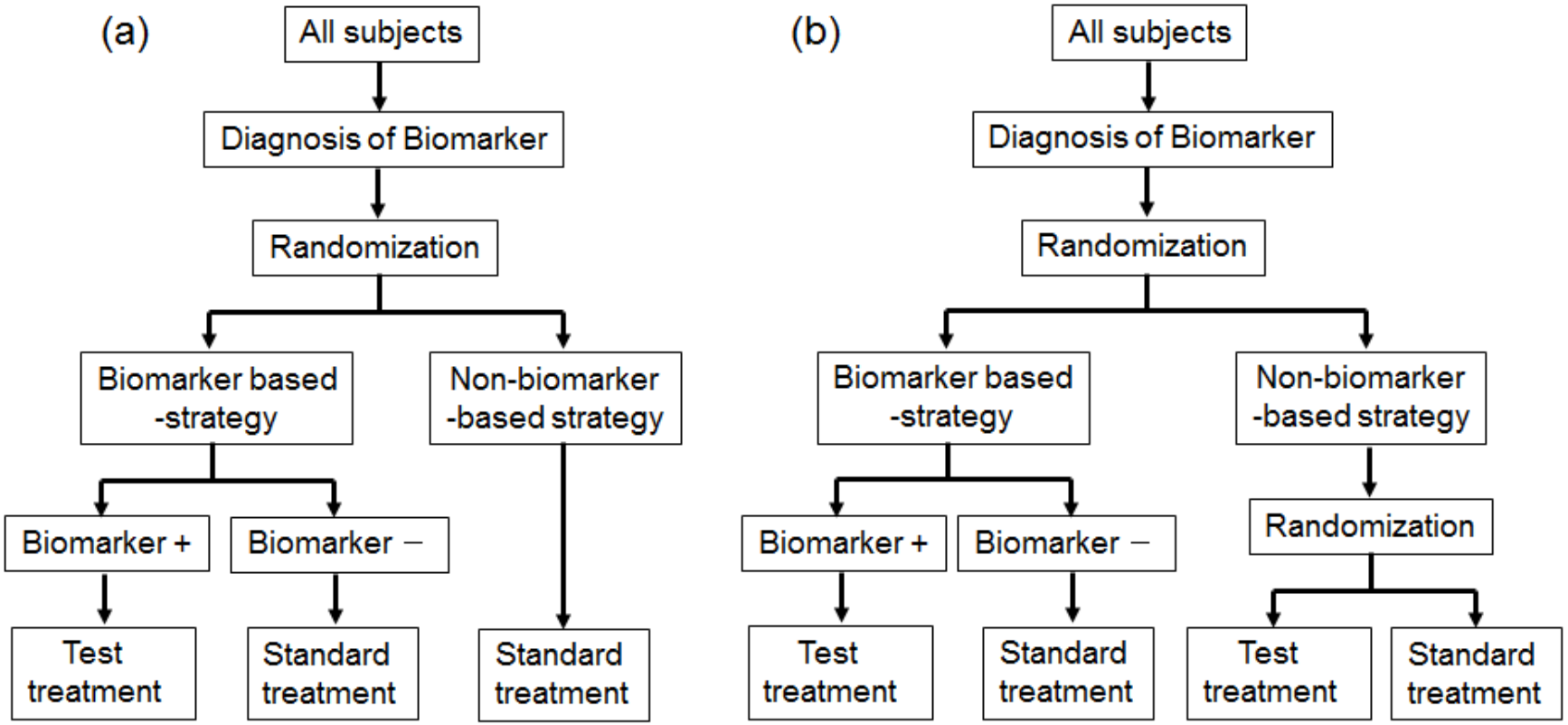
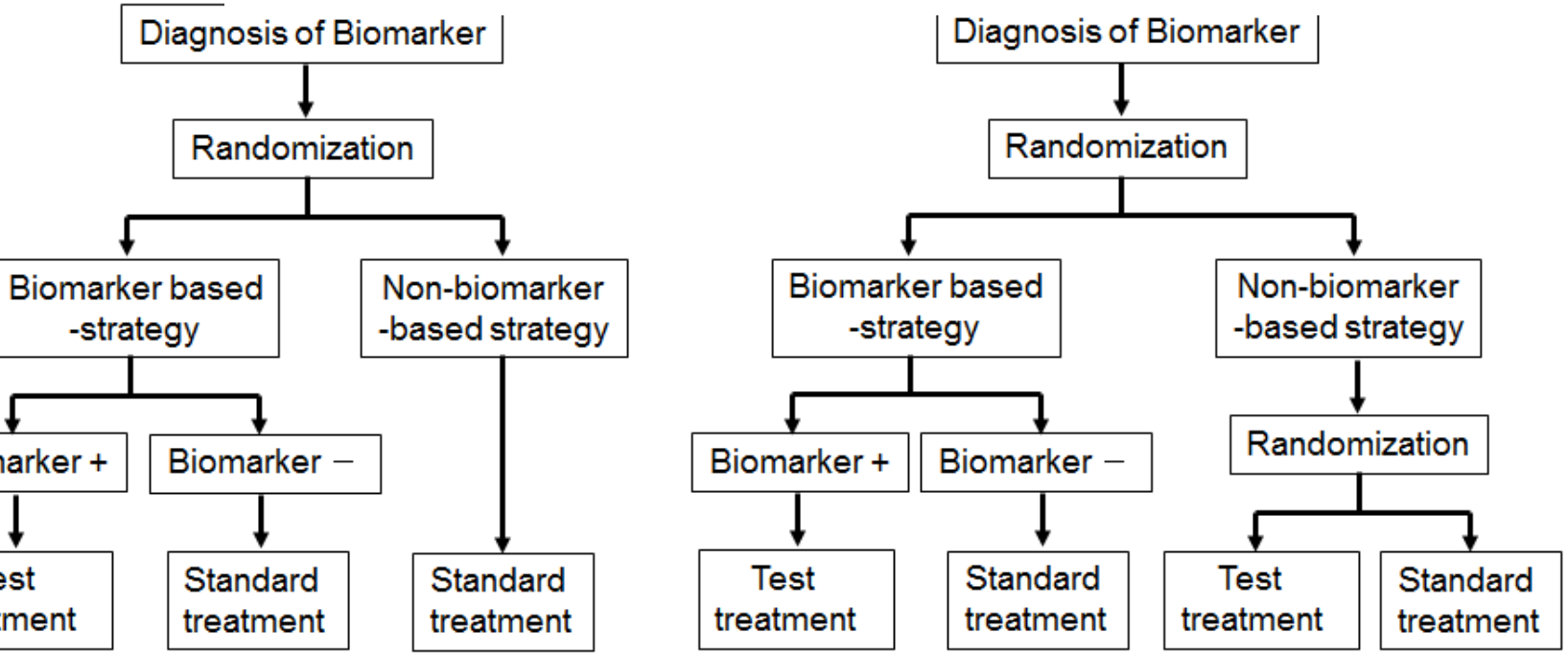
# *Biomarker-Strategy Design*




