

# Trial Designs To Assess Biomarkers in Clinical Practice

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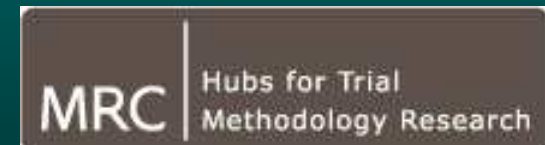
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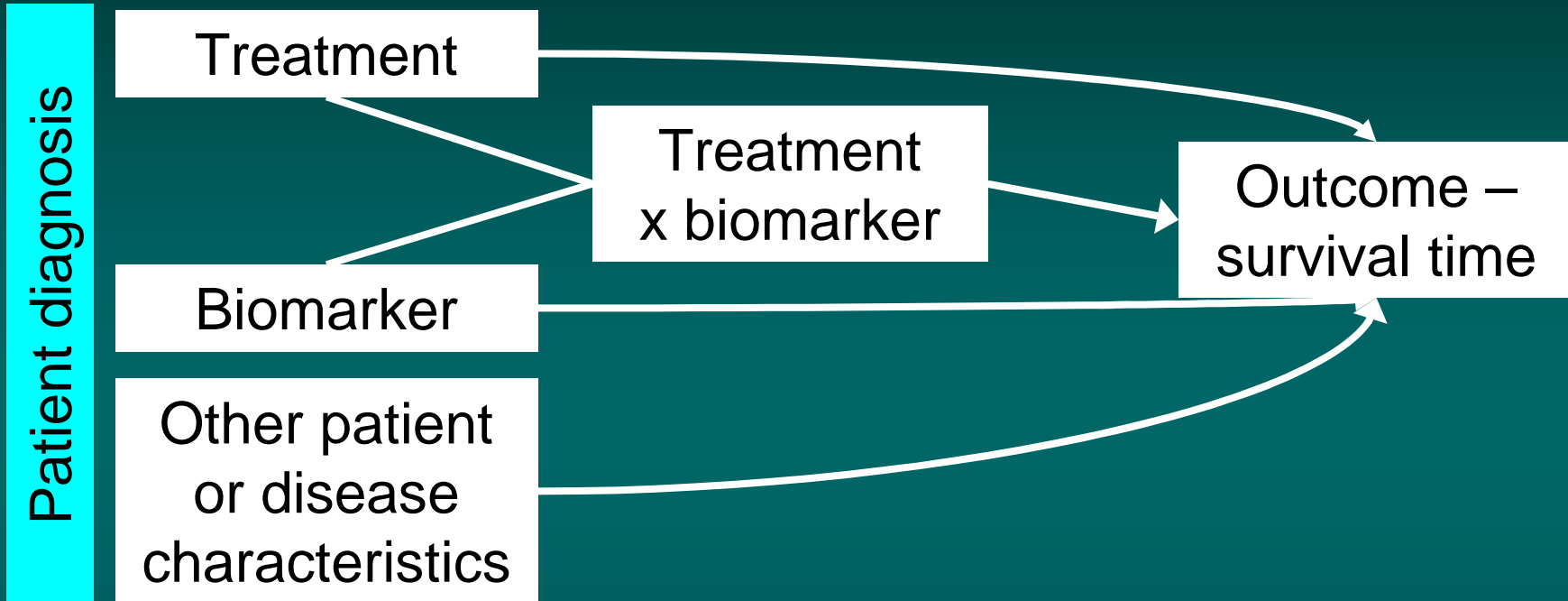
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Prague, August 24<sup>th</sup> 2009

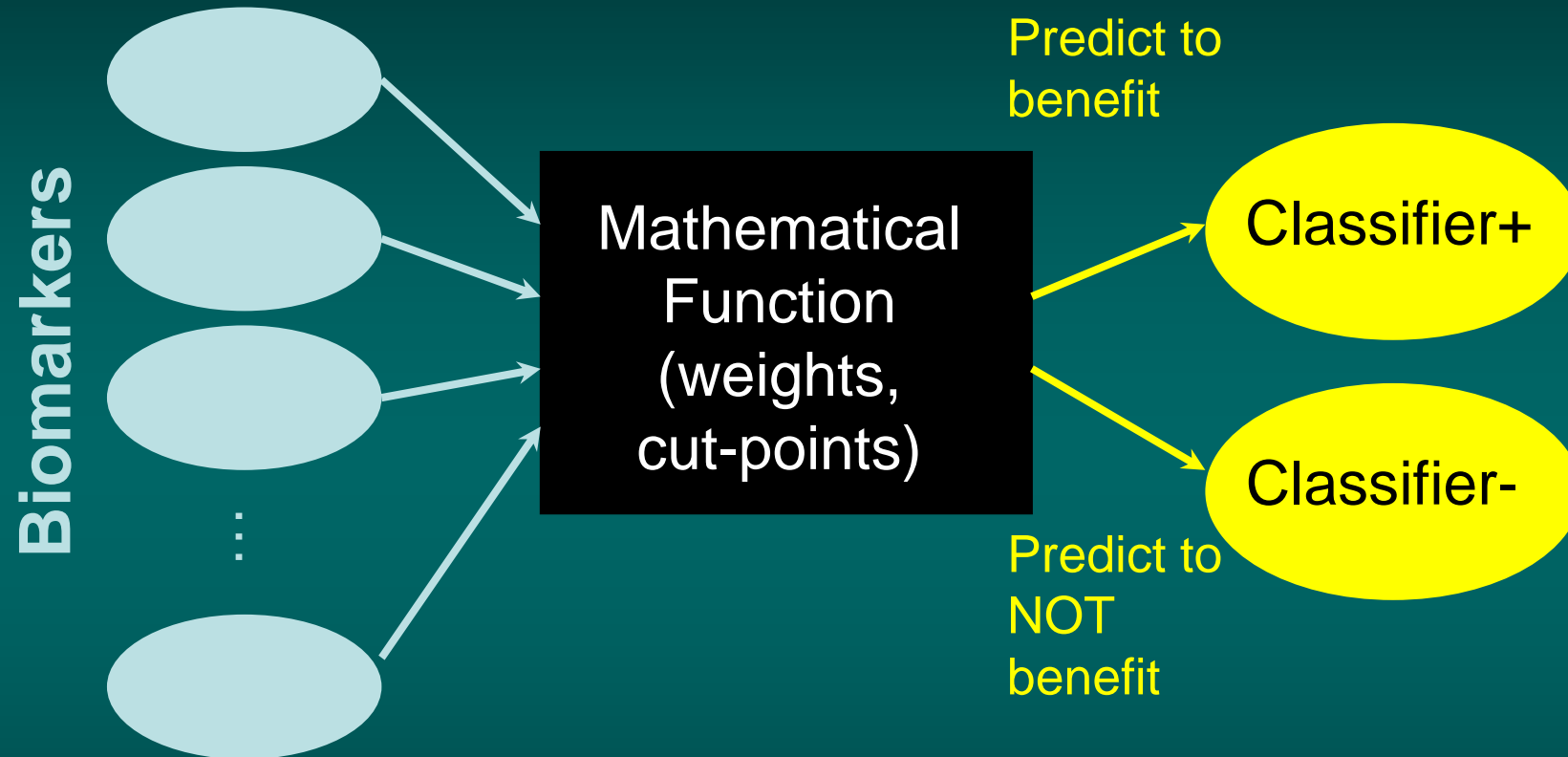
# Introduction



## Aim of presentation:

- Summarise biomarker trial designs from literature, highlighting advantages and disadvantages of each
- Key design issue: sensitivity and specificity

# Biomarker Classifiers



DNA, RNA, proteins  
Standardise  
laboratory techniques

Predict to  
benefit

Classifier+

Predict to  
NOT  
benefit

Classifier-

Classifier needs to be:  
quick, cheap, reliable,  
reproducible, high  
sensitivity and specificity

# Biomarker Research Pathway

**Discovery**

Identify potential biomarkers

**Development**

Develop a classifier using these biomarkers

**Validation**

Test the classifier on independent set of patients to assess predictive accuracy

**Application**

Prospective study to assess the use of the classifier in clinical practice

**Change Clinical Practice**

# Clinical Trial Designs Assessing Application of Biomarkers in Clinical Practice

**Discovery**



**Development**



**Validation**



**Application**



**Change Clinical Practice**

References:

Sargent DJ et al Journal of Clinical Oncology 2005; 23: 2020-2027

Simon R Clin Cancer Research 2008; 14: 5984-5992 (plus many more!)

**Clinical Trial**

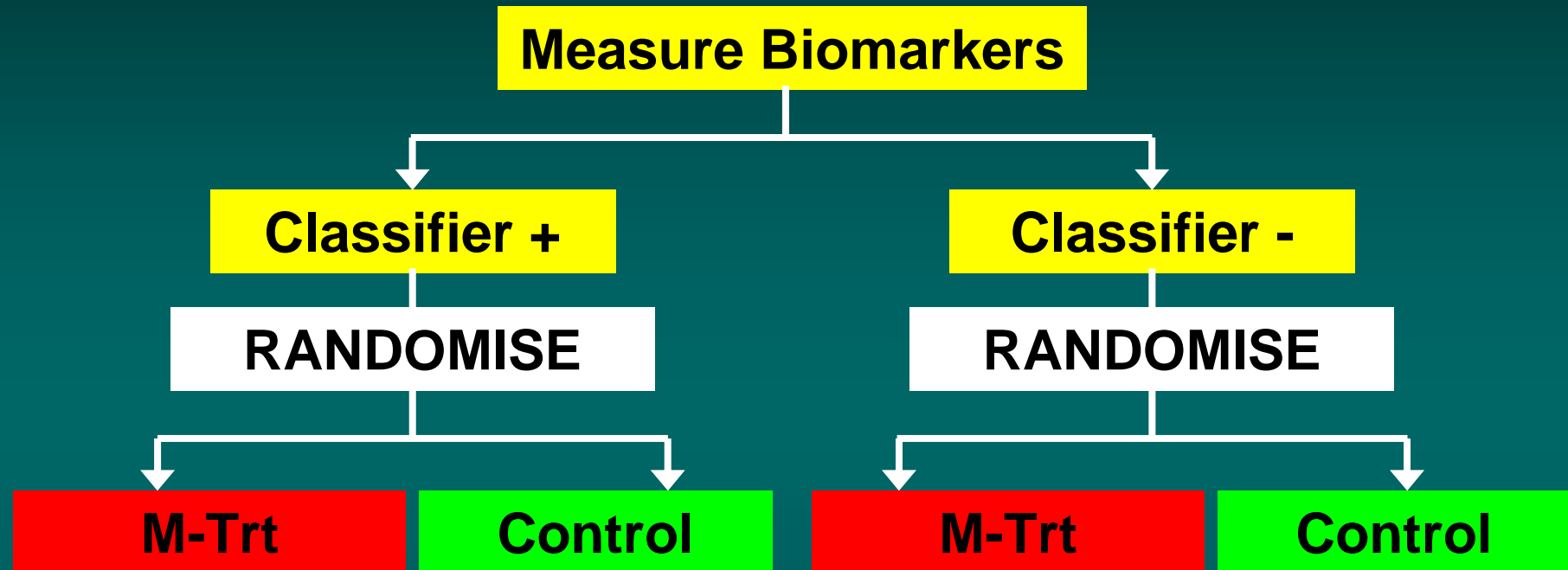
**1a) Stratified Trial Design**

**1b) Targeted Trial Design**

**1c) Marker by Treatment Interaction Design**

**2) Marker-Based Strategy Design**

# (1a) Stratified Trial Design

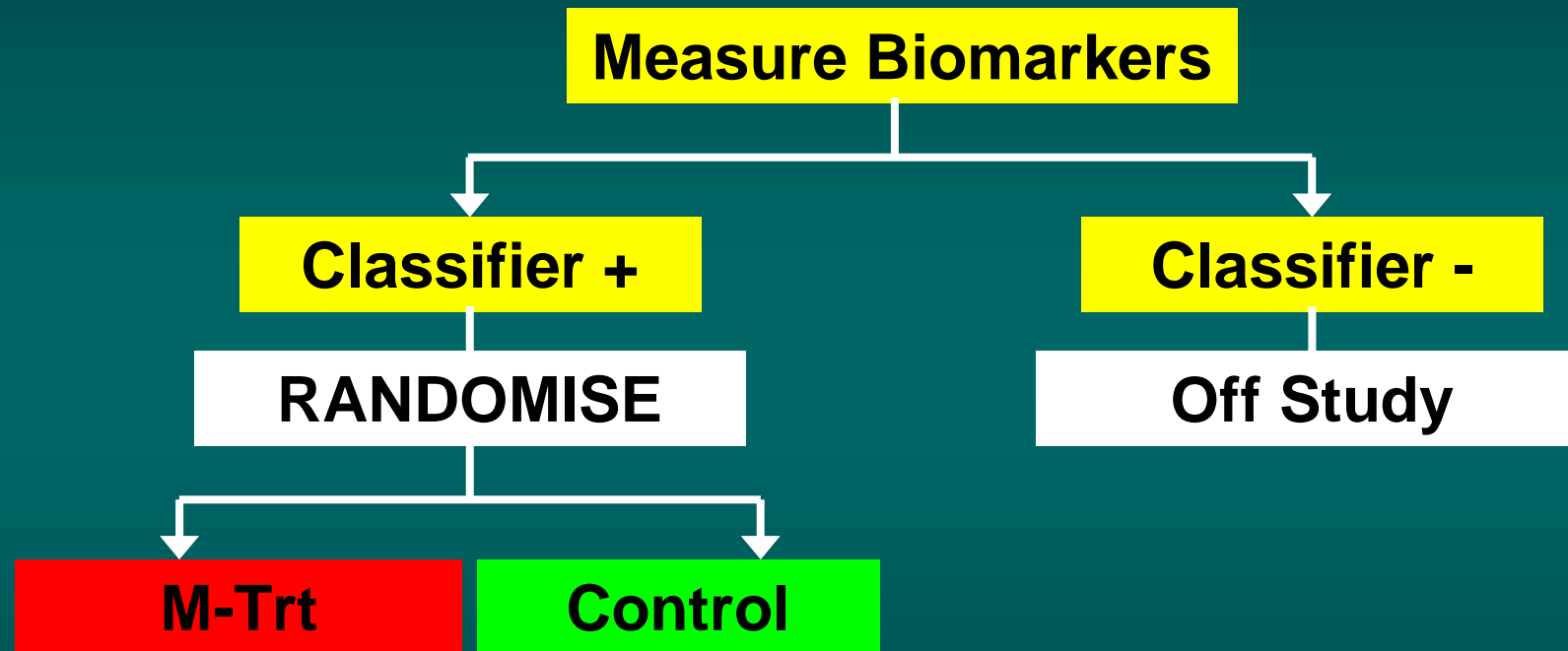


Research Hypothesis:  
M-Trt superior to Control in  
Classifier+ patients

Research Hypothesis:  
M-Trt superior to Control in  
Classifier- patients

- Pre-defined complete statistical analysis plan is crucial
- Ensures only patients with adequate specimens are included
- Tests practicalities of using classifier in clinical practice

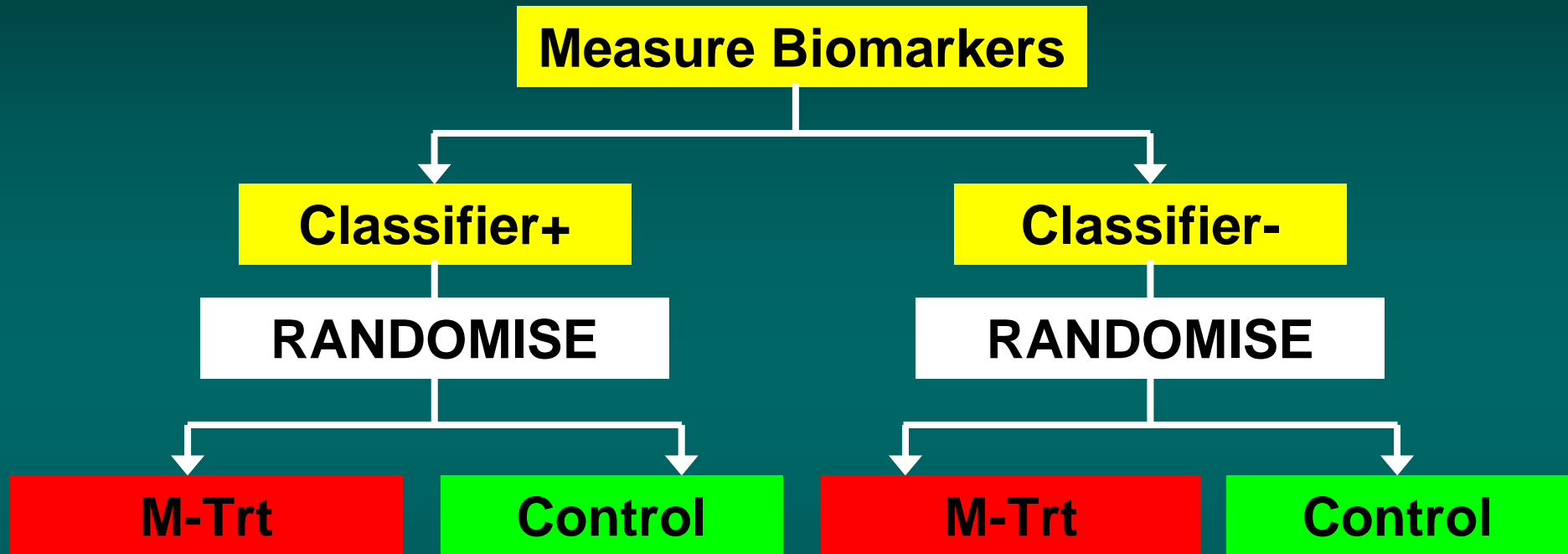
# (1b) Targeted Trial Design (Enrichment Design)



Research Hypothesis:  
M-Trt superior to Control in  
Classifier+ patients

Untestable Hypothesis:  
M-Trt not effective in  
Classifier- patients

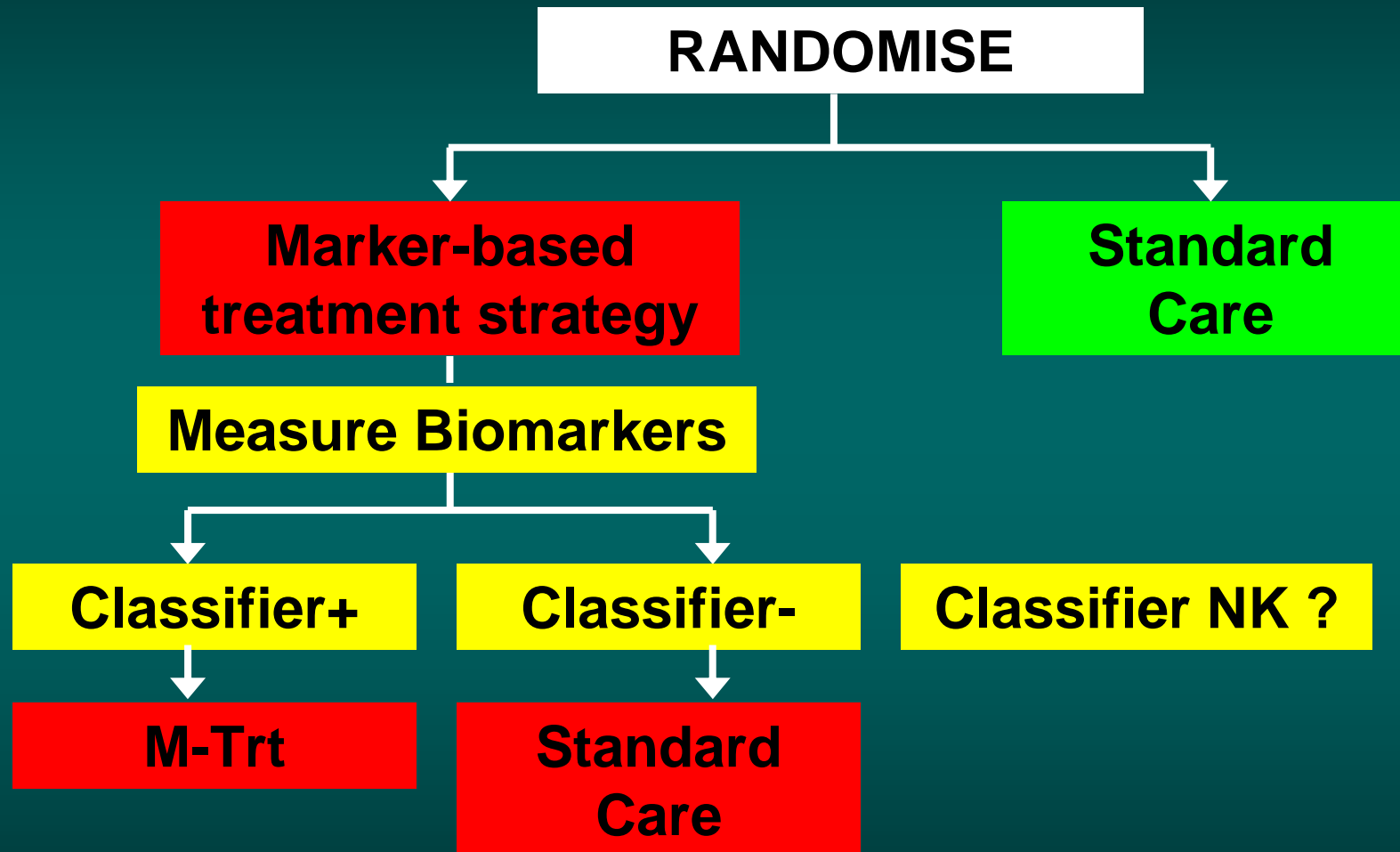
# (1c) Marker by Treatment Interaction Design



Hypothesis: Effect of M-Trt compared to Control differs for the two classifier groups

**Require 4 times number of patients for interactions of the same size as treatment alone (Schmoor et al Stats in Med 2000)**

## (2) Marker-Based Strategy Design



Research Hypothesis: Marker-based treatment strategy is superior to standard care

# Issue: Sensitivity and Specificity of Classifier

Sensitivity =  $p(\text{correctly classifying a true classifier+}) = s_e$

Specificity =  $p(\text{correctly classifying a true classifier-}) = s_p$

True prevalence of classifier+ =  $p$

	True Classifier+	True Classifier-	Total
Measured Classifier+	$s_e p N$	$(1-s_p)(1-p)N$	$[s_e p + (1-s_p)(1-p)]N$
Measured Classifier-	$(1-s_e)pN$	$s_p(1-p)N$	$[(1-s_e)p + s_p(1-p)]N$
Total	$pN$	$(1-p)N$	$N$

# Simple Example

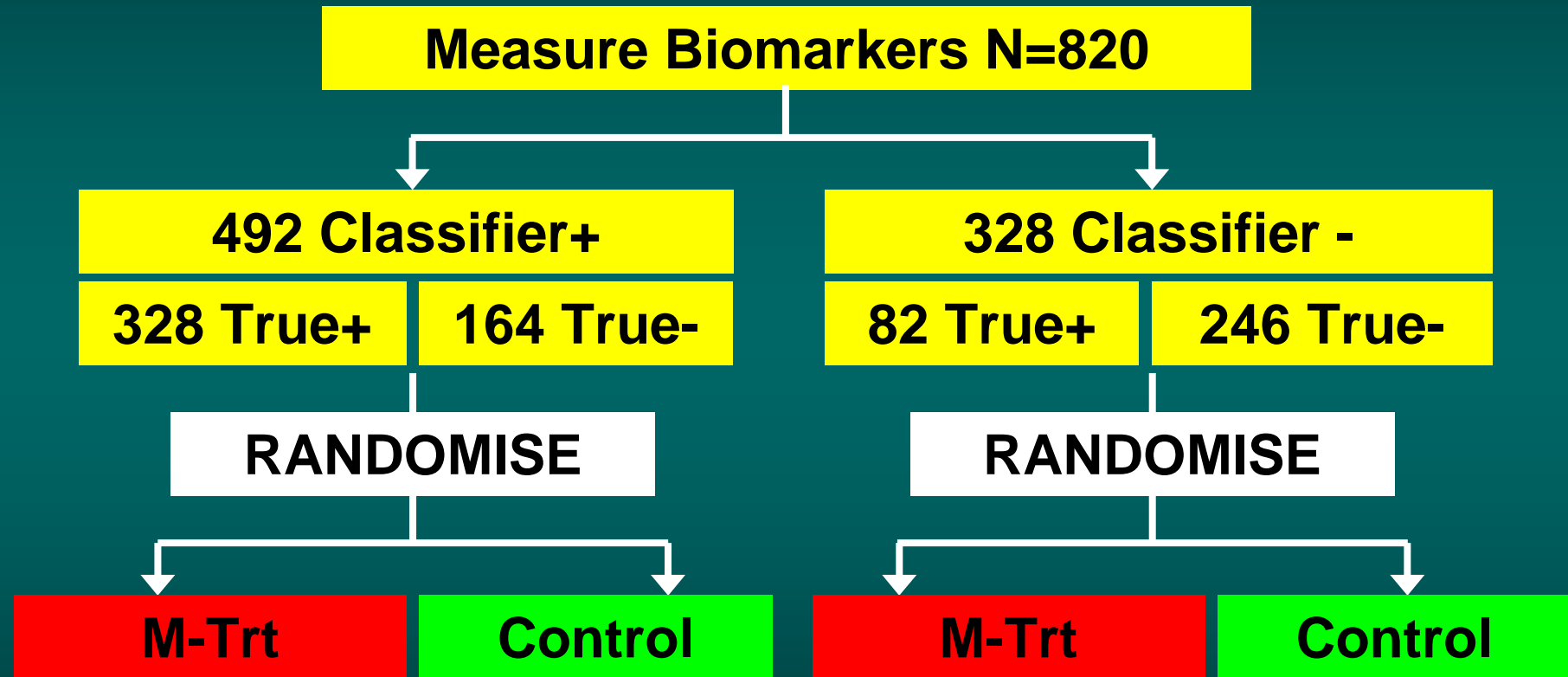
Sensitivity =  $S_e = 0.80$

Specificity =  $S_p = 0.60$

True prevalence of classifier+ =  $p = 0.50$

	True Classifier+	True Classifier-	Total
Measured Classifier+	328	164	492 (60%)
Measured Classifier-	82	246	328 (40%)
Total	410 (50%)	410 (50%)	820

# (1) Stratified Trial Design: Effect of Sensitivity and Specificity



# How does Sensitivity and Specificity of Classifier Affect Statistical Power

Reference:

Hoering, LeBlanc, Crowley; Clinical Cancer Research 2008;14:4358-4367

## Simulation

- For study size  $N$ , samples are generated from 8 populations
  - treatment arm x true classifier status x measured classifier status
- Survival times generated from exponential distribution with hazard rate  $\lambda$
- Recruitment times generated from Uniform(0,5)
- Follow-up time = 3 years after end of recruitment
- Survival times censored at the end of the follow-up period
- Implemented in SAS, 1000 simulations

# Simulation: Results for Stratified Design

Prevalence of true classifier+ = 50%

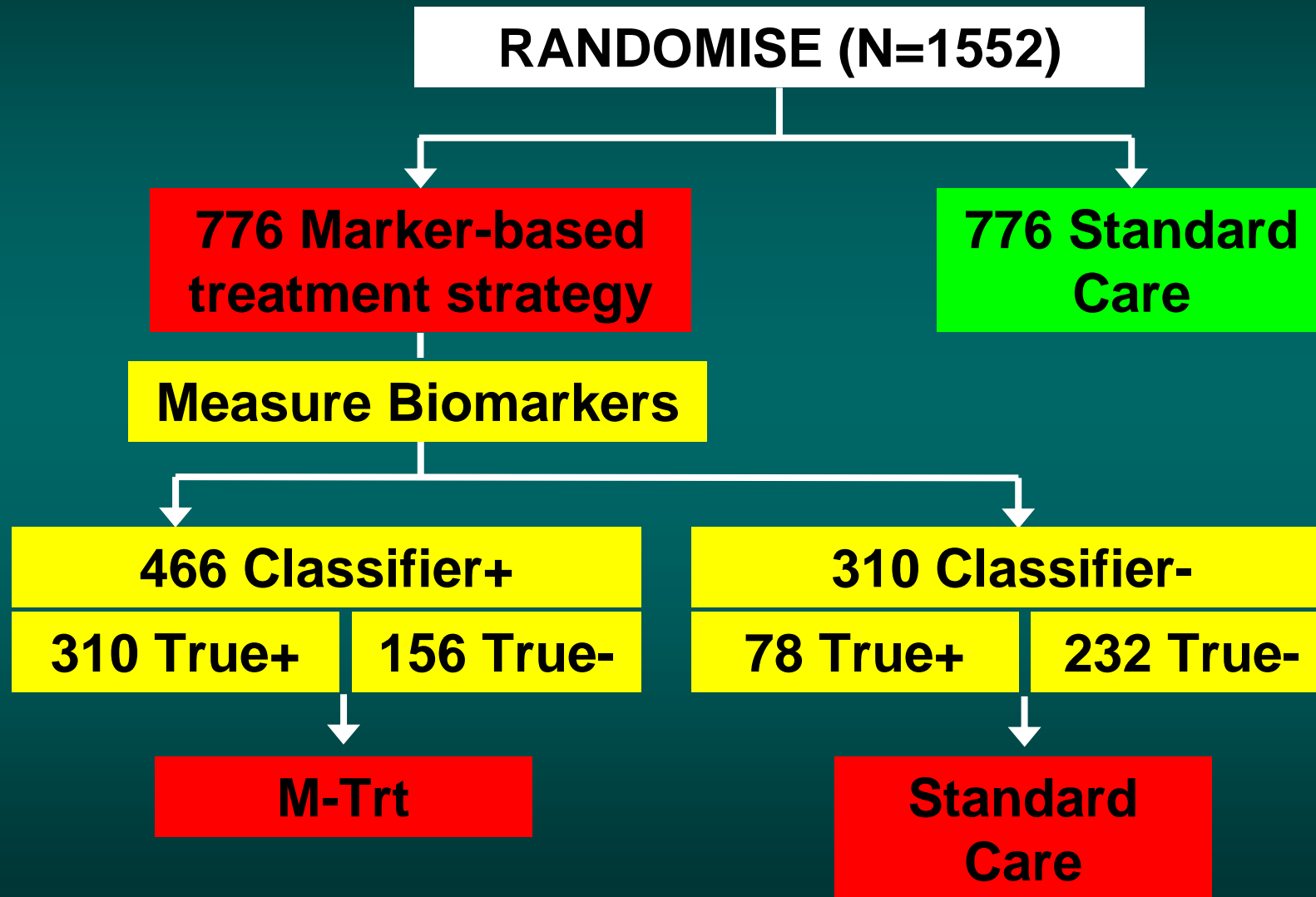
Control treatment:  $\lambda_- = \lambda_+ = 0.15$  (i.e. not prognostic)

Experimental treatment:  $\lambda_- = 0.15$   
 $\lambda_+ = 0.10$

$\Rightarrow HR_- = 1.00$        $HR_+ = 0.67$        $HR_{int} = 0.67$

	Sensitivity	100%	80%	80%	60%	60%
	Specificity	100%	80%	60%	80%	60%
Testing treatment effect N=820	HR <sub>-</sub>	1.00	0.94	0.92	0.88	0.87
	HR <sub>+</sub>	0.67	0.73	0.78	0.75	0.80
	Power	81%	62%	53%	49%	39%
Testing interaction N=1640	HR <sub>int</sub>	0.67	0.79	0.85	0.86	0.94
	Power	84%	43%	23%	20%	10%

## (2) Marker-Based Strategy Design: Effect of Sensitivity and Specificity



# Simulation: Results for Marker-Based Strategy Design

Prevalence of true classifier+ = 50%

Control treatment:

$\lambda_- = 0.15$   $\lambda_+ = 0.135$  (i.e. prognostic)

Experimental treatment:

$\lambda_- = 0.15$   
 $\lambda_+ = 0.10$

⇒  $HR = (0.5 \times 0.10 + 0.5 \times 0.15) / (0.5 \times 0.135 + 0.5 \times 0.15) = 0.88$

	Sensitivity	100%	80%	80%	60%	60%
	Specificity	100%	80%	60%	80%	60%
Testing Strategy Effect N=1552	HR	0.83	0.86	0.86	0.89	0.89
	Power	84%	43%	23%	23%	9%

N=3460

66%

# Summary

- Biomarker classifiers that have been developed and validated need to be tested in a randomised setting before use in clinical practice
- Practicalities of biomarker measurement is a crucial aspect of the trial design
- Different trial designs should be considered to determine which is most appropriate and efficient for the given situation
- Statistical power is affected by
  - Sensitivity and specificity of the classifier
  - Prevalence of classifier+ patients
  - Prognostic impact of the classifier
  - Level of treatment effect in classifier- patients
  - Randomisation allocation ratio