

# Multi-Arm Multi-Stage Trials

## A role for MAMS trials in rare diseases?

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# Structure of presentation

1. Multi-Arm Multi-Stage (MAMS) Designs
2. Application in Prostate Cancer
3. Applications in Rare Diseases
4. Conclusions

# 1. Multi-Arm Multi-Stage Designs

1. MAMS Designs
2. Application in Prostate Cancer
3. Applications in Rare Diseases
4. Conclusions

# Setting

- 'New' is more often not better than standard
- Academia
  - 624 NCI sponsored phase III trials (Arch Int Med 2008)
  - ~30% of trials 'statistically significant'
  - ~40% of trials 'new' therapy preferred
- Industry
  - Agents successful at phase I: only 10-20% receive a marketing authorisation
  - Success rate of phase III trials ~30-40%

# Setting

- Typical (academic) Phase III trial
  - Years of investment from the key players
  - 5 to 10 years from idea to result
  - Hundreds or thousands of patients
  - Hundreds of research staff
  - Cost millions in development
- Yet, high chance of finding new treatment is not better

# Principles of a New Strategy

- Need better mechanism for phase III choice
  - Than single arm phase II trial
- Test many new promising treatments
  - In the same timescale
- Potential to discontinue unpromising arms
  - Quickly and reliably
- Start to randomise as quickly as possible
- Maximise potential for a 'positive trial'
- **Multi-Arm, Multi-Stage trials**

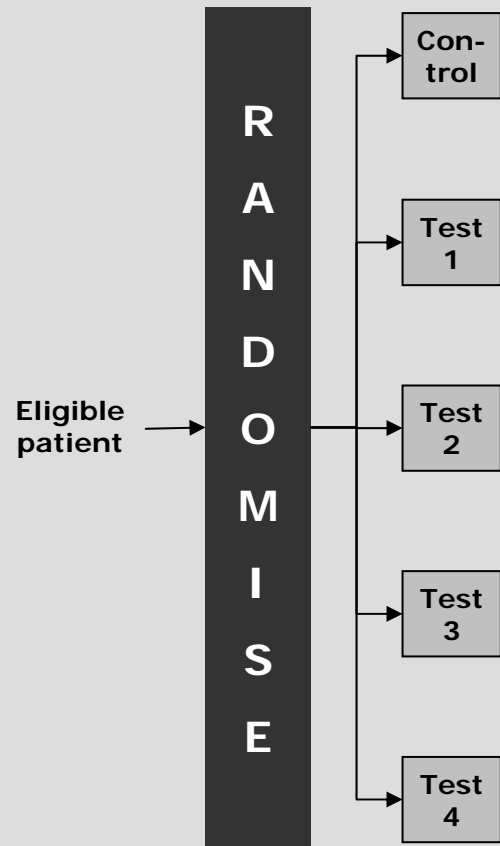
# Activity (phase II stages)

- Ask the question:
  - Are there reasons why we should continue investigating a treatment?
  - Need to see sufficiently encouraging activity to continue assessment
- Testing for a lack-of-activity
  - Emphasis not testing for activity but for lack-of-sufficient-benefit
  - Focus away from insufficiently active regimens

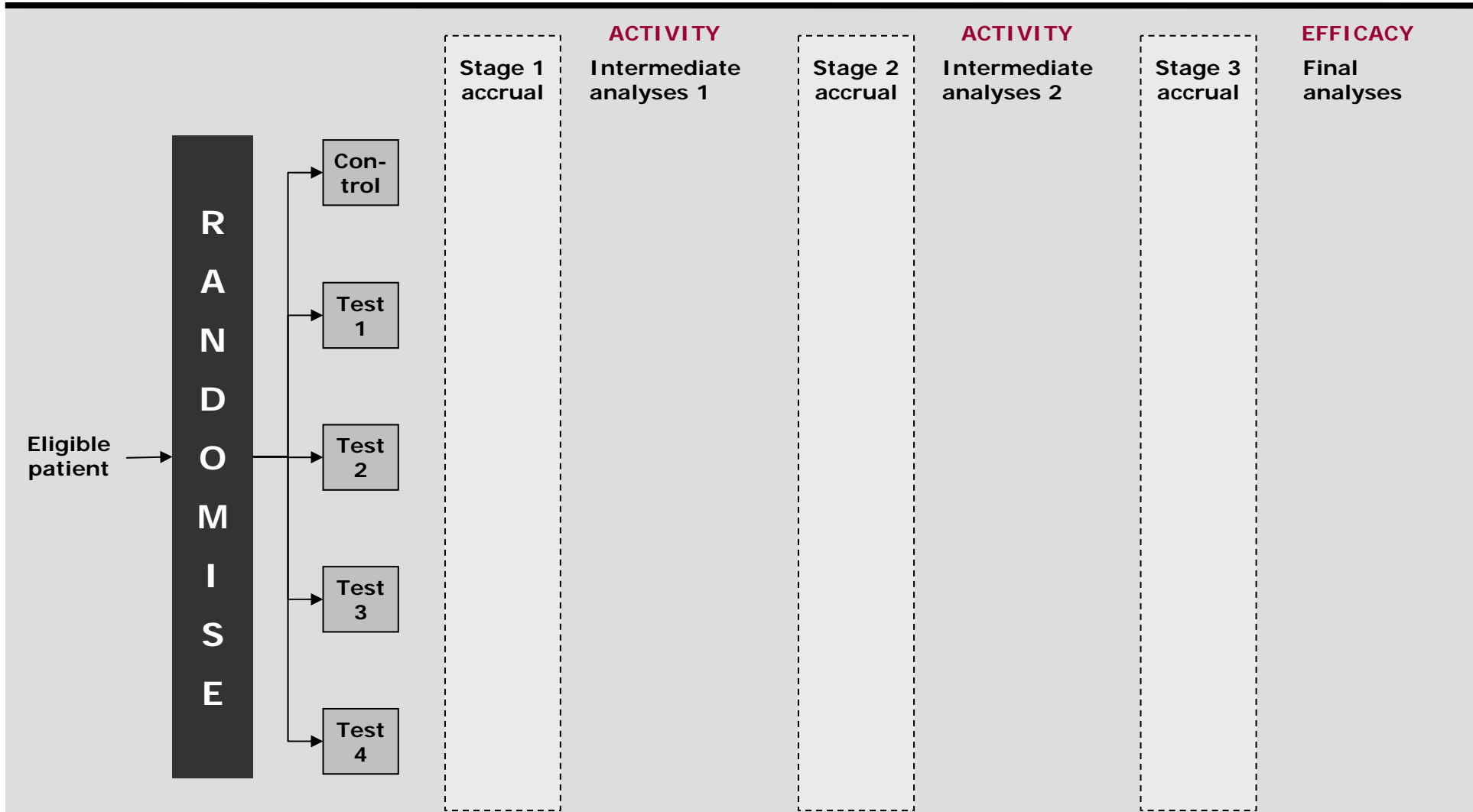
# Activity phase II stages

- In Activity Stages use earlier outcomes
  - Even if interested in longer-term outcomes
  - Focus on Event-Free Survival (EFS)
- More EFS events than deaths
  - Therefore, more power for EFS than survival
- Design assumes:
  - To see an effect on OS you have to see an effect on FFS
  - Just because you see an effect on FFS does not mean that you will see an effect on OS

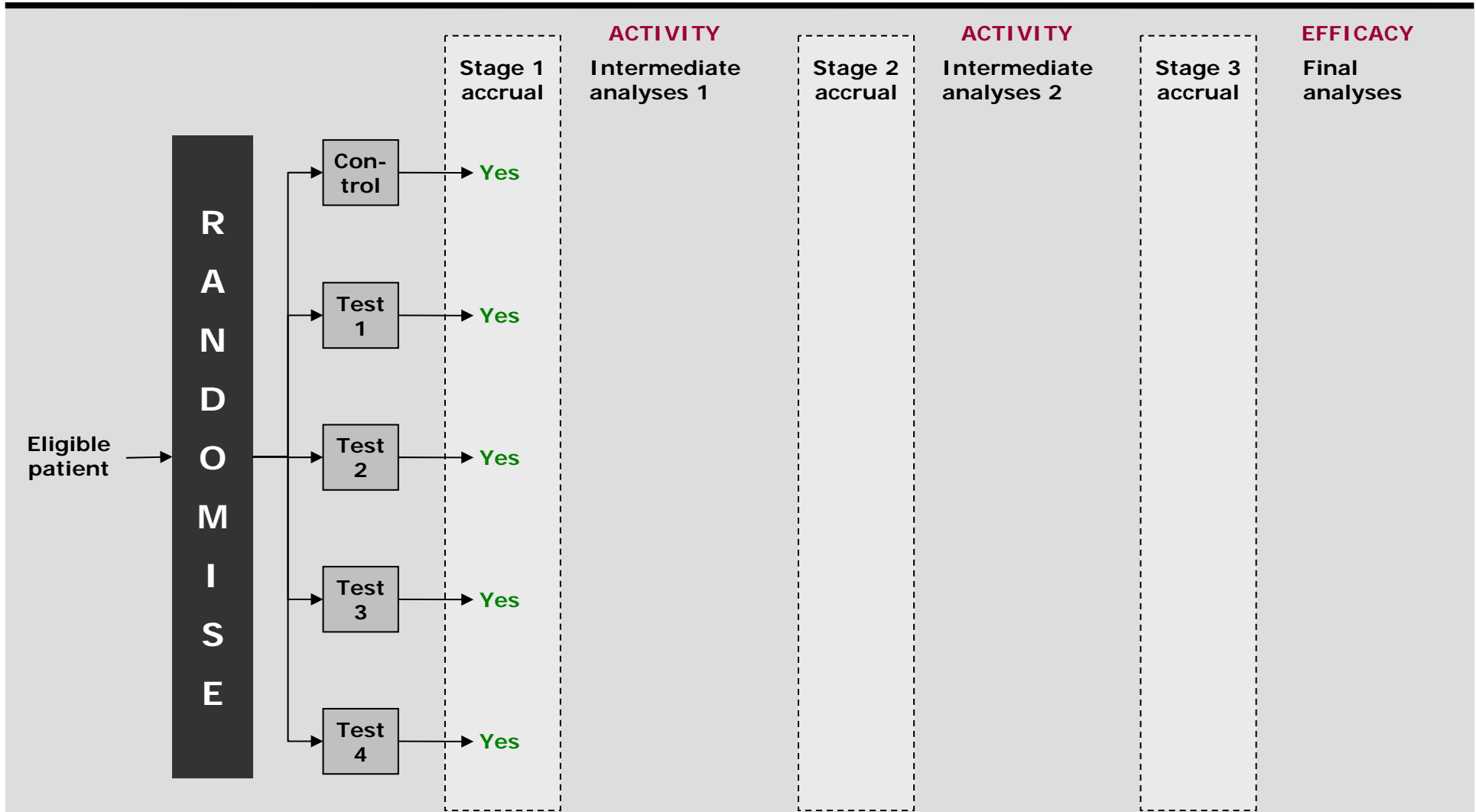
# Multi-Arm, Multi-Stage Trials



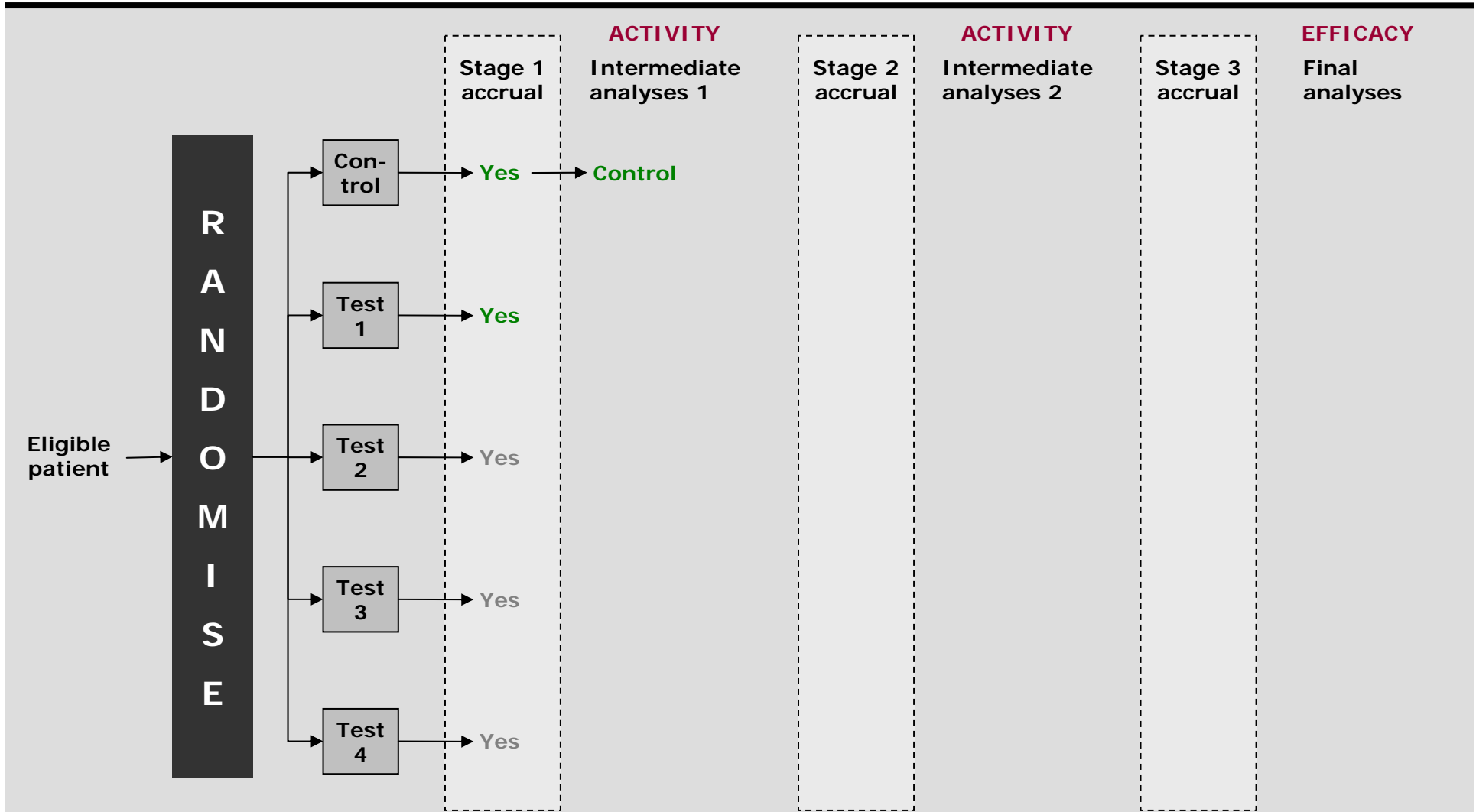
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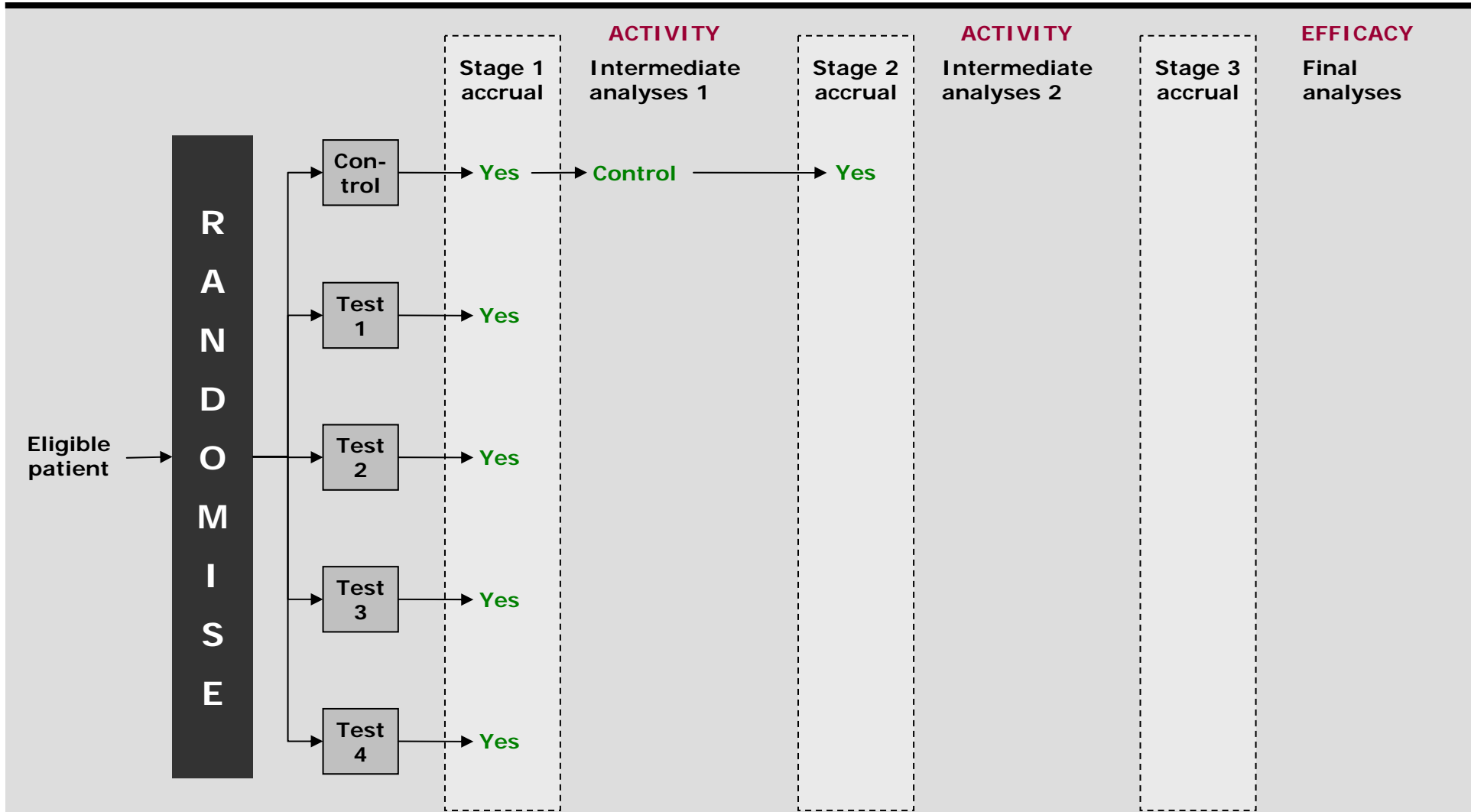
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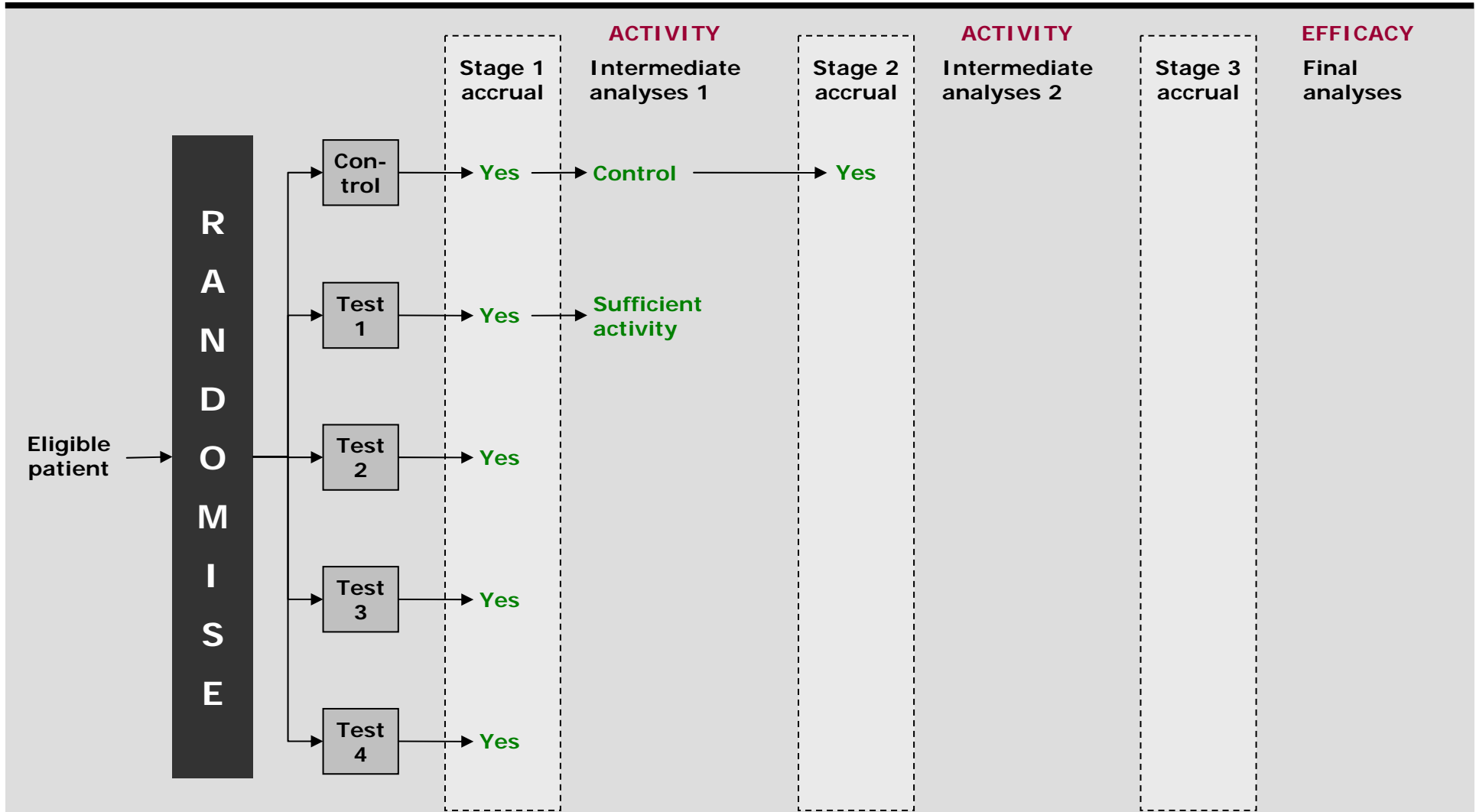
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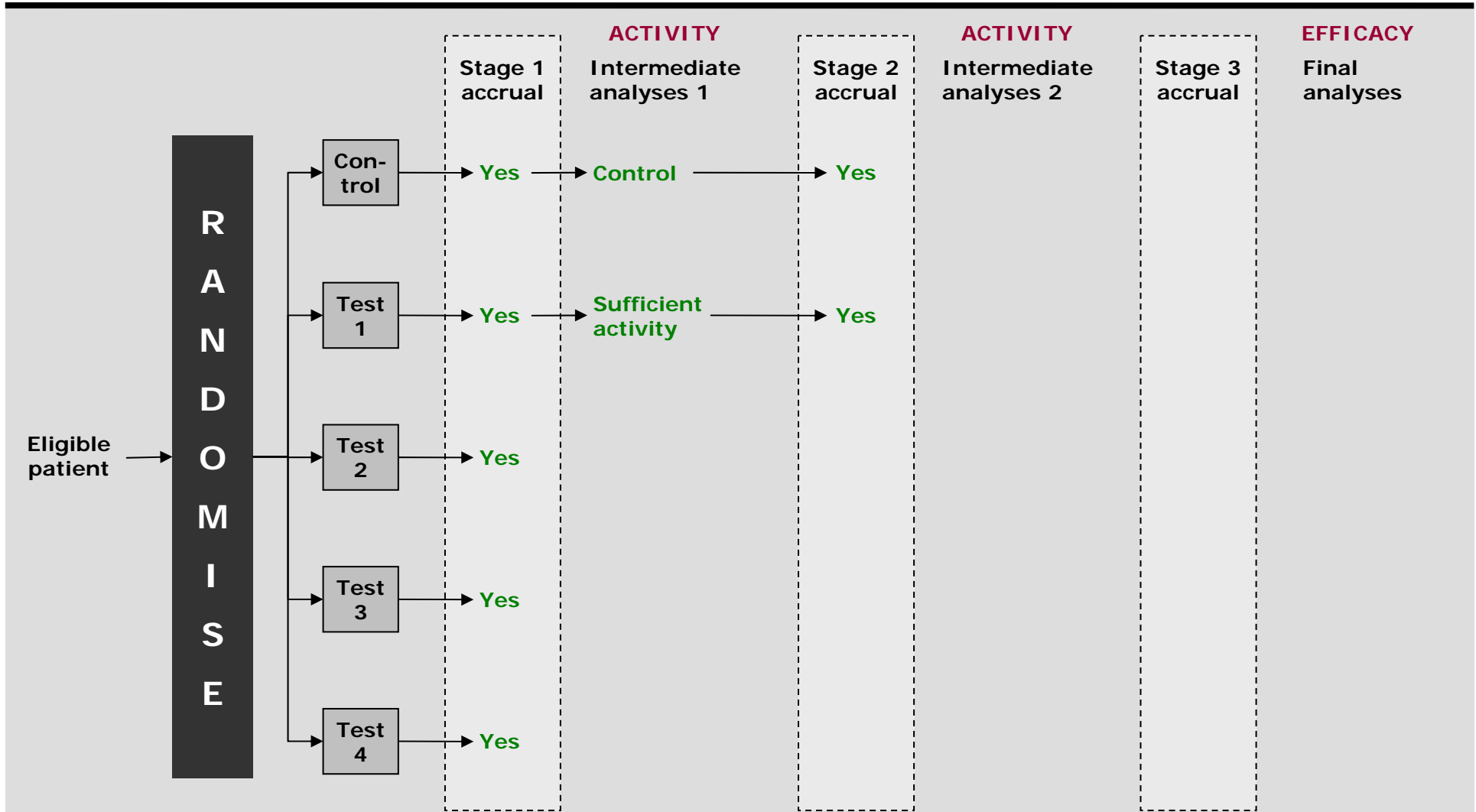
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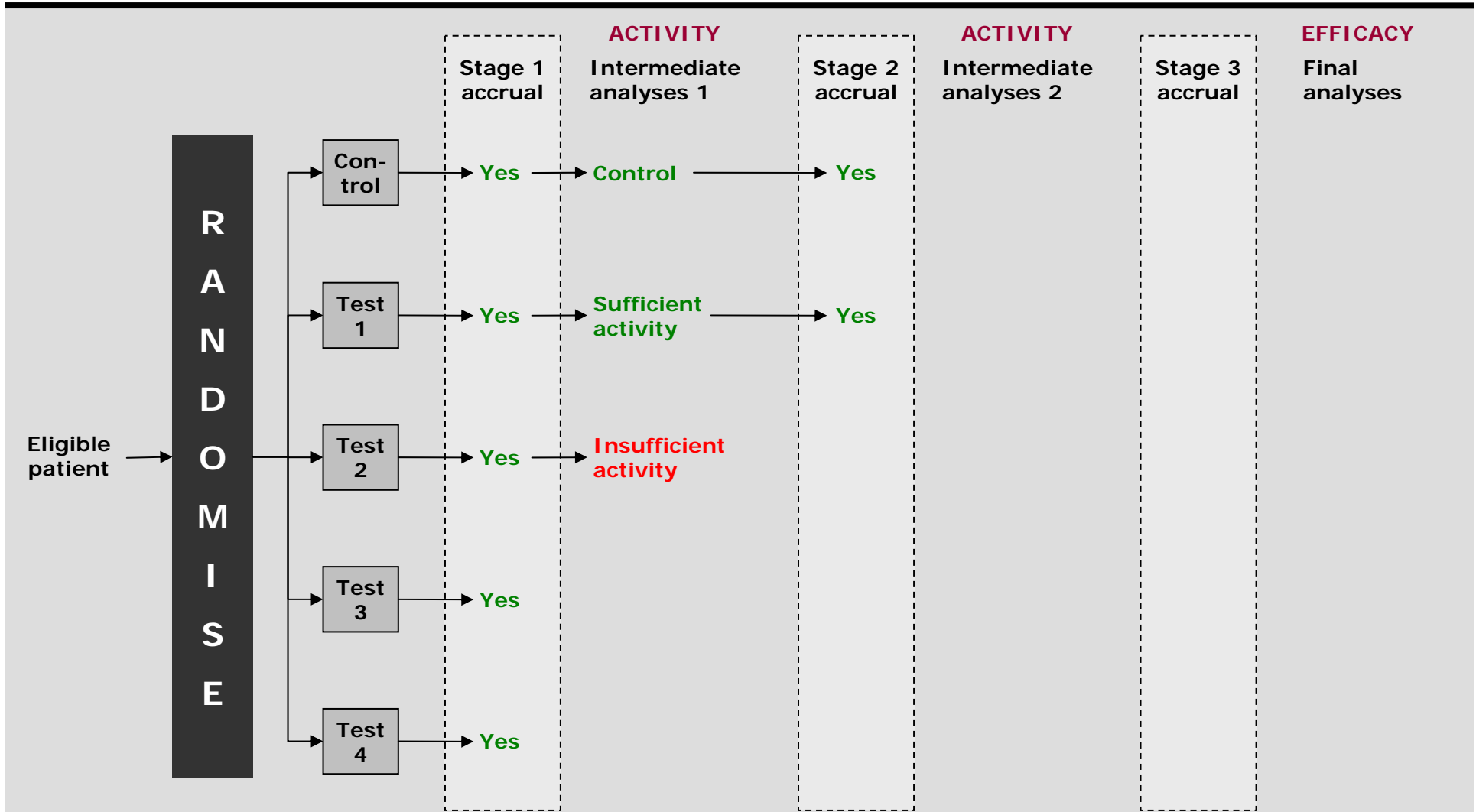
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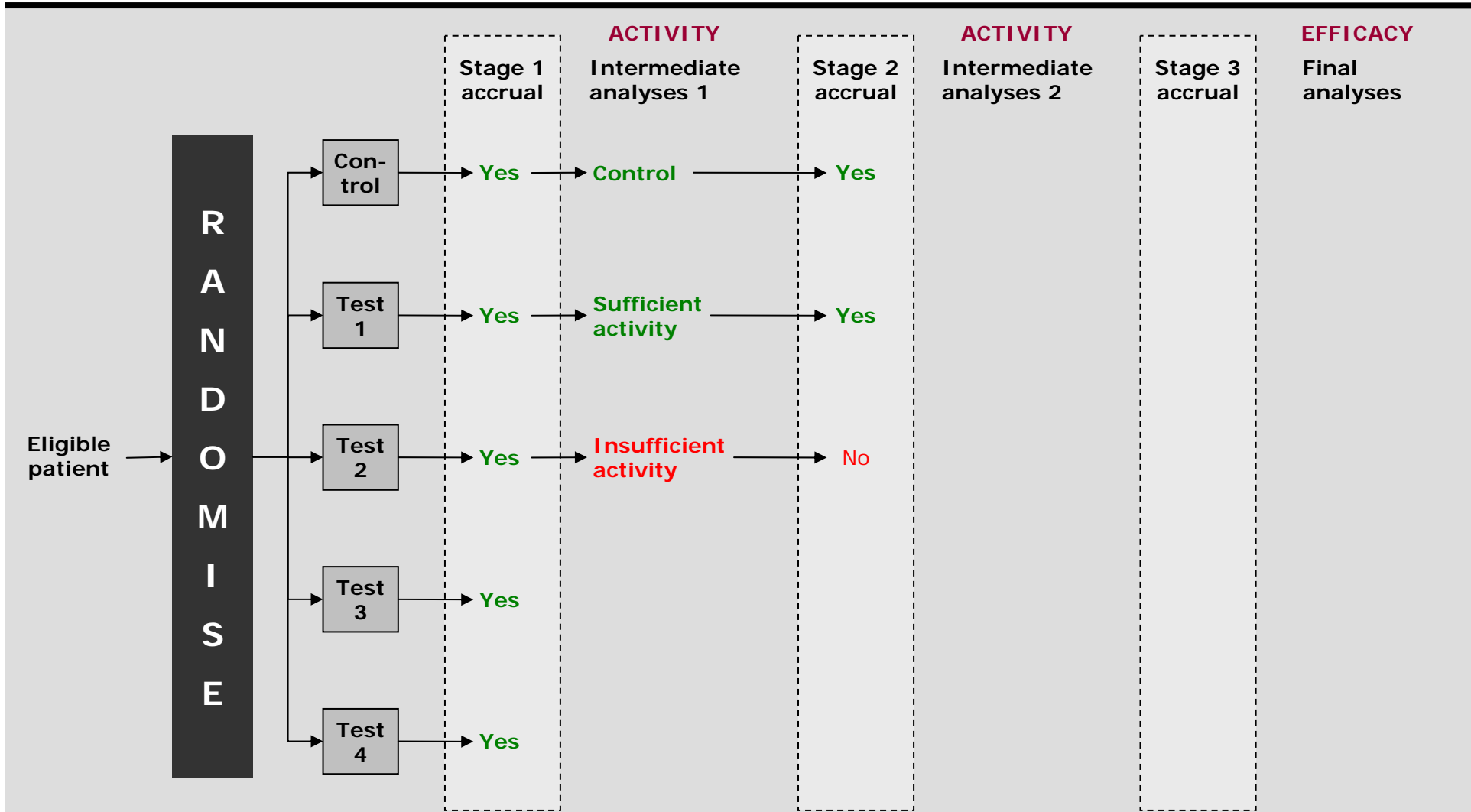
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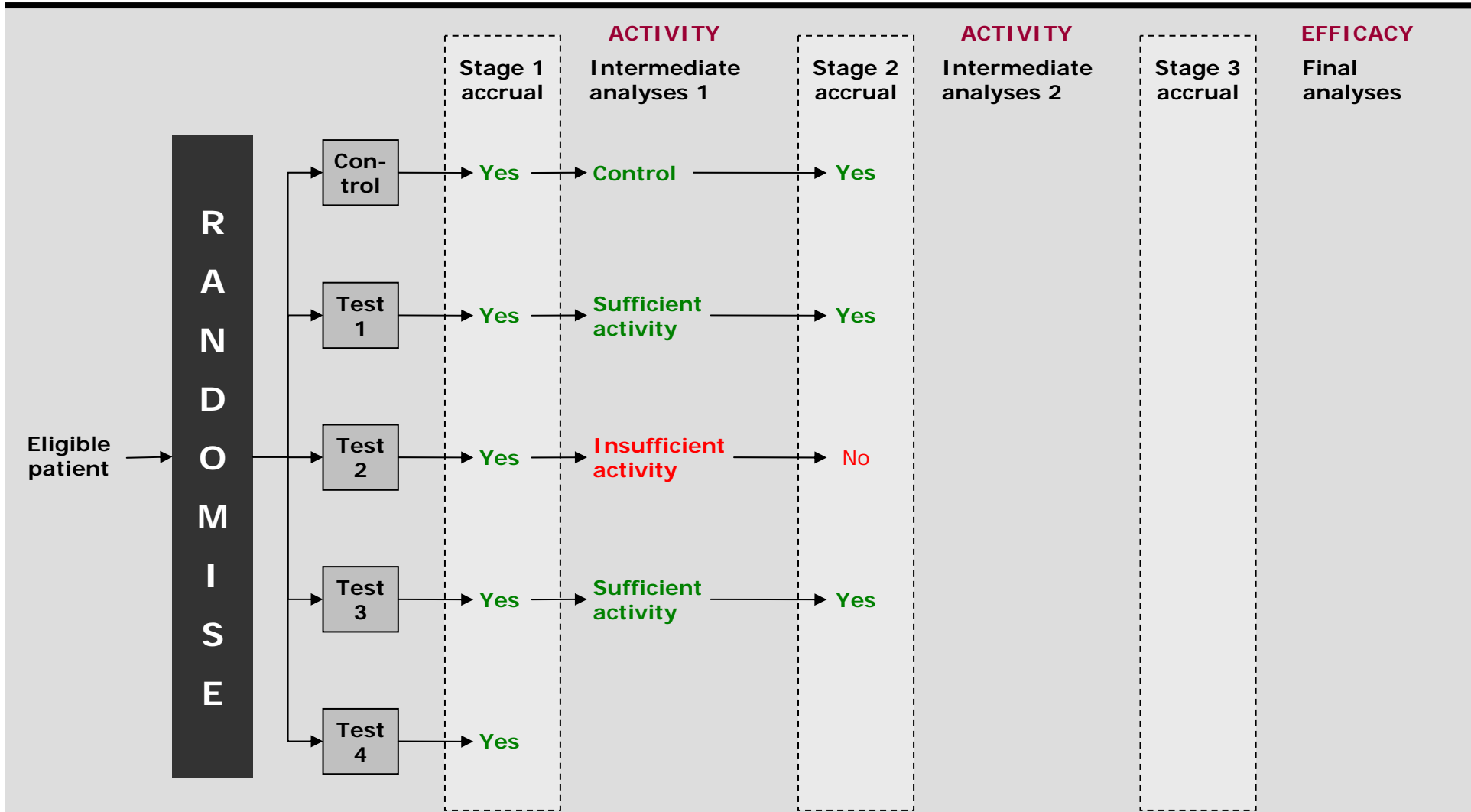
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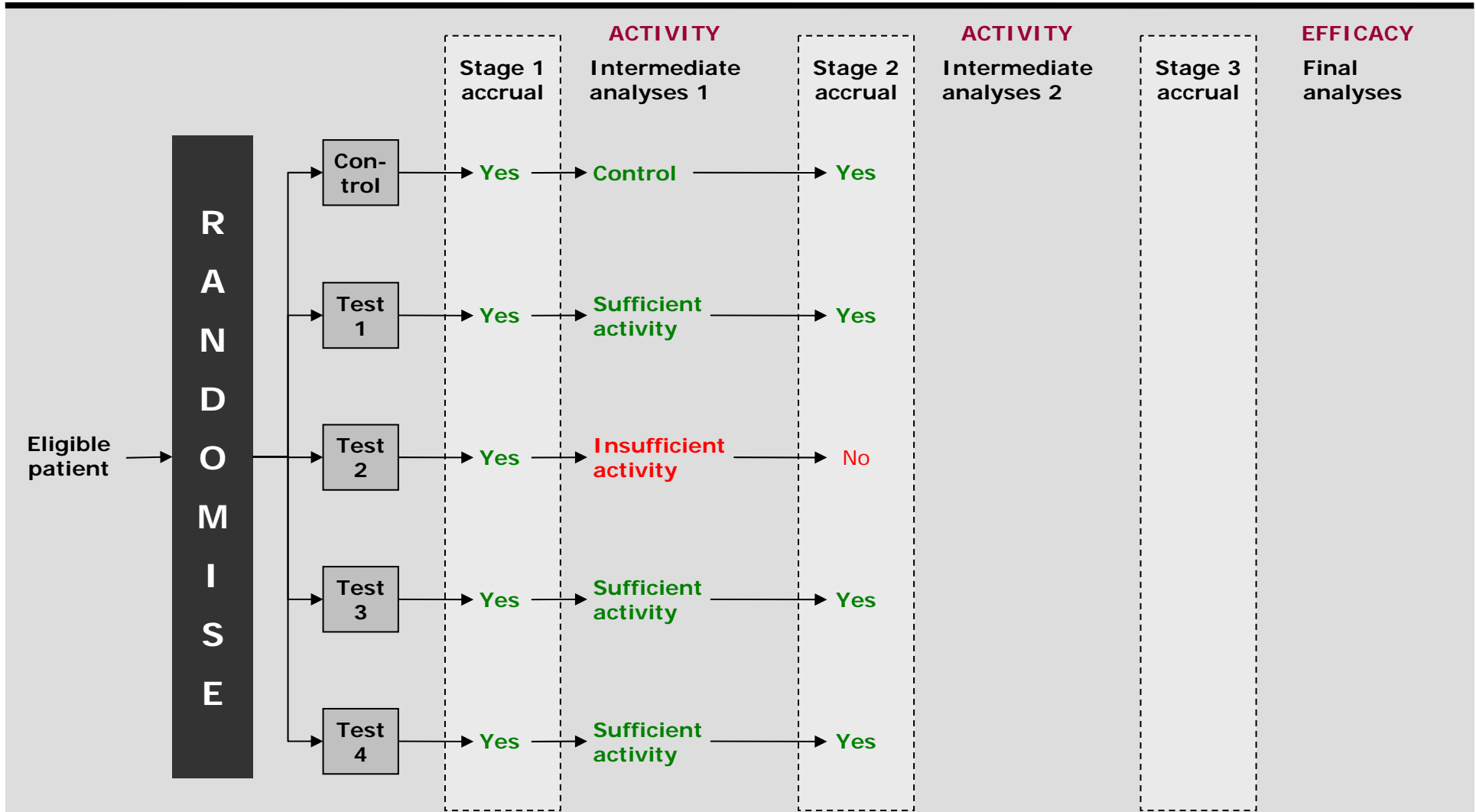
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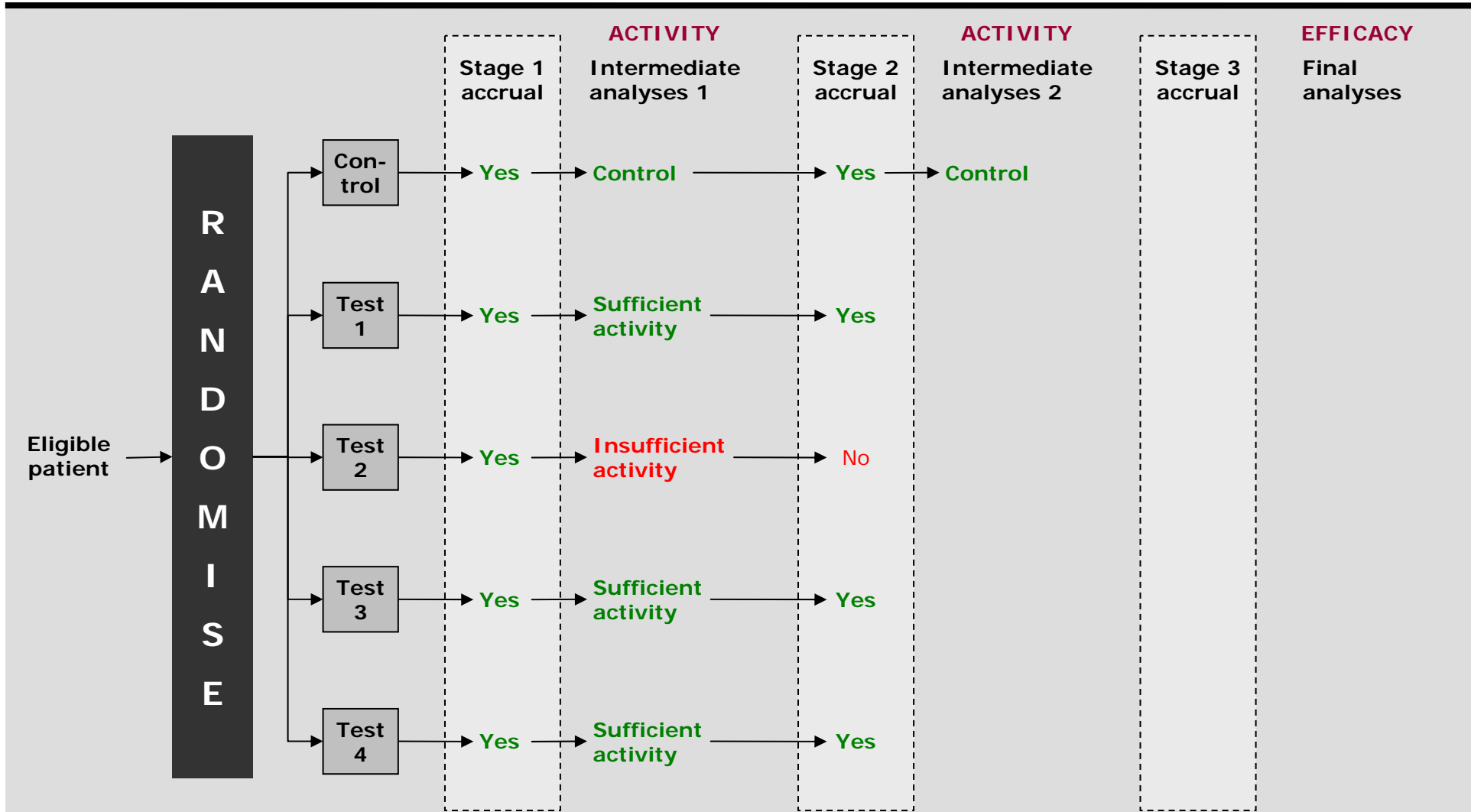
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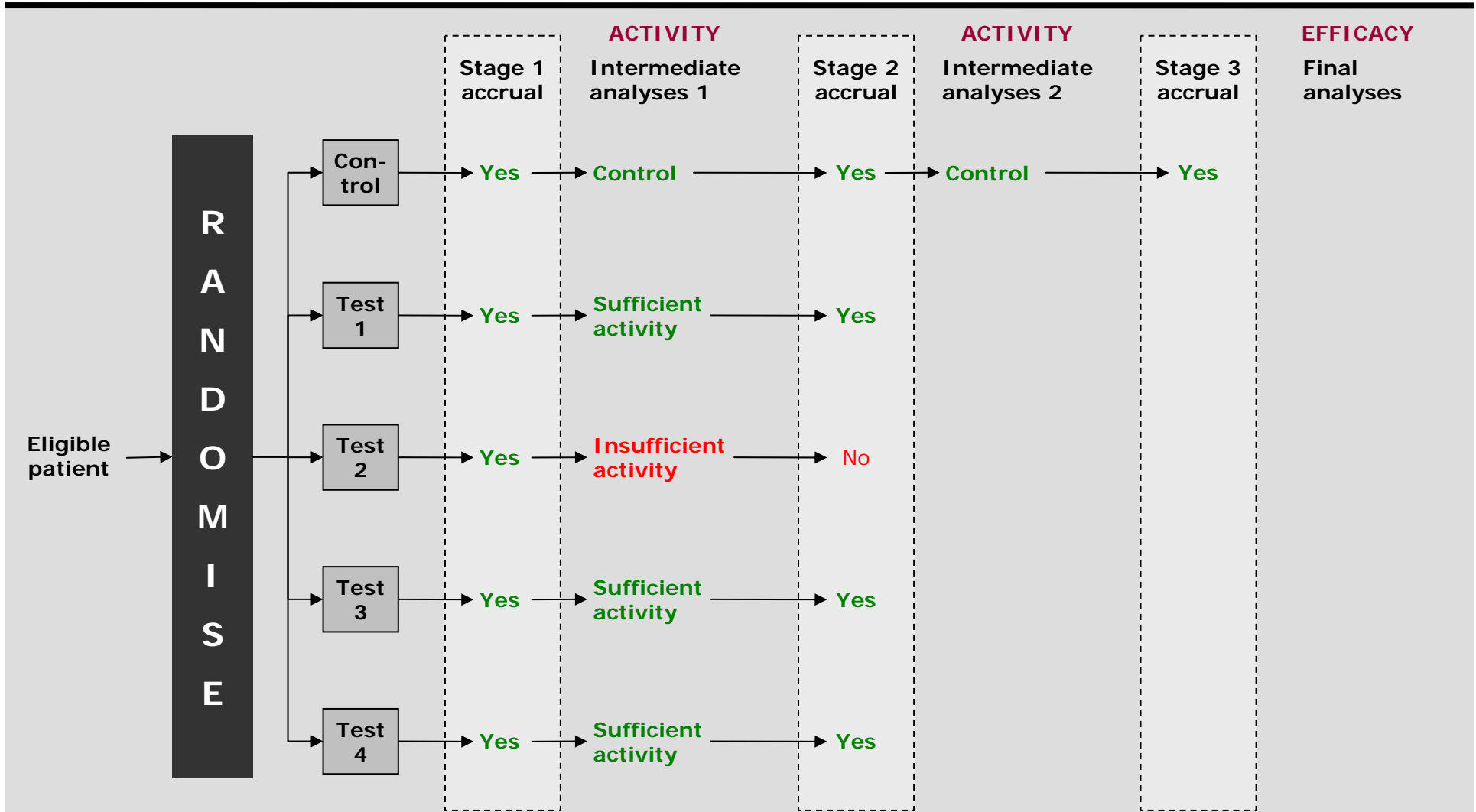
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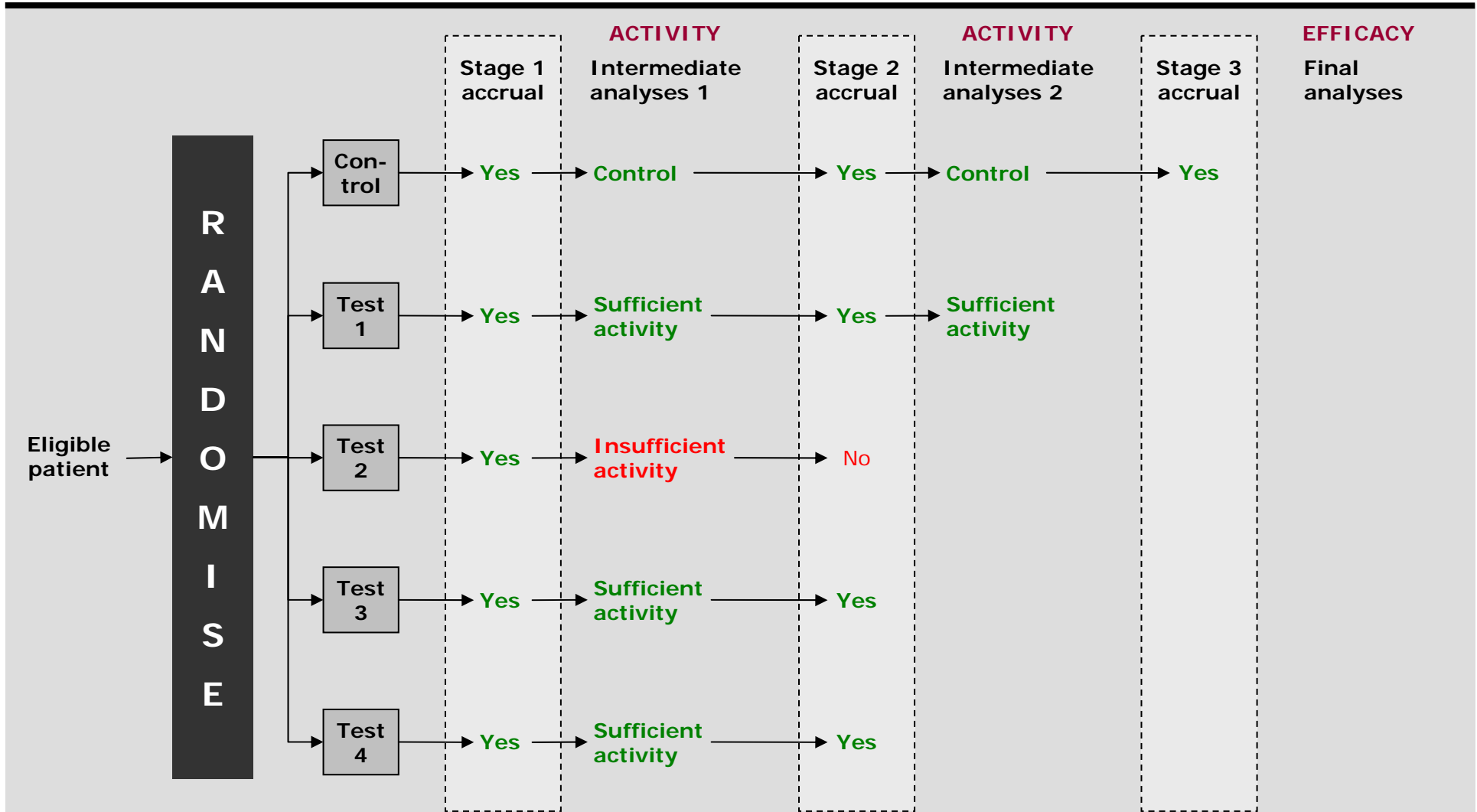
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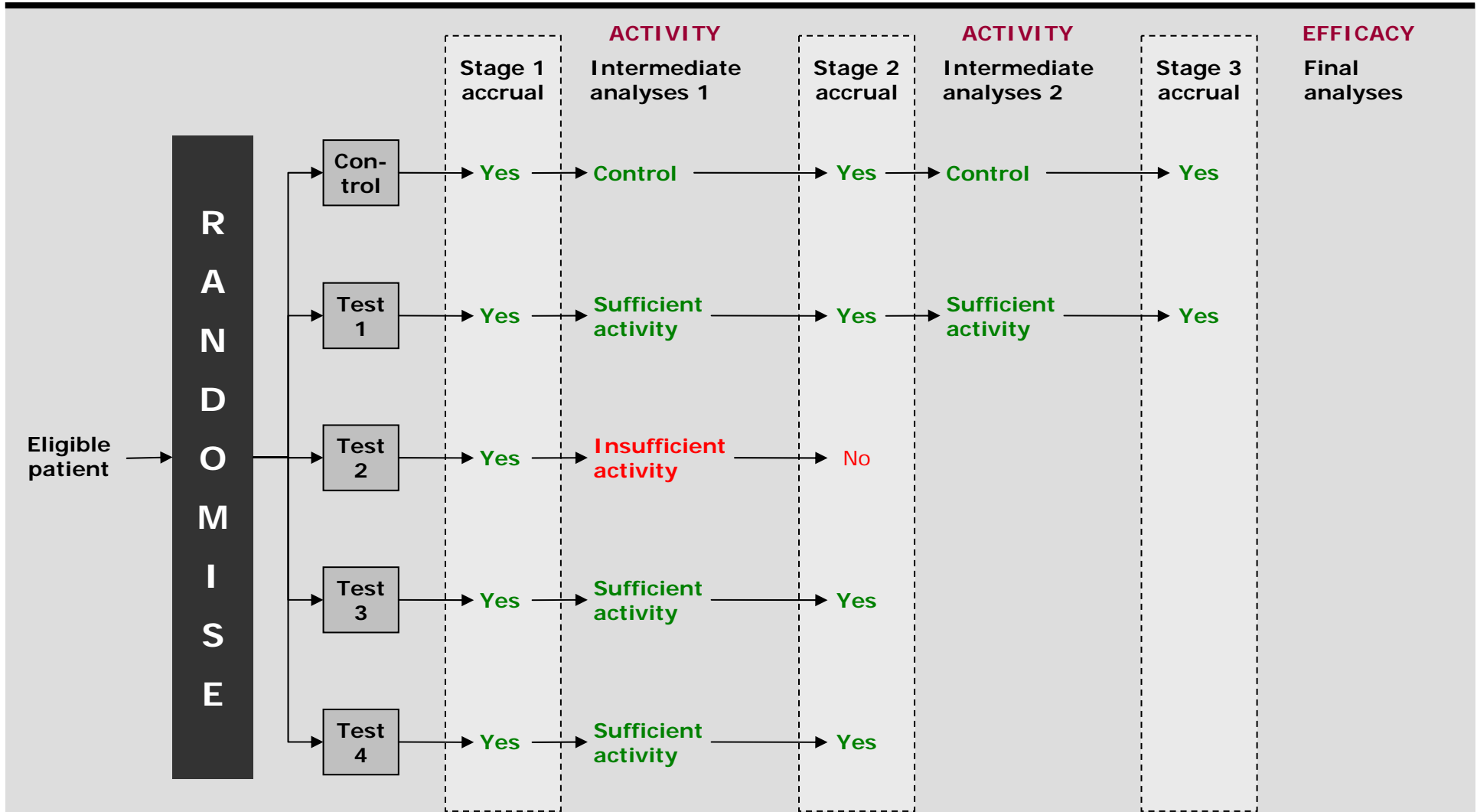
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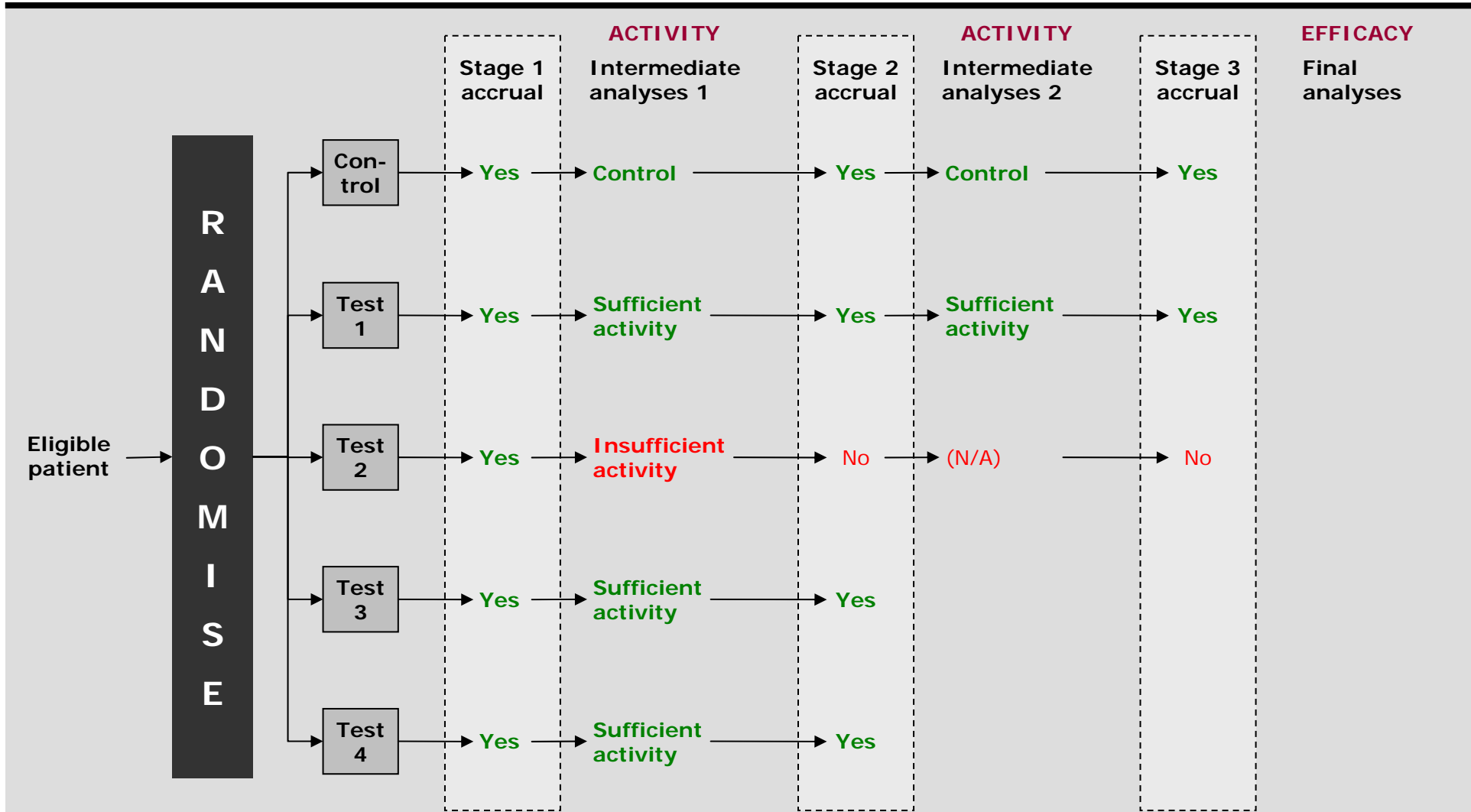
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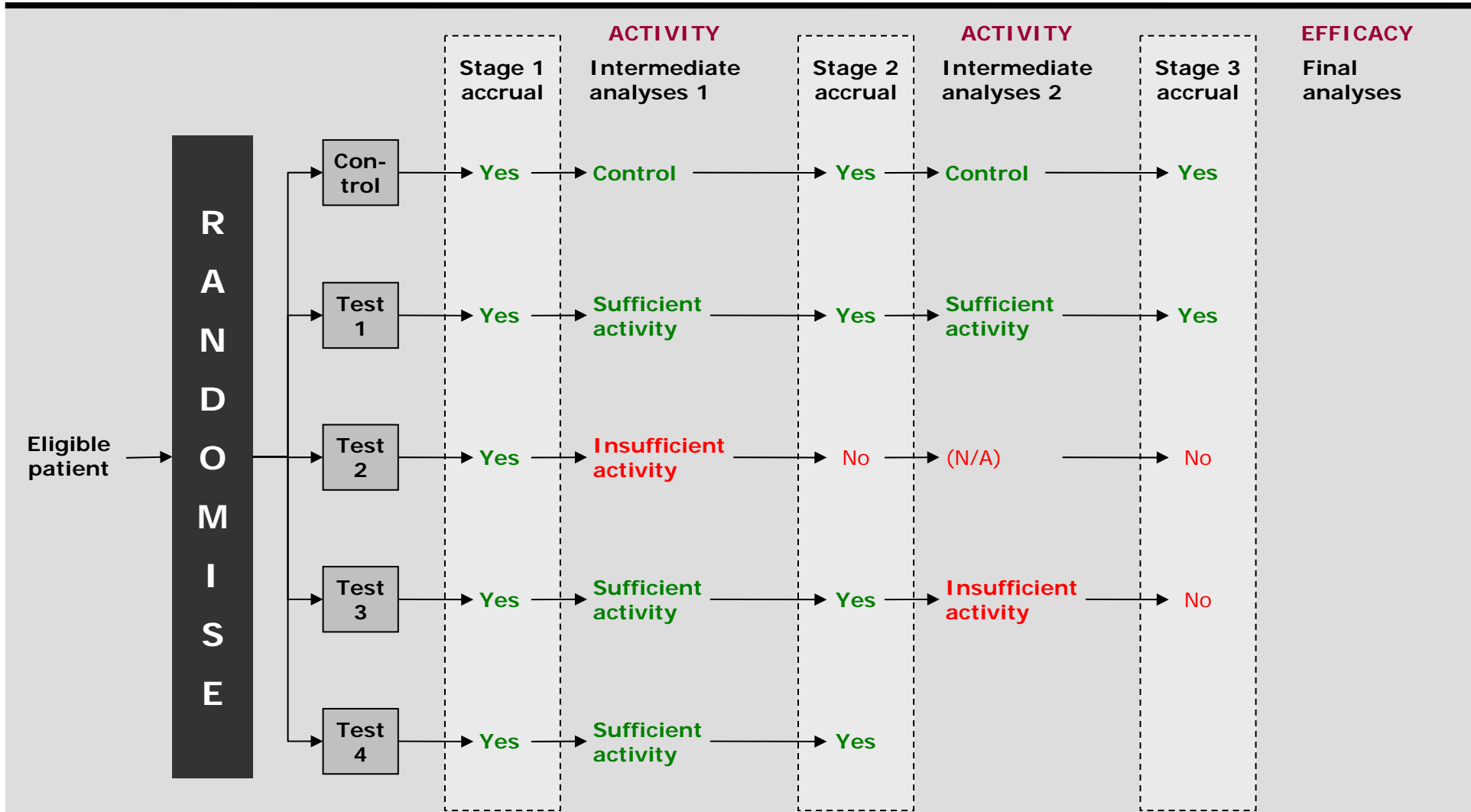
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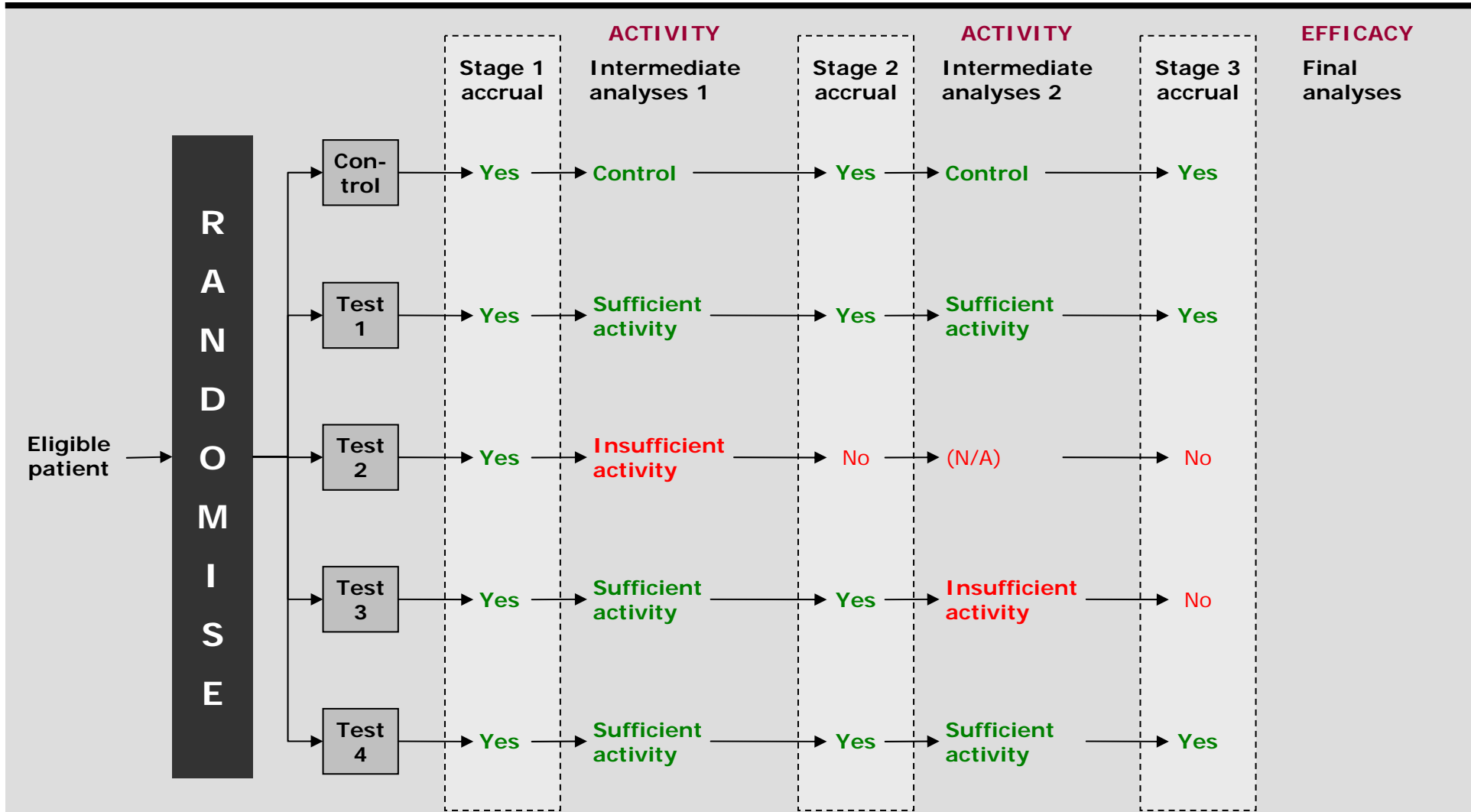
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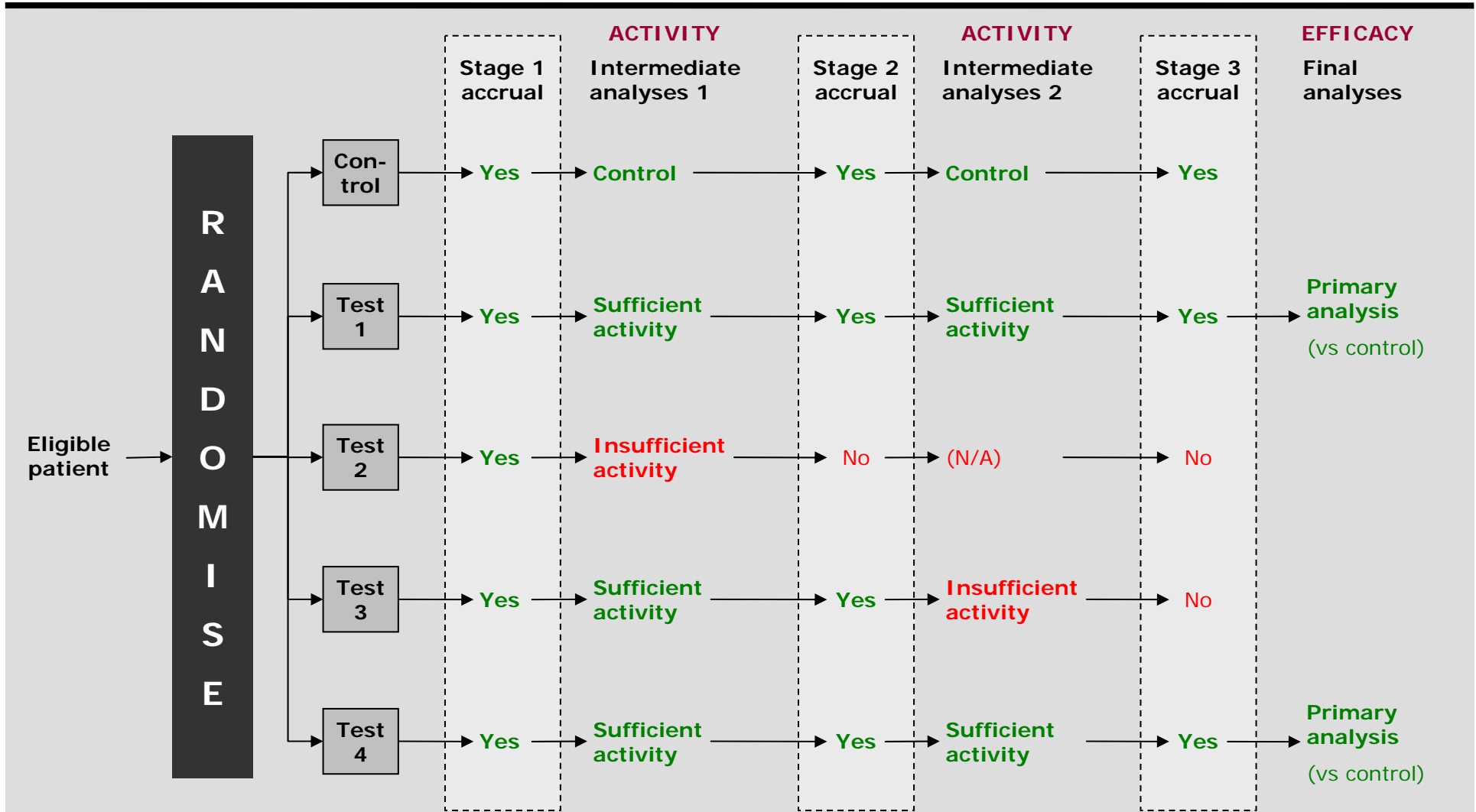
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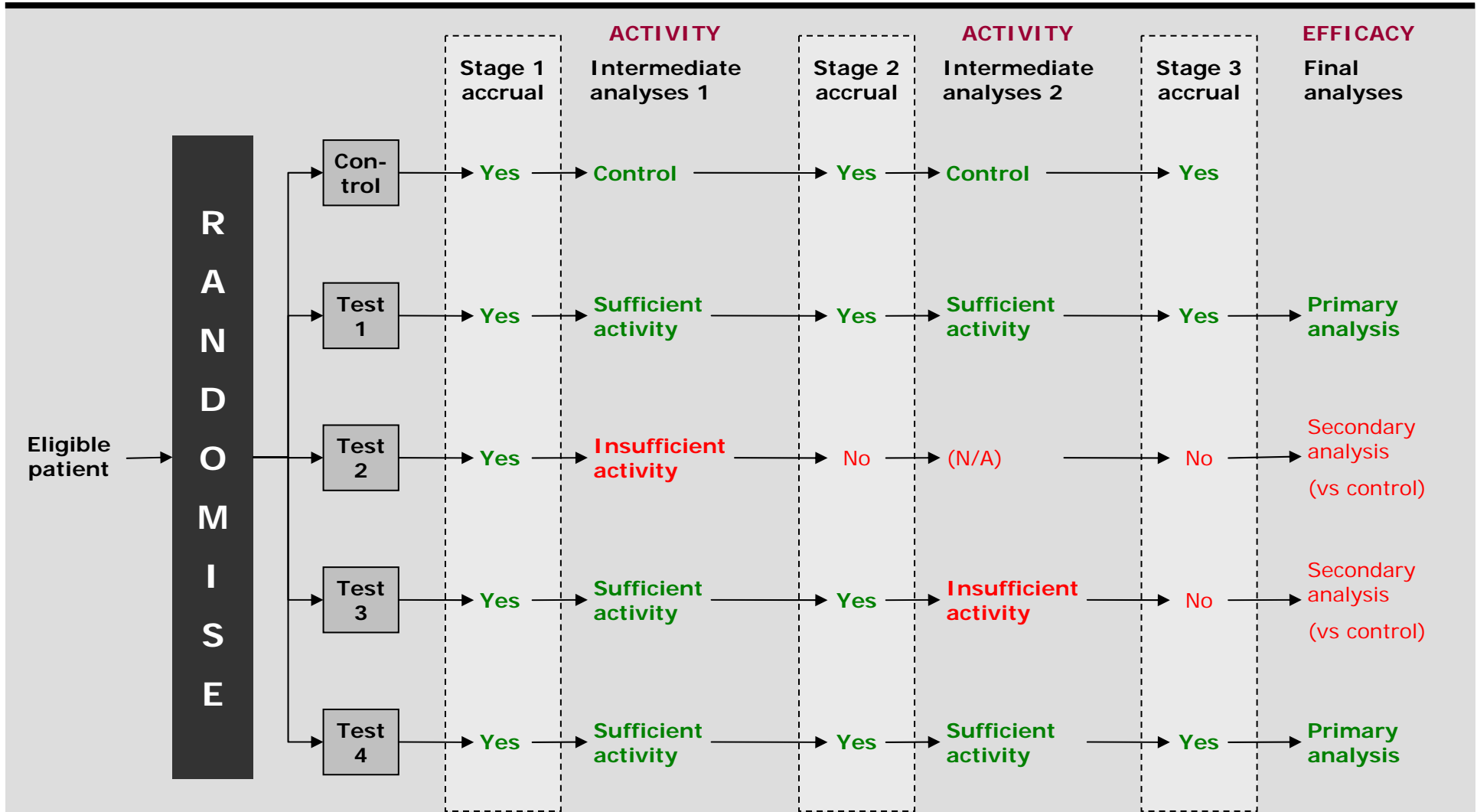
# Multi-Arm, Multi-Stage Trials



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# Multi-Arm, Multi-Stage Trials



# Advantages of MAMS

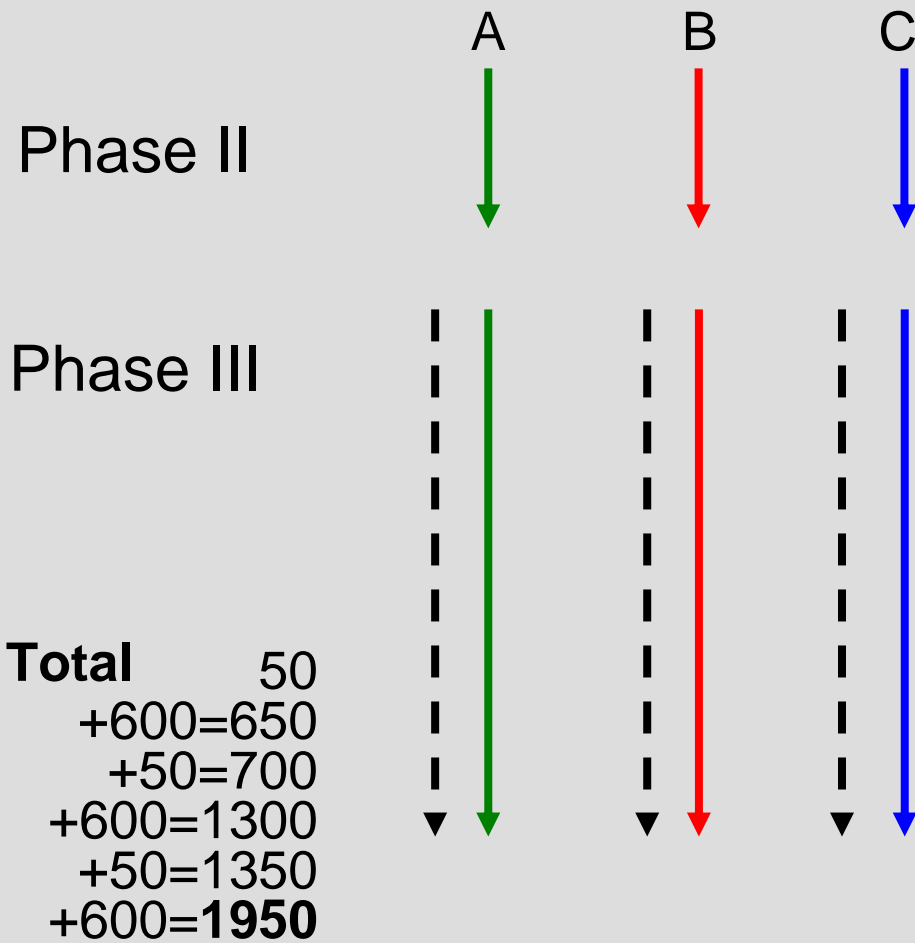
- » More answers
  - Fewer patients
  - Less overall time

# Advantages of MAMS

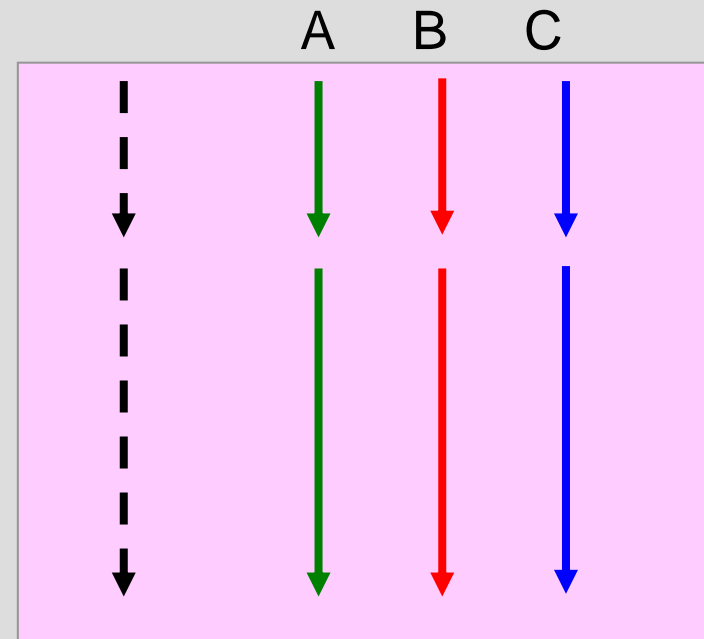
- Fewer patients
- Less overall time
  - Randomised from the start
  - Concurrent (not sequentially)
  - No delay between Phase II & Phase III assessment
  - Fewer applications for finance and approvals
    - One protocol
    - One grant application(s)
    - One CTA submission (per country)
    - One ethics submission (per country)
    - One R&D approval (per site)
  - Saves many years!

# Traditional vs MAMS

## Traditional Approach



## Multi-Arm, Multi-Stage



Phase II = 50 pts, Phase III = 600pts

# Advantages of MAMS

- Fewer patients
- Less overall time
- Increased flexibility
  - Focus trial resources on more active arms

# Advantages of MAMS

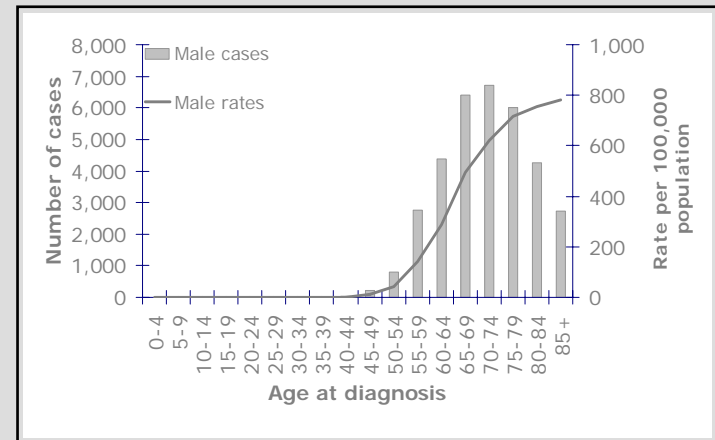
- Fewer patients
- Less overall time
- Increased flexibility
- Reduced costs
  - Limited resources trial
  - Responsibility to use fairly and efficiently
  - Value

## 2. Application in Prostate Cancer

1. MAMS Designs
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# Impact

- Most common male cancer
- Rising rates of diagnosis
  - Aging population
  - Awareness
  - PSA screening
- Hormone-sensitive disease
  - No new therapies for years
  - Median survival = 4 to 5 years (FFS = 2 years)

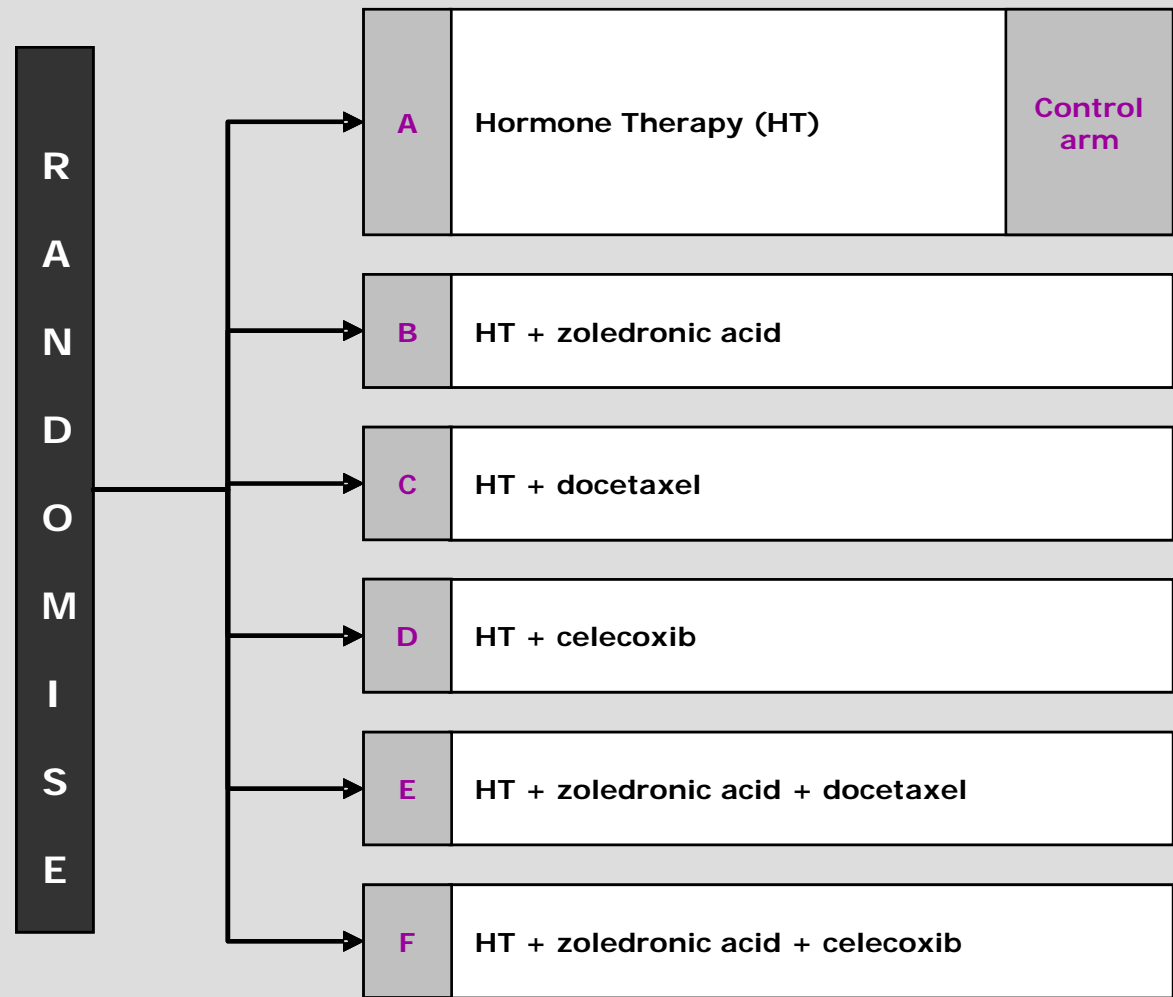


UK diagnosis: 34,000 in 2005  
UK deaths: 10,000 in 2006  
Global deaths: 250,000 in 2000

# Design rationale

- Many interesting agents
  - Different classes and modes of action
- No obvious reason to choose one
  - Many used in later stages of disease
  - Don't want to choose arbitrarily
- Quicker and efficient to use MAMS design
  - Assess 3 agents plus 2 combinations

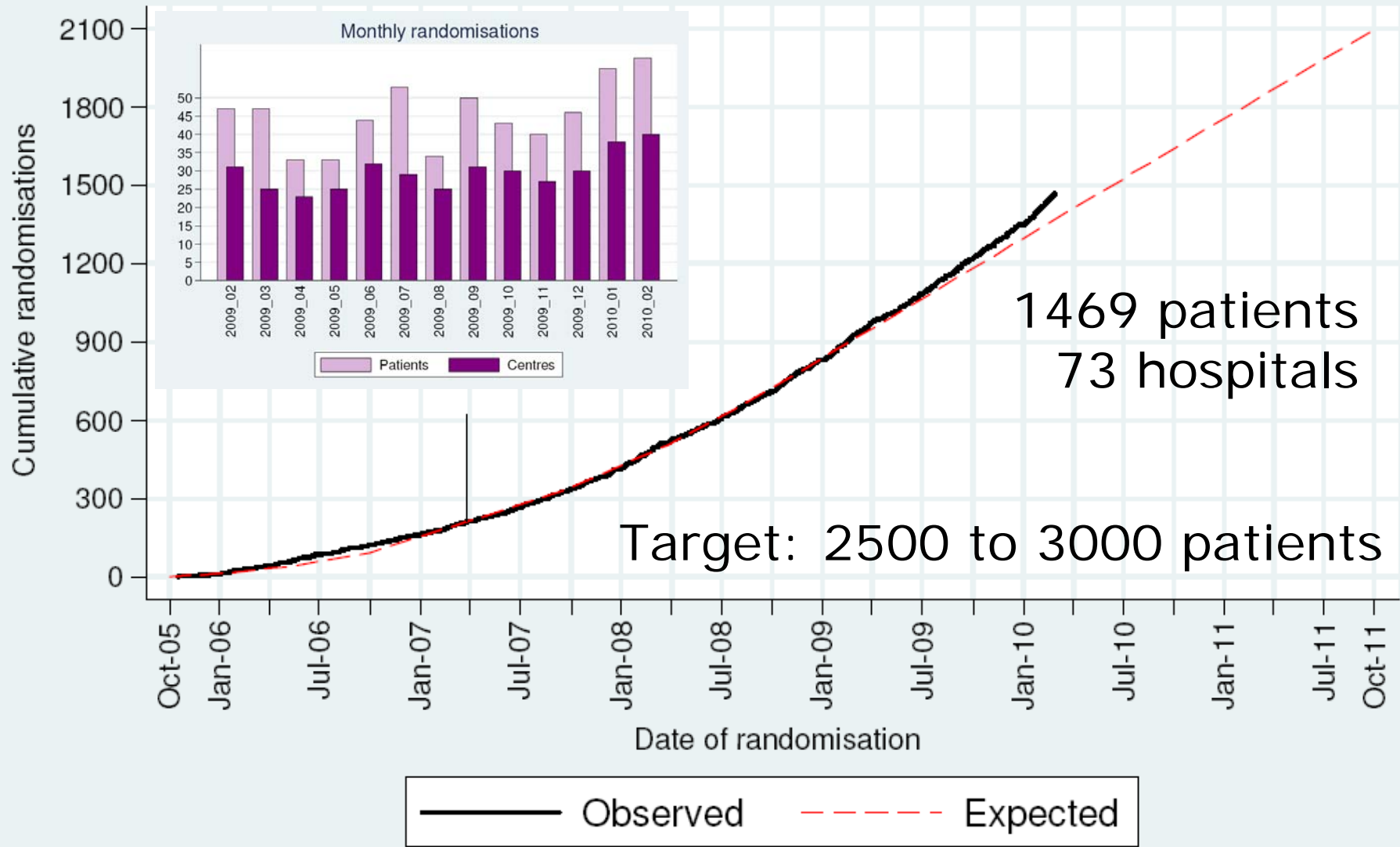
# Trial Design



# Groups to convince

- Medical community
- Patients
- Industry partners
- Funding bodies
- Regulatory and ethical committees
  
- Worry about:
  - Apparent complexity
  - Conservatism
- But, approved!

# Current recruitment

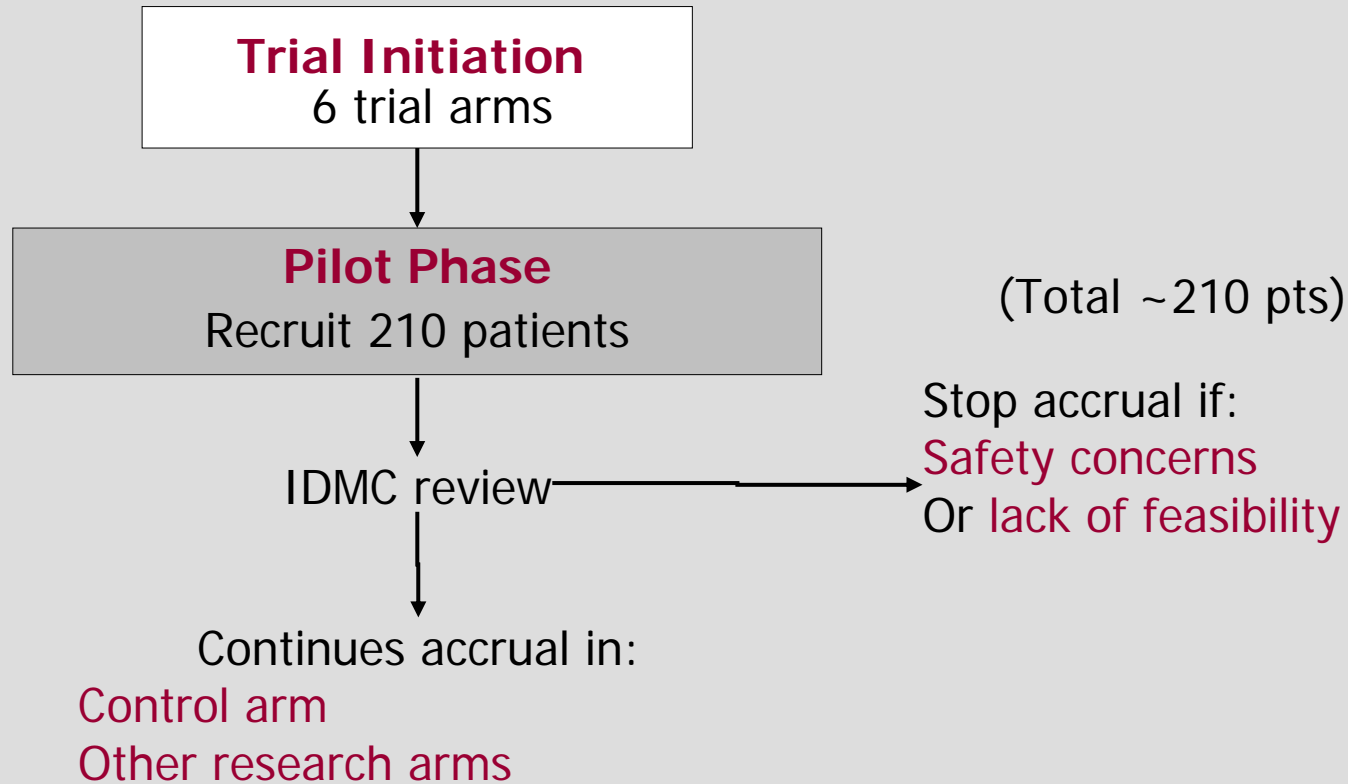


# Trial Design Stages

Stage	Outcome Measures	
	Primary	Secondary
Pilot	<b>Safety</b>	Feasibility
Activity I-III (phase II)	<b>Failure-free survival</b> (PSA-driven)	Overall survival Toxicity (safety) Skeletal-related events
Efficacy IV (phase III)	<b>Overall survival</b>	Failure-free survival Toxicity (safety) Skeletal-related events Quality of life

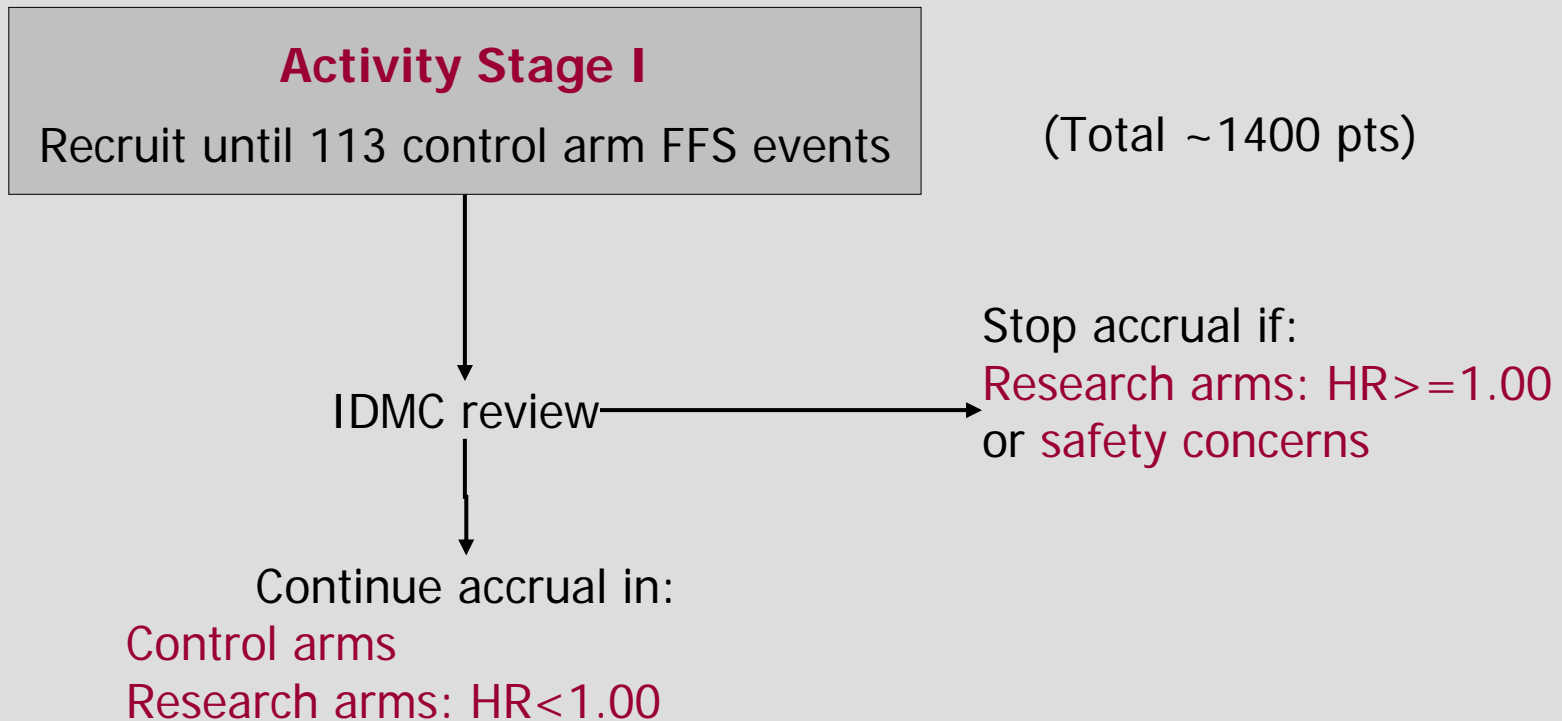
**Target:** Improvement survival at 4-yr 50% - 60% (HR = 0.75)

# Trial Stage - Pilot



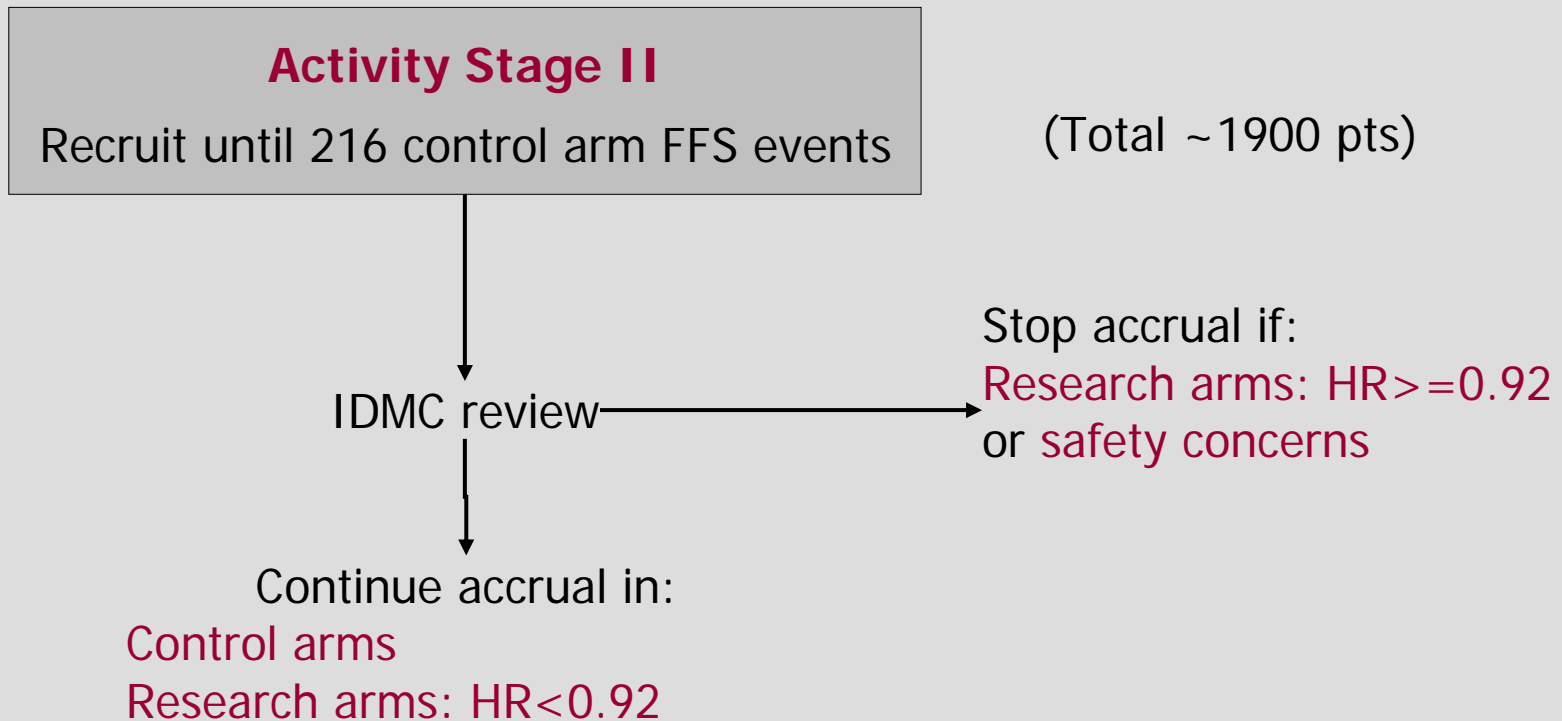
**Key** IDMC = Independent Data Monitoring Committee  
FFS = Failure Free survival

# Trial Stage - Activity Stage I



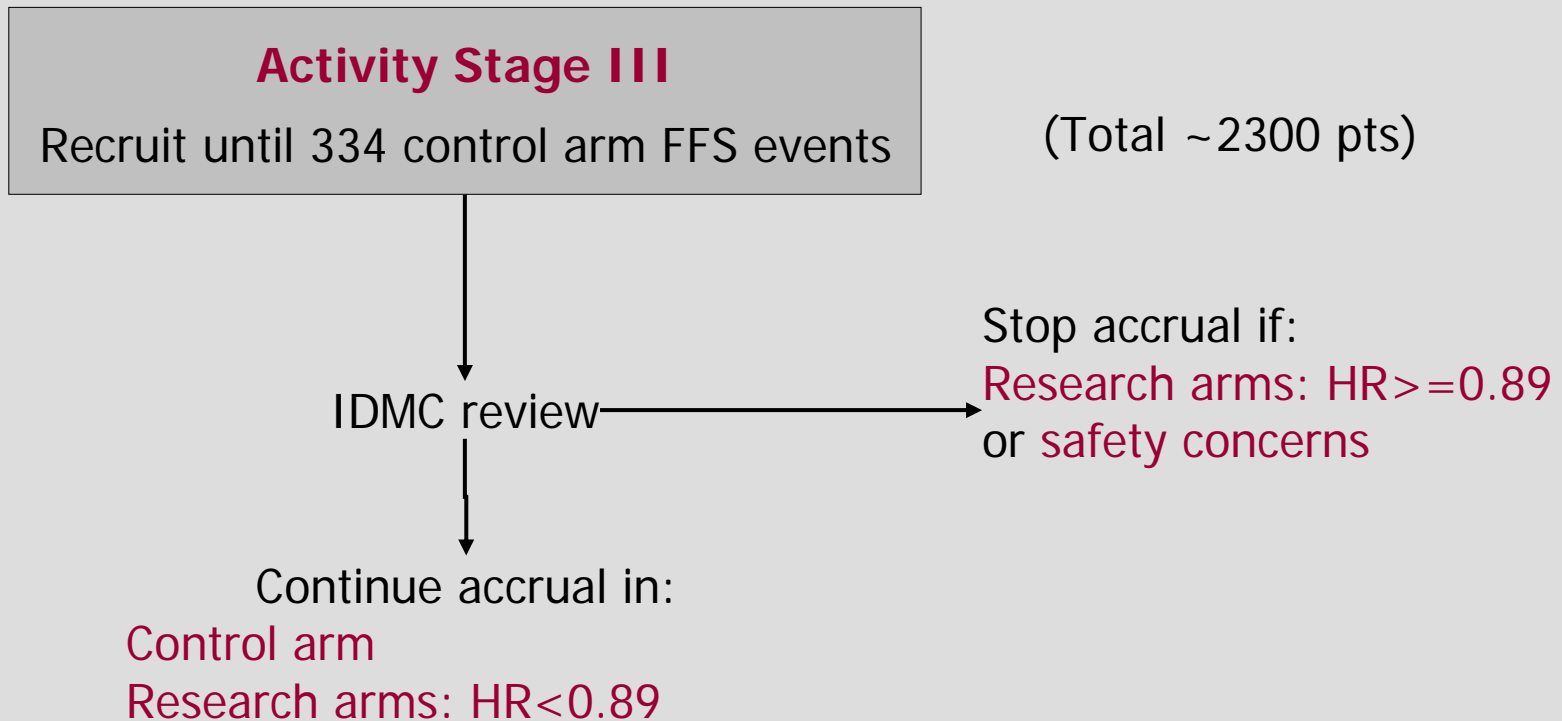
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# Trial Stage - Activity Stage II



**Key** IDMC = Independent Data Monitoring Committee  
FFS = Failure Free survival

# Trial Stage - Activity Stage III



**Key** IDMC = Independent Data Monitoring Committee  
FFS = Failure Free survival

# Trial Stage – Efficacy Stage IV

## Efficacy Stage IV

Recruit/Follow to 405 control arm deaths

(Total ~2500 to 3000 pts)



### Main Analyses

- (1) Overall survival: research arms vs C in arms recruiting in Efficacy Stage IV
- (2) 2<sup>o</sup> outcome measures: research arms vs C in arms recruiting in Efficacy Stage IV
- (3) All outcome measures: research arms stopping accrual early

## 3. Applications in Rare Diseases

1. MAMS Designs
2. Application in Prostate Cancer
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# Other MAMS trials

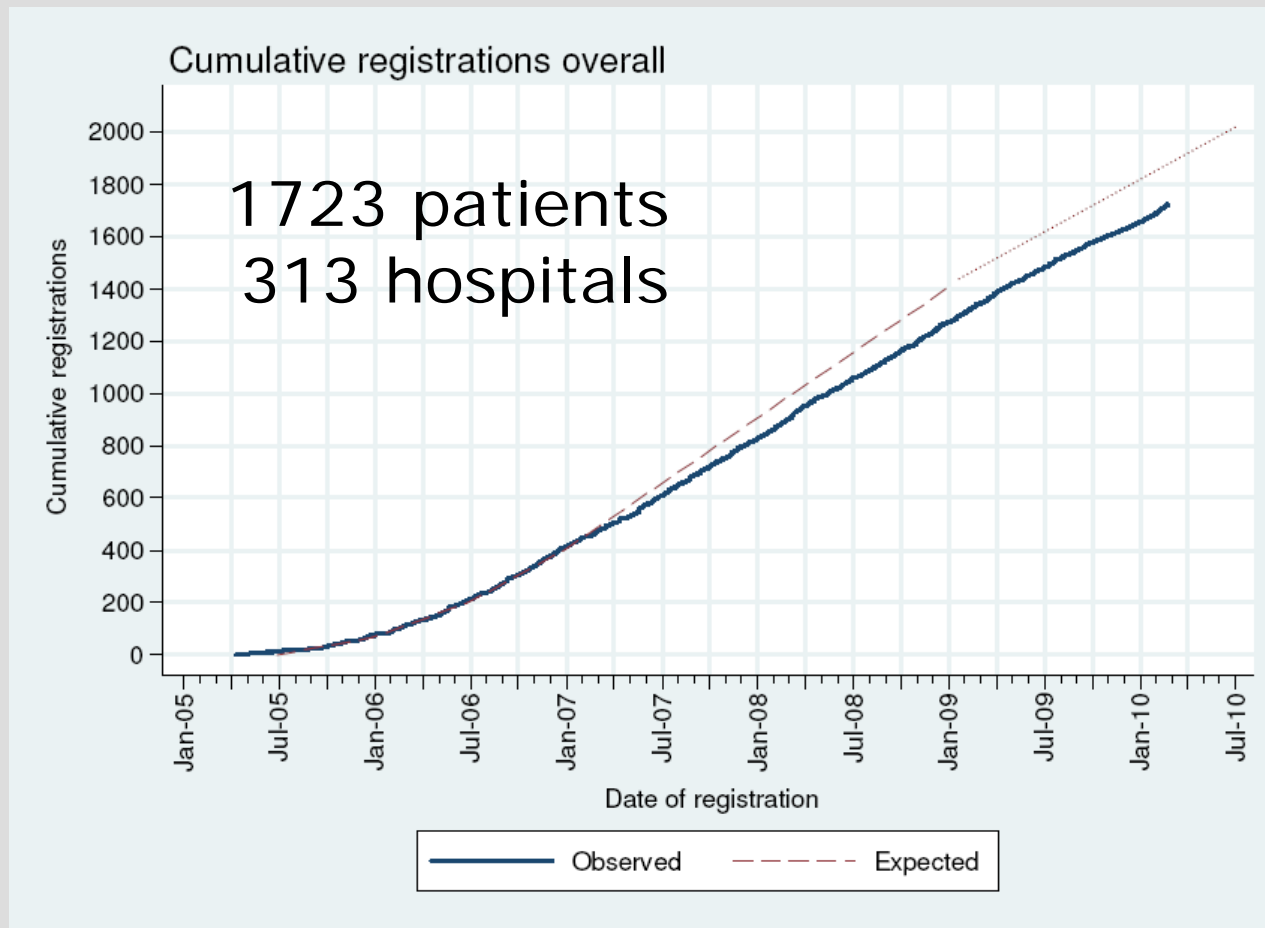
- ICON 6
  - 3-arm, 4-stage trial in 2nd line ovarian cancer using progression-free survival as the intermediate outcome measure

- MAMS approach can work in rare diseases
- Wherever multiple valid questions exist
  - Role of MTP?
  - 3 or 4 drugs?
  - Zoledronic acid?
  - New agents?
- Wherever good accrual is achievable
  - Achievable with collaboration
  - EURAMOS-1 registers 400 patients/year
- Wherever researchers are innovative

# EURAMOS-1

Good accrual is achievable

Innovative Researchers

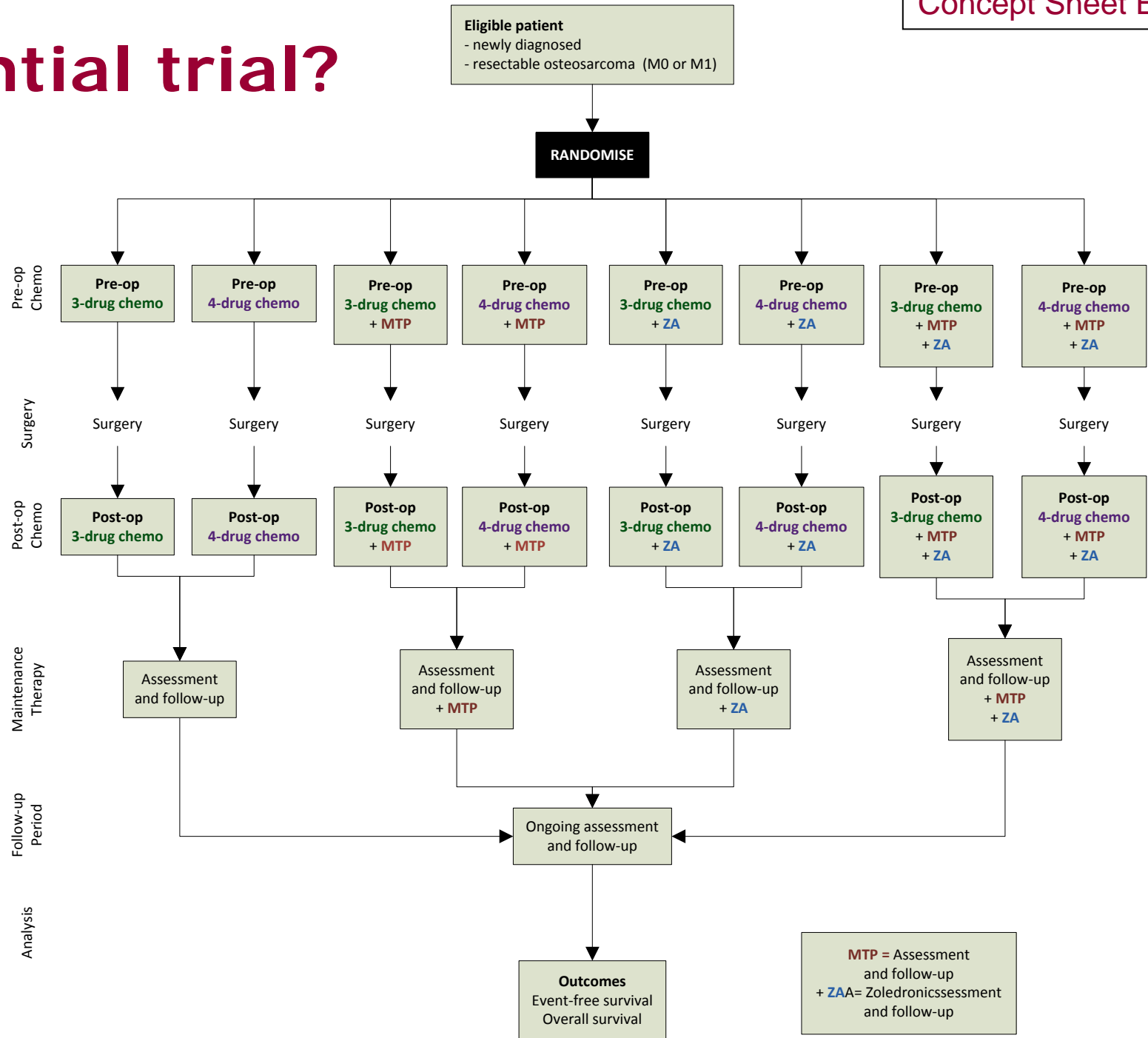


Answers 2 questions:

Good responders:  
Maintenance  
PegIntron

Poor Responders:  
MAP vs MAPIE

# Potential trial?



# Rare diseases

- With 400 patients / year
- And 5 years of accrual
- Plus 1.5 years follow-up
- Could answer 3 important questions
- In 6.5 years
  
- Even if all research arms better than control

# Outcome measures

- Focus on earlier but clinically useful OMs
  - Event-Free Survival
  - Survival outcomes more difficult to power
- Target clinically meaningful differences
  - Improve event-free survival:  $HR = 0.67$

## 4. Conclusions

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# Key points – 1

- Often many interesting questions
- Most new treatments prove no better than standard-of-care
- Change the question to:
  - How do we improve outcomes for this disease?
  - As rapidly as possible?

# Key points – 2

- MAMS trials speed evaluations
  - Test many treatments at the same time
  - Use lack of benefit analyses
- MAMS trials are
  - Feasible
  - Efficient
  - Supported by patients, clinicians, companies

# References – MAMS trials

- Royston P, Parmar MKB, Qian W  
Novel Designs for Multi-Arm Clinical Trials with Survival Outcomes, with an Application in Ovarian Cancer. *Statistics in Medicine* 2003;22: 2239 – 2256.
- Barthel FM-S, Royston P, Parmar MKB  
A menu-driven facility for sample size calculation in multi-arm, multi-stage randomised controlled trials with a survival-time outcome. *The Stata Journal* 2007 (submitted)
- Parmar MKB  
Speeding up the Evaluation of New Agents in Cancer. *J.Natl.Cancer Inst.* 100 (17):1204-1214, 2008.

# References - STAMPEDE

- Sydes MR, MKB Parmar, ND James *et al*  
Issues in applying multi-arm multi-stage (MAMS)  
methodology to a clinical trial in prostate cancer: the MRC  
STAMPEDE trial. *Trials* 10 (39), 2009.
- James ND, Sydes MR, Clarke NW *et al*  
STAMPEDE: Systemic Therapy for Advancing or Metastatic  
Prostate Cancer -- A Multi-Arm Multi-Stage Randomised  
Controlled Trial. *Clinical Oncology* 20 (8):577-581, 2008.
- James ND, Sydes MR, Clarke NW *et al*  
Systemic therapy for advancing or metastatic prostate  
cancer (STAMPEDE): a multi-arm, multistage randomized  
controlled trial. *BJU.Int* 103 (4):464-469, 2009.

# Contacts



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# Contacts



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# EXTRA SLIDES

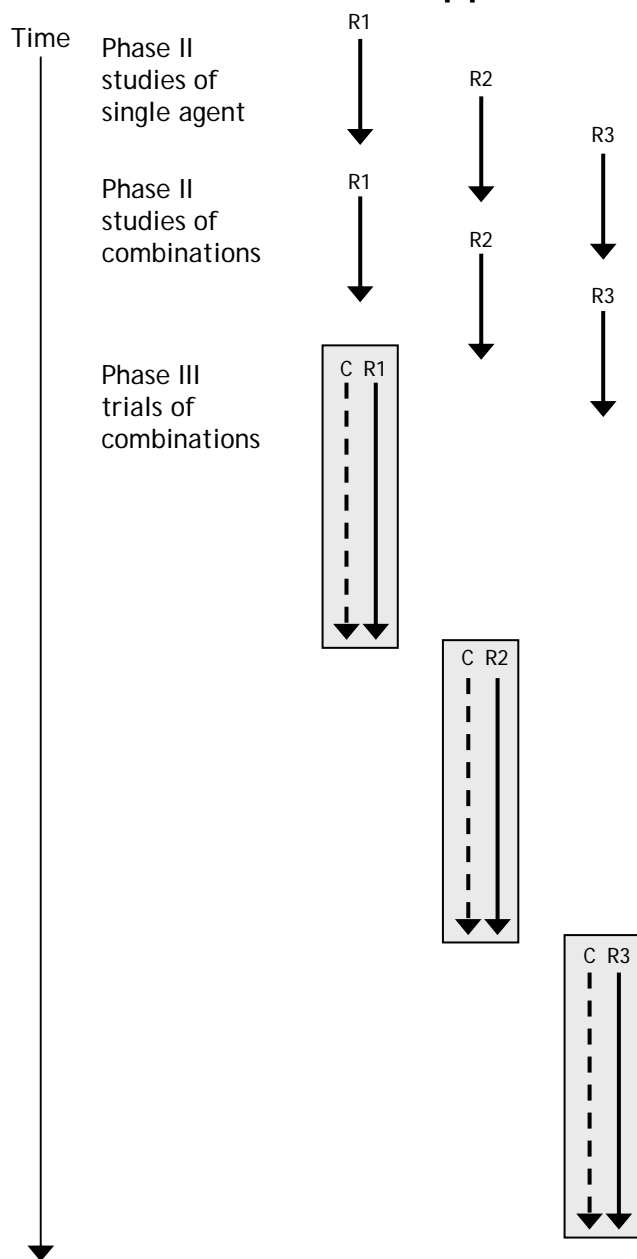
# Arms to compare

- Different drugs
  - Classes
  - Combinations
- Same drug
  - Dose levels
  - Duration
  - Timing
  - Method of administration
- Non-drug therapy

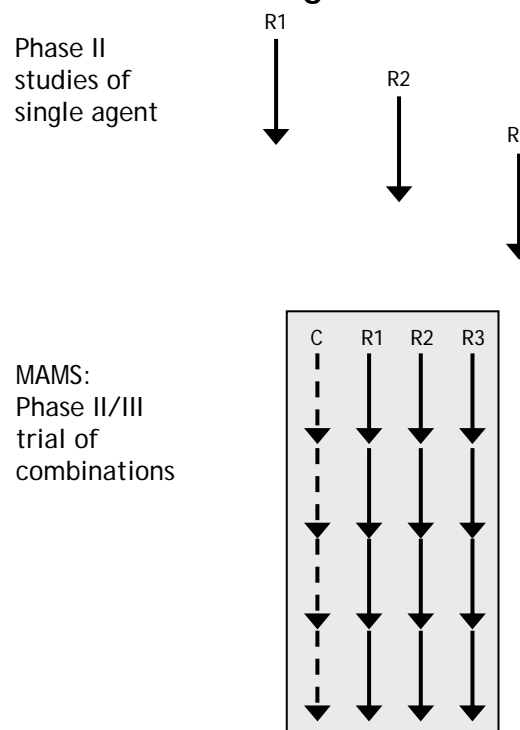
# Statistical Issues

- Pair-wise comparison of each research vs control
- Randomisation ratio  
(A:B:C:D:E:F) = 2:1:1:1:1:1
  - Two control arm patients for every research arm patients
  - Efficient for power
- Randomisation centrally
  - Computer based algorithm
  - Minimisation with an additional random element
  - 7 stratification factors for balancing groups

## A - Traditional approach



## B - MAMS design



### Notes

C = control arm; R1 = research arm R1; R2 = Research arm R2; R3 = research arm R3

Assumes that single agent studies would be carried out before combination studies

Assumes that phase II studies require smaller numbers of patients and so smaller number of centres. Therefore, phase II studies of different agents may be carried out concurrently

Assumes that phase III trials require larger numbers of patients and a network of centres that can only run one trial at a time: therefore, phase III trials of different agents must be carried out sequentially

MAMS design rolls phase II assessment of combinations into the same trial as the phase III assessment of effectiveness

# Impact of accrual rates

Accrual/ Year	Total pts	Duration (yrs)	Difference in pts	Difference in length
350	2960	8.5	-451	20 months
<b>500</b>	<b>3411</b>	<b>6.8</b>	0	0
750	4046	5.4	635	-17 months
Assuming: median FFS=24m, median OS=48m, 6 arms recruiting at each stage				

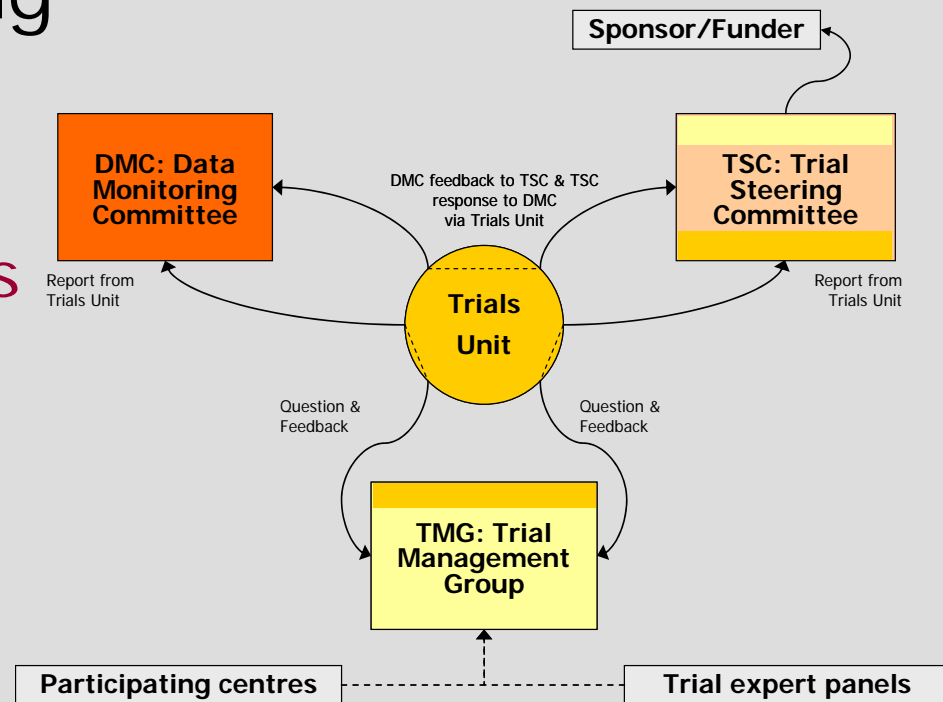
# Assumptions in STAMPEDE

- Broad eligibility spectrum
  - Patients starting hormone therapy
    - Newly metastatic
    - New & locally advanced
    - Previously treated & relapsing
  - Assume more patients are M0 than M1
  - Failure-free survival (FFS): median = 2 years
  - Overall survival (OS): median = 4 years

# Issues in intermediate analyses

# Moving through stages

- IDMC review interim data
  - Safety and activity data
  - Recommendations to TSC and TMG
- Education and training
  - For all committees
  - Trust in relationships
  - Hypothetical examples



# Who sees this interim data?

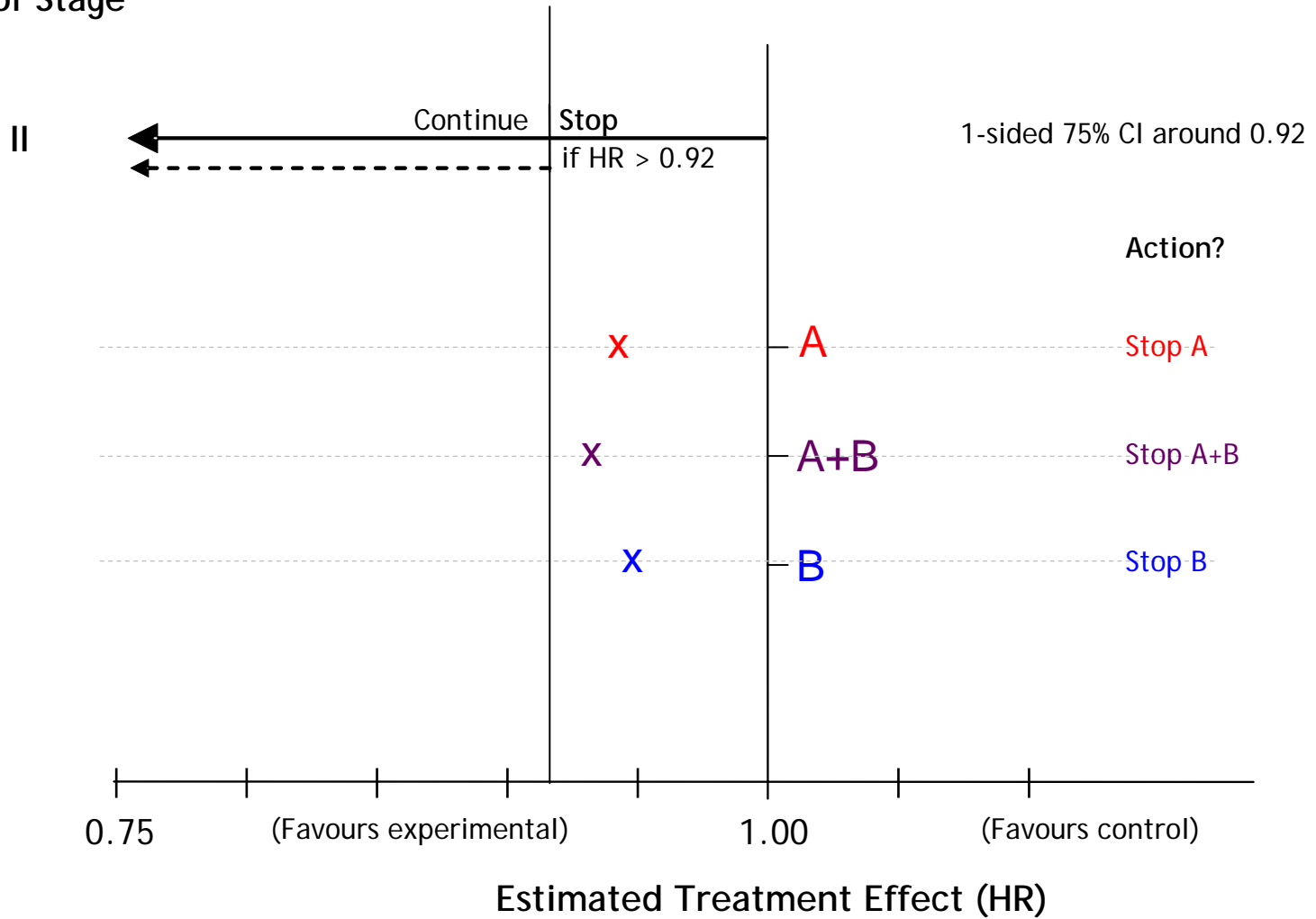
- Continuing arms
  - Researchers not taken out of equipoise by implicit intermediate information
  - Should reinforce need to continue randomisation to gain stronger evidence
- Intermediate assessments require only modest levels of evidence to continue accrual
  - Considers activity and not efficacy
  - This point will be particularly emphasised to investigators

# Dropping arms or agents

- If combination arm stopped for lack of sufficient effect
  - Should “single” agent arm stop too?
- If single agent arm stopped for lack of sufficient effect
  - Should combination arm stop too?
- Training and discussion