**Cobo, M.; Isla, D.; Massuti, B.; Montes, A.; Sanchez, J.M.; Provencio, M.; Viñolas, N.; Paz-Ares, L.; Lopez-Vivanco, G.; Muñoz, M.A.; *et al. Customizing cisplatin based on* quantitative excision repair cross-complementing 1 mRNA expression: A Phase III trial in non-small-cell lung cancer. *J. Clin. Oncol. 2007, 25, 2747–2754***

# *Biomarker-Strategy Design*

Generally less efficient than the traditional randomized design.

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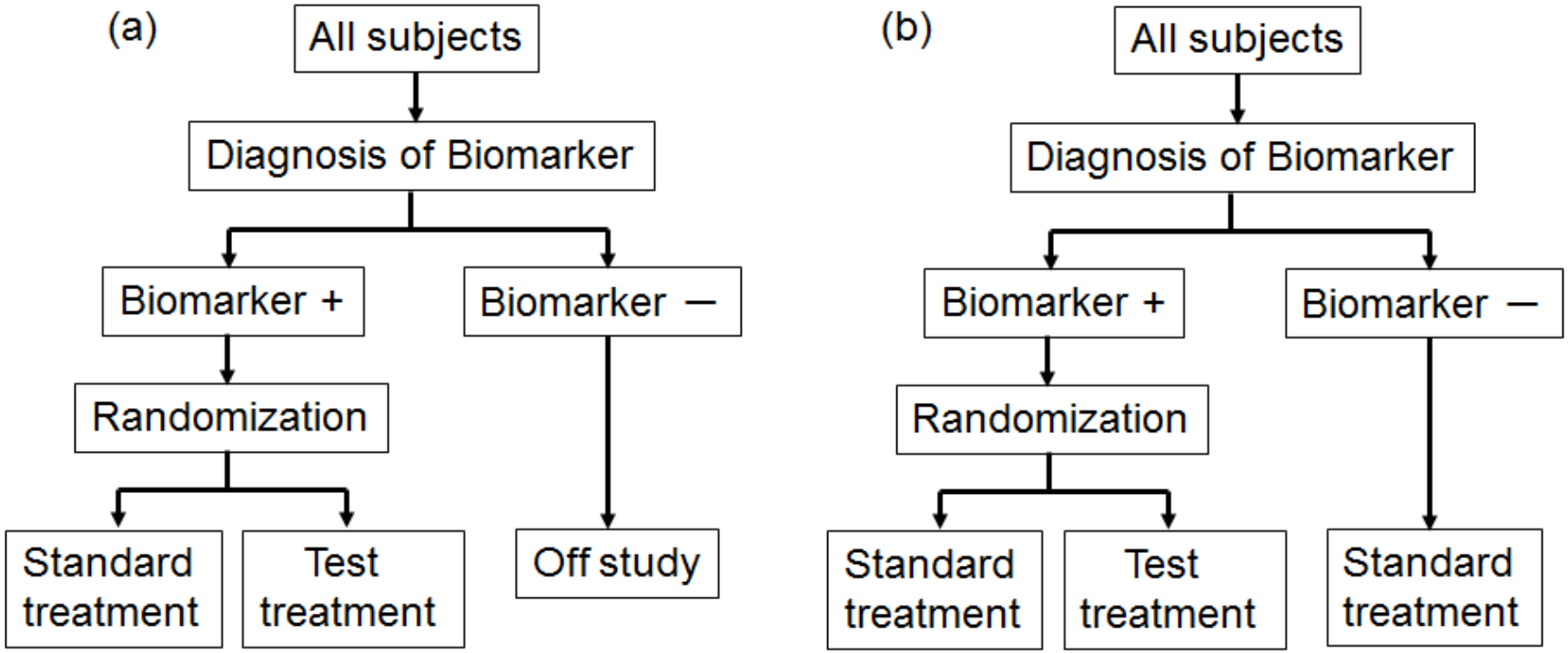
# *Enrichment Design and Hybrid Design*

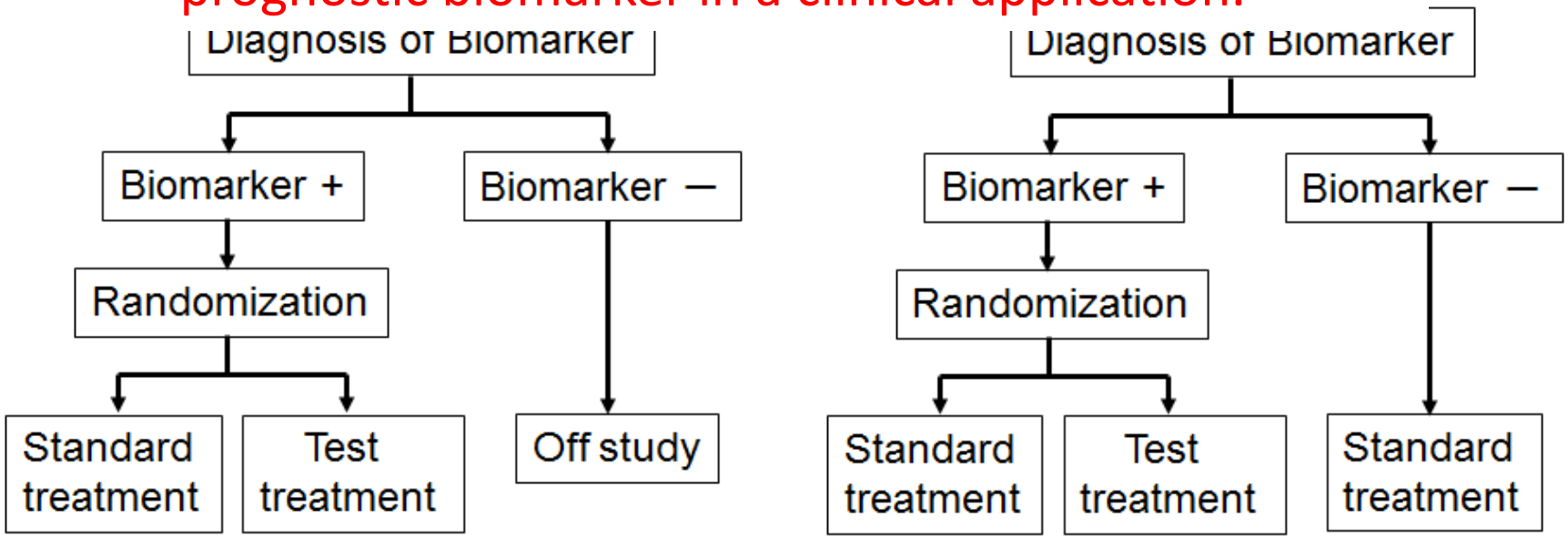



**Slamon, D.J.; Leyland-Jones, B.; Shak, S.; Fuchs, H.; Paton, V.; Bajamonde, A.; Fleming, T.; Eiermann, W.; Wolter, J.; Pegram, M.; *et al. Use of chemotherapy plus a monoclonal antibody* against HER2 for metastatic breast cancer that overexpresses HER2. *N. Engl. J. Med. 2001, 344,* 783–792.**

**Piccart-Gebhart, M.J.; Procter, M.; Leyland-Jones, B.; Goldhirsch, A.; Untch, M.; Smith, I.; Gianni, L.; Baselga, J.; Bell, R.; Jackisch, C.; *et al. Trastuzumab after adjuvant chemotherapy in* HER2-positive breast cancer. *N. Engl. J. Med. 2005, 353, 1659–1672.***

# *Enrichment Design and Hybrid Design*

(a) Possible to test the prospective validation of a prognostic biomarker in a clinical application.

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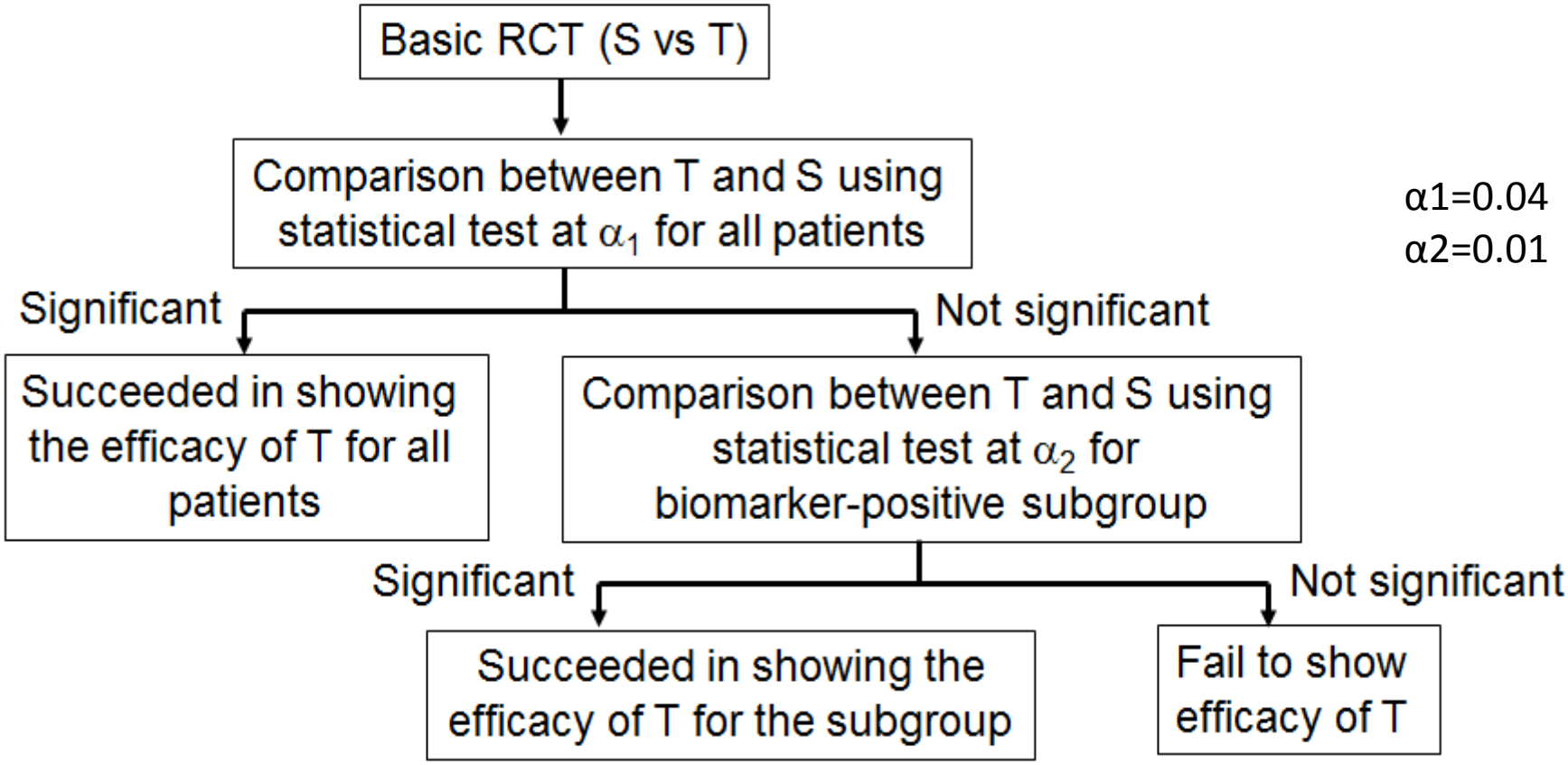
# *Adaptive Signature Design*

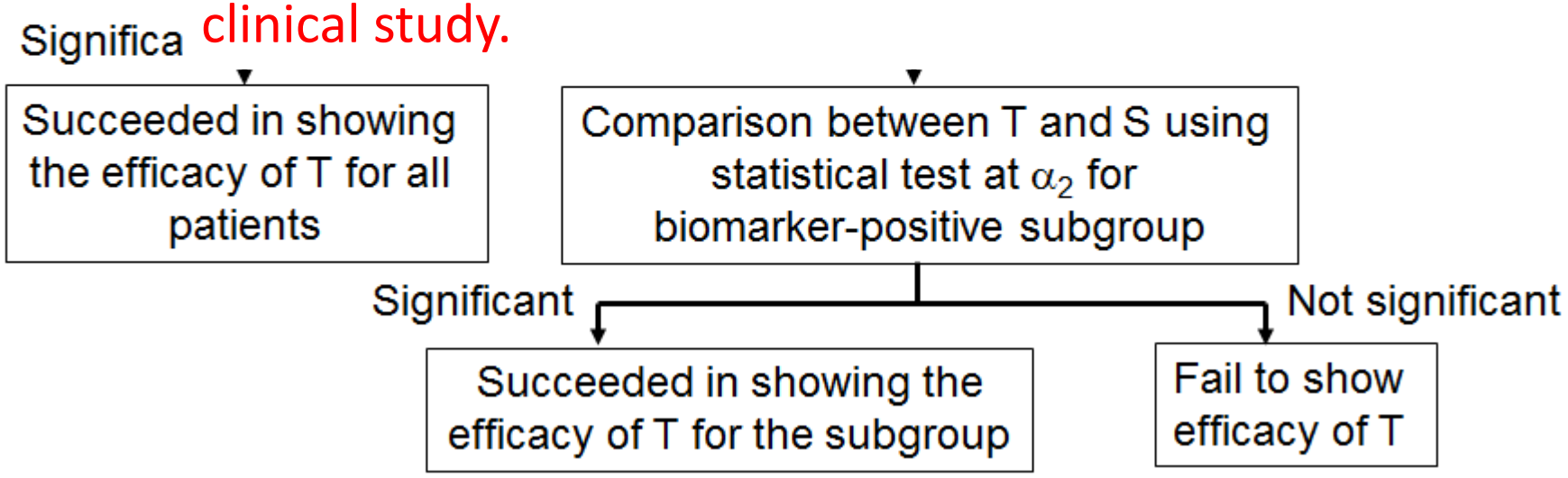



α1=0.04
α2=0.01

**Freidlin, B.; Simon, R. Adaptive signature design: An adaptive clinical trial design for generating and prospectively testing a gene expression signature for sensitive patients. *Clin. Cancer Res.*2005, *11, 7872–7878.***

# *Adaptive Signature Design*

The BMs-identification should be pre-specified.
This design would be a practical approach when evidence about the predictive biomarker is insufficient before conducting the clinical study.

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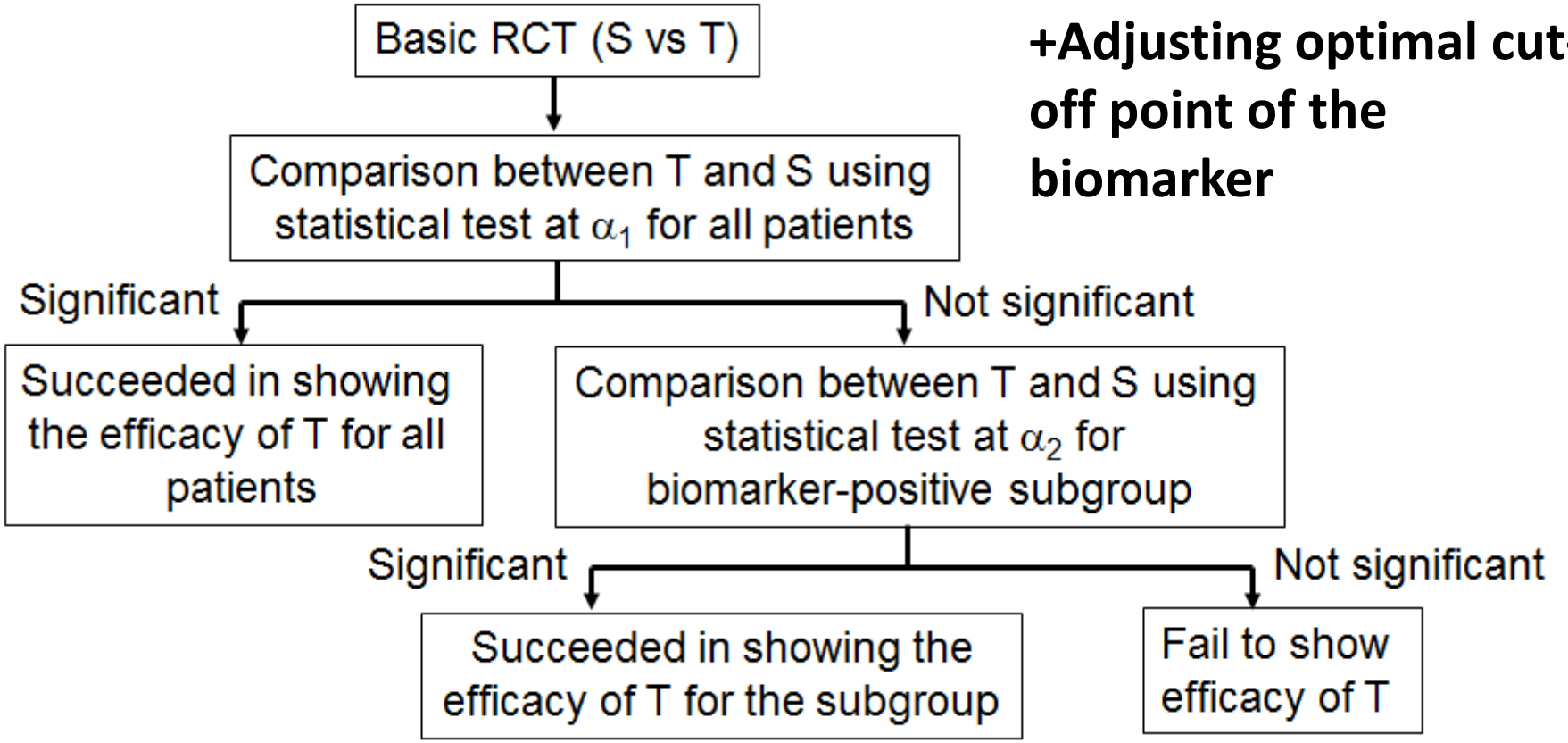
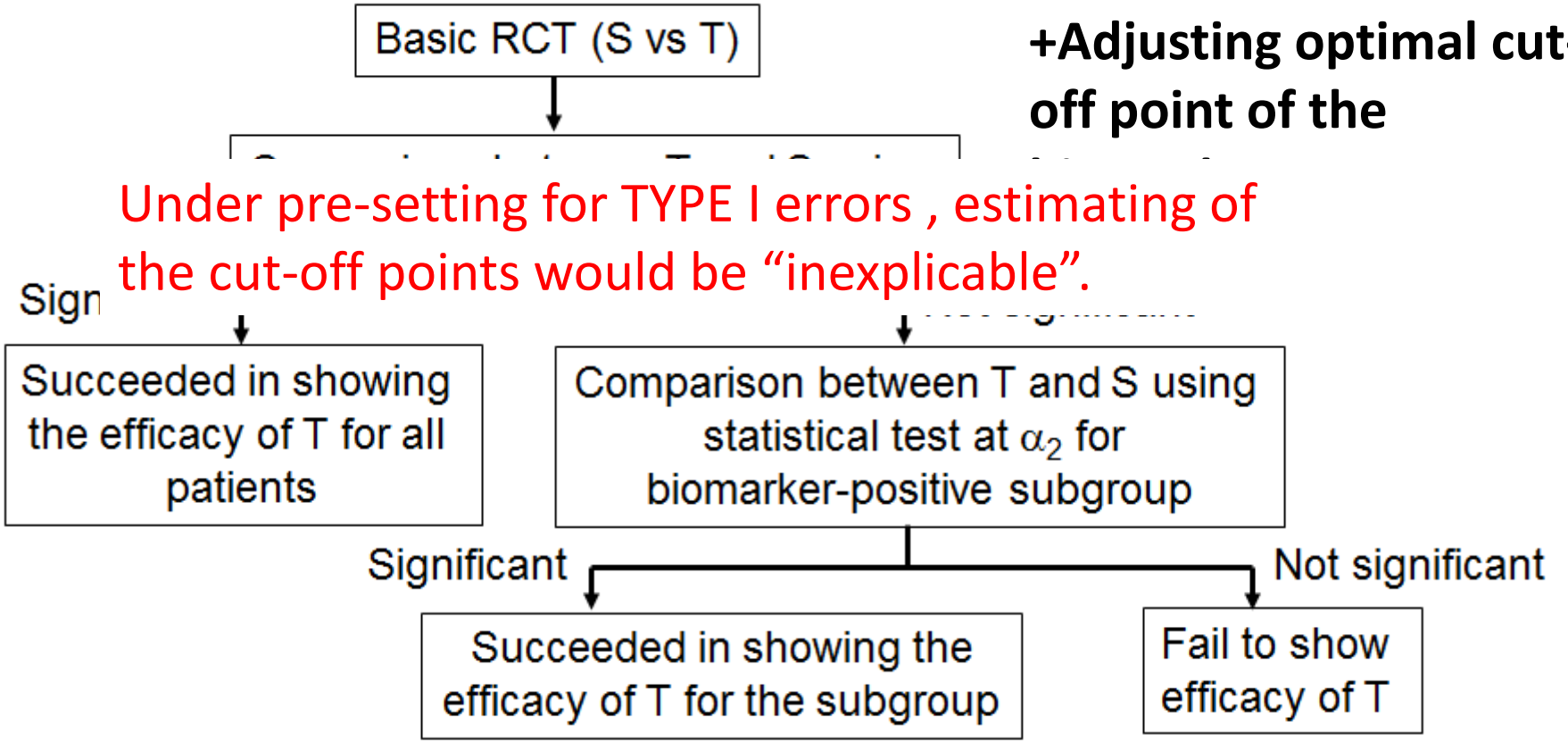
# *Biomarker-Adaptive Threshold Design*




**+Adjusting optimal cut-off point of the biomarker**

**Jiang, W.; Freidlin, B.; Simon, R. Biomarker adaptive threshold design: A procedure for evaluating treatment with possible biomarker-defined subset effect. *J. Natl. Cancer Inst. 2007, 99,*1036–1043.**

# *Biomarker-Adaptive Threshold Design*

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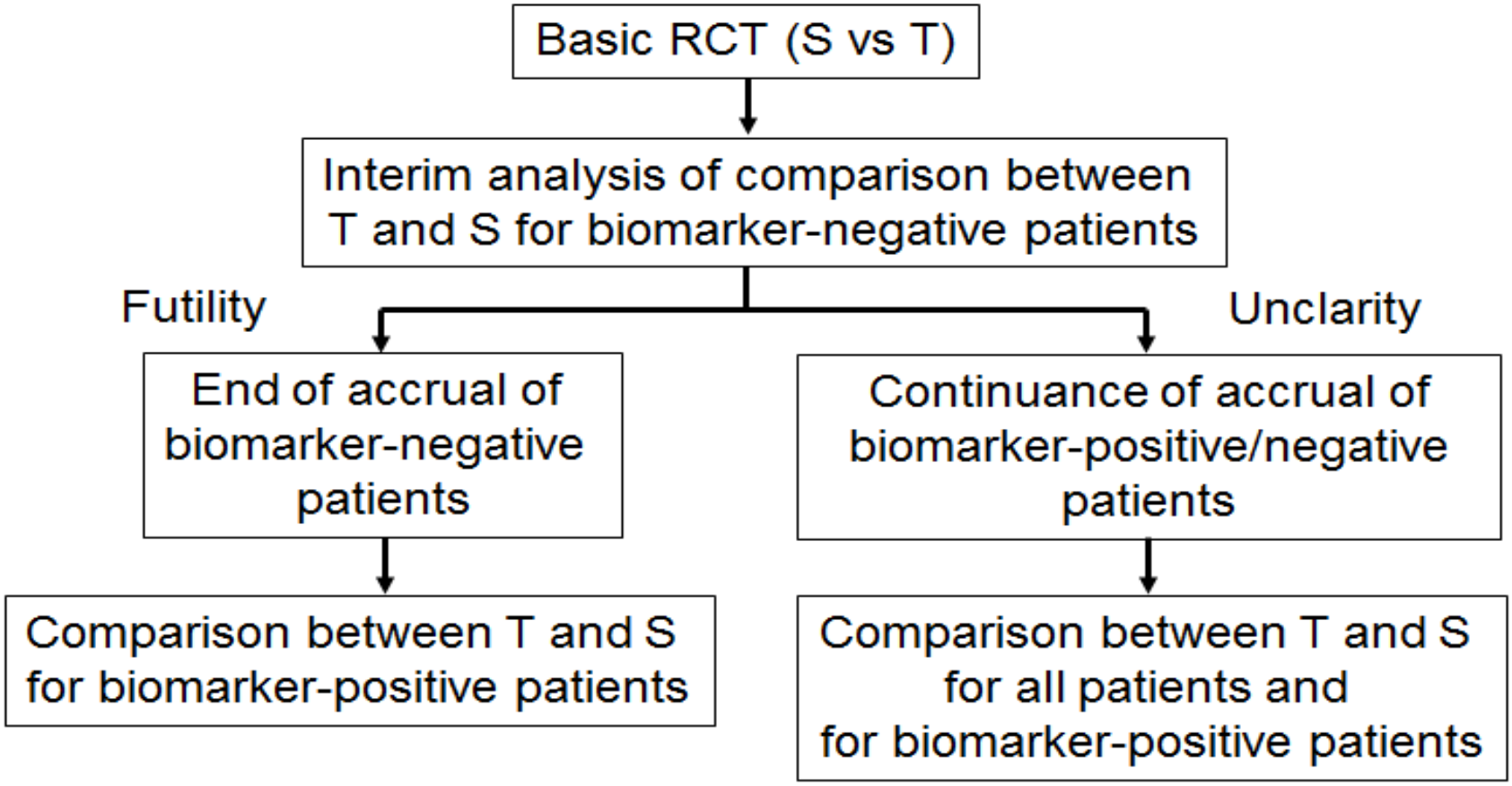
# *Adaptive Accrual Design*

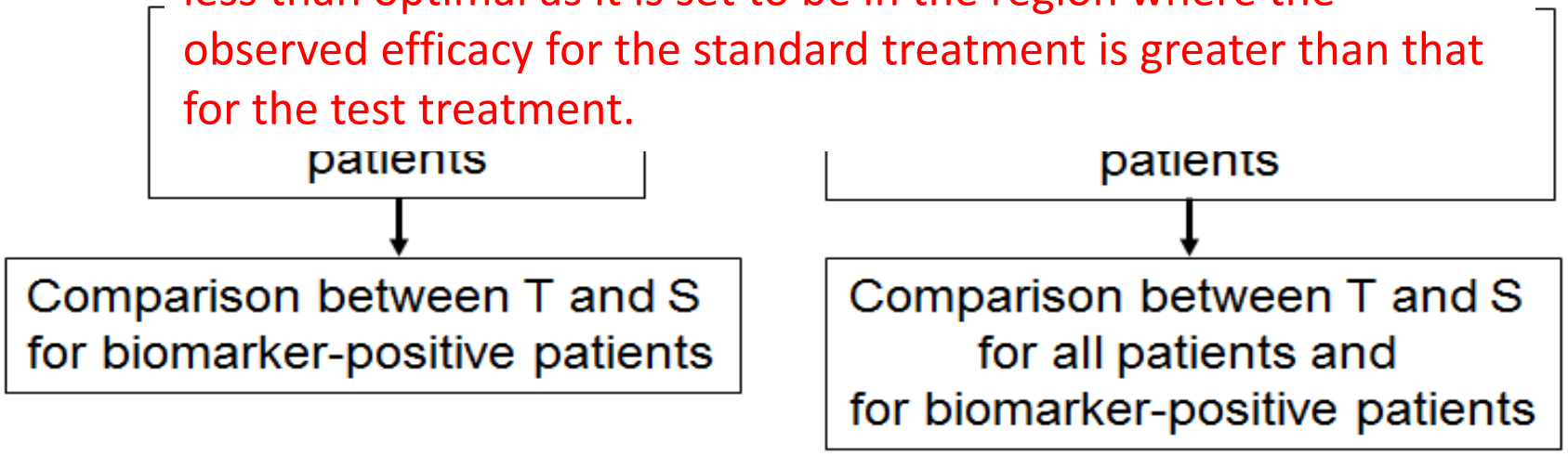



**Wang, S.J.; O'Neill, R.T.; Hung, H.M.J. Approaches to evaluation of treatment effect in randomized clinical trials with genomic subset. *Pharm. Stat. 2007, 6, 227–244.***

# *Adaptive Accrual Design*

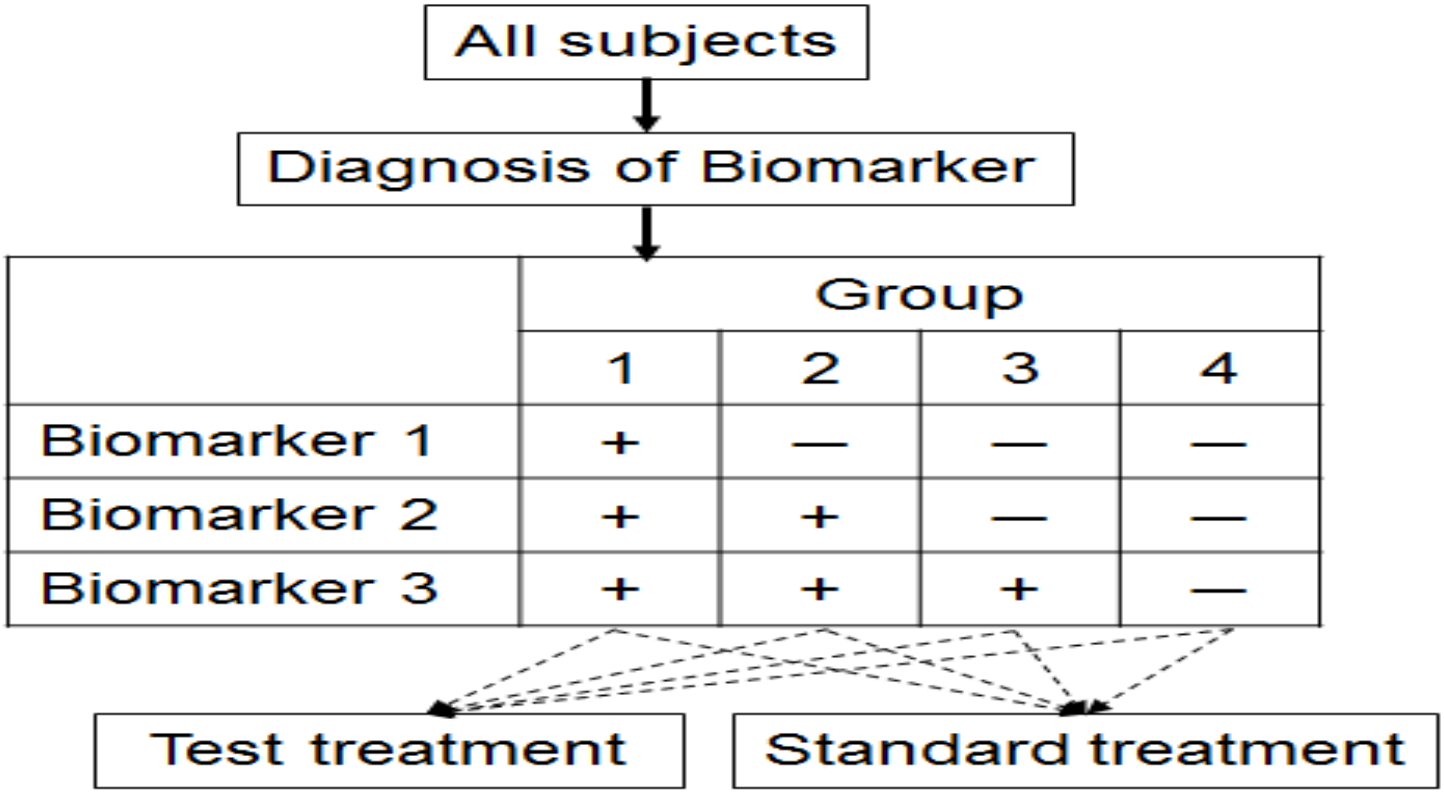
A greater power than a standard RCT design (non-adaptive trial); however, the design accrues many more biomarker-positive patients and may require a much longer trial duration depending on the prevalence of the biomarker.

In addition, the futility boundary is somewhat conservative and less than optimal as it is set to be in the region where the observed efficacy for the standard treatment is greater than that for the test treatment.




**Wang, S.J.; O'Neill, R.T.; Hung, H.M.J. Approaches to evaluation of treatment effect in randomized clinical trials with genomic subset. *Pharm. Stat. 2007, 6, 227–244.***

# *Bayesian Adaptive Design*




**Zhou, X.; Liu, S.; Kim, E.S.; Herbst, R.S.; Lee, J.J. Bayesian adaptive design for targeted therapy development in lung cancer: A step towards personalized medicine.** ***Clin. Trials 2008, 5, 181–193.***

# Statistical Issues

- Confounding and Interaction
  - Not only enrollment bias,  also in association between BMs and Clinical Outcomes
  - Subgroup analysis and Model-based analysis
- Multiplicity
  - Futility, Enrichment, Adaptive, Biomarker classification
- Statistical Significance vs. Clinical significance
- Bayes vs. Non-Bayes

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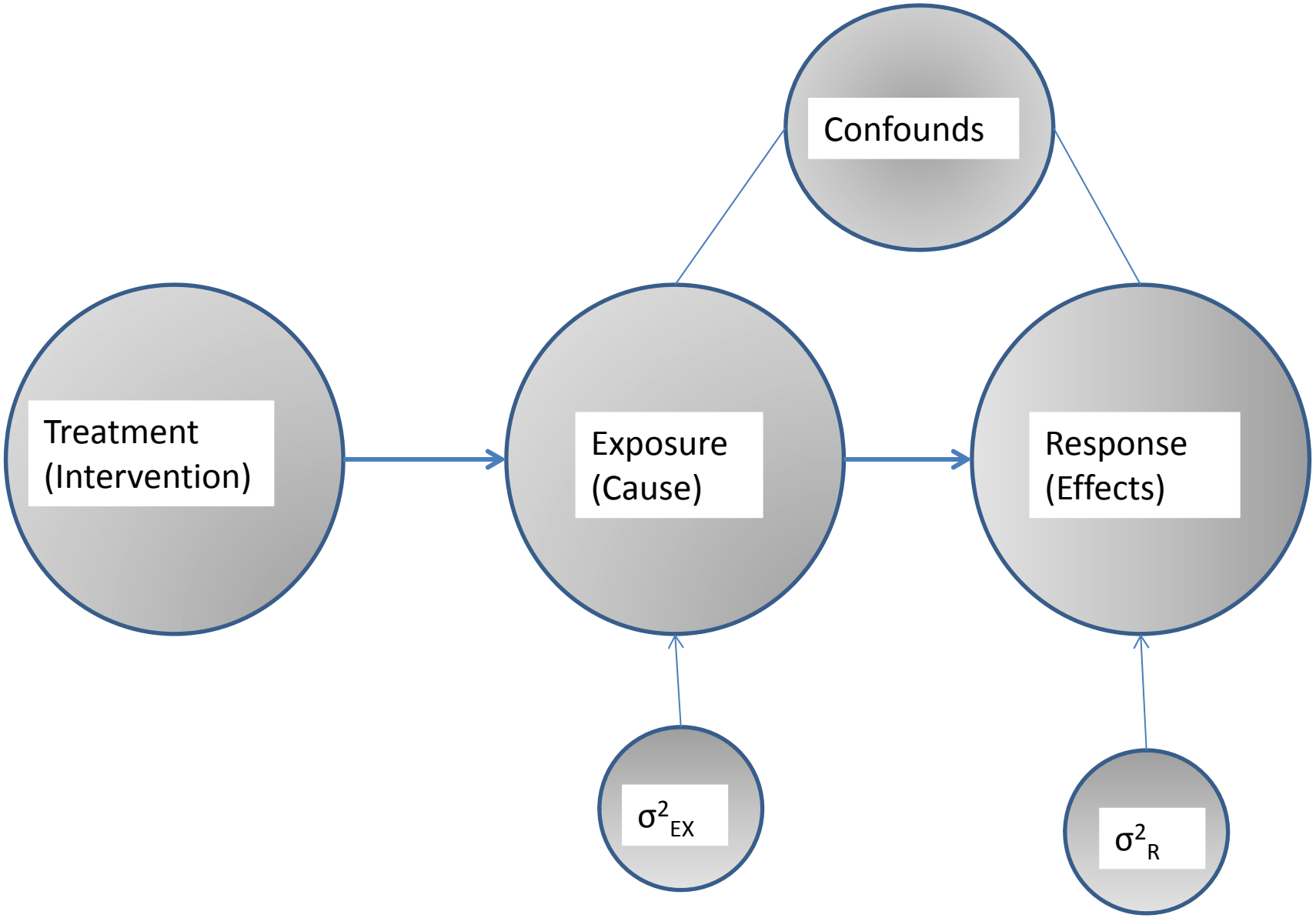
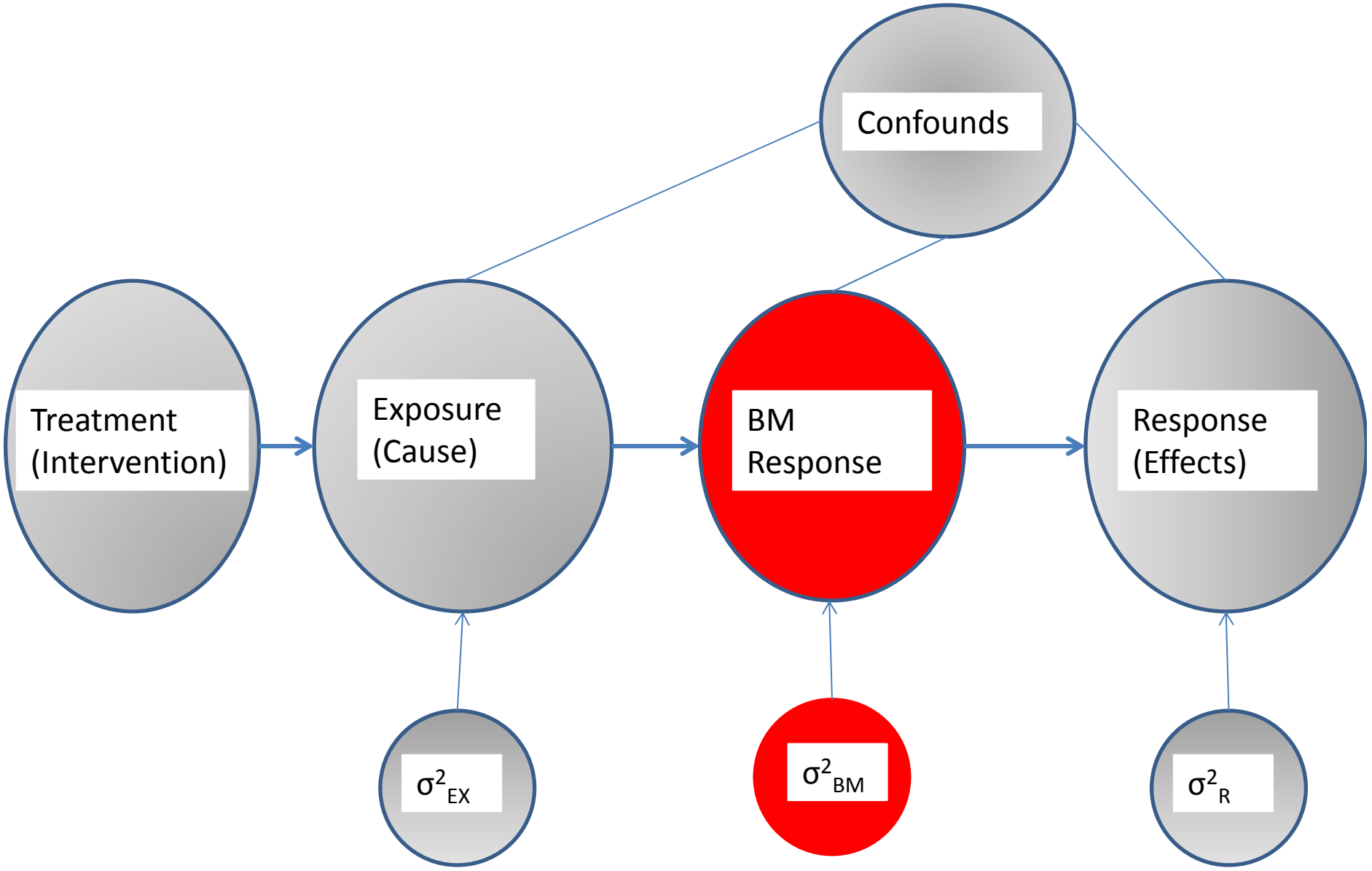



Directed Acyclic Graph for Causal-Effect relationships between Dose/Exposure/Response




Directed Acyclic Graph for Causal-Effect relationships between Treatment/Exposure/BM/Response

# Today's conclusion

- We need …..
  - Prospective discussion among all stakeholders

    as like NCI Biomarker study registry *(http://win.biomarkerregistry.org)*

  - Intensive Collaboration among all stakeholders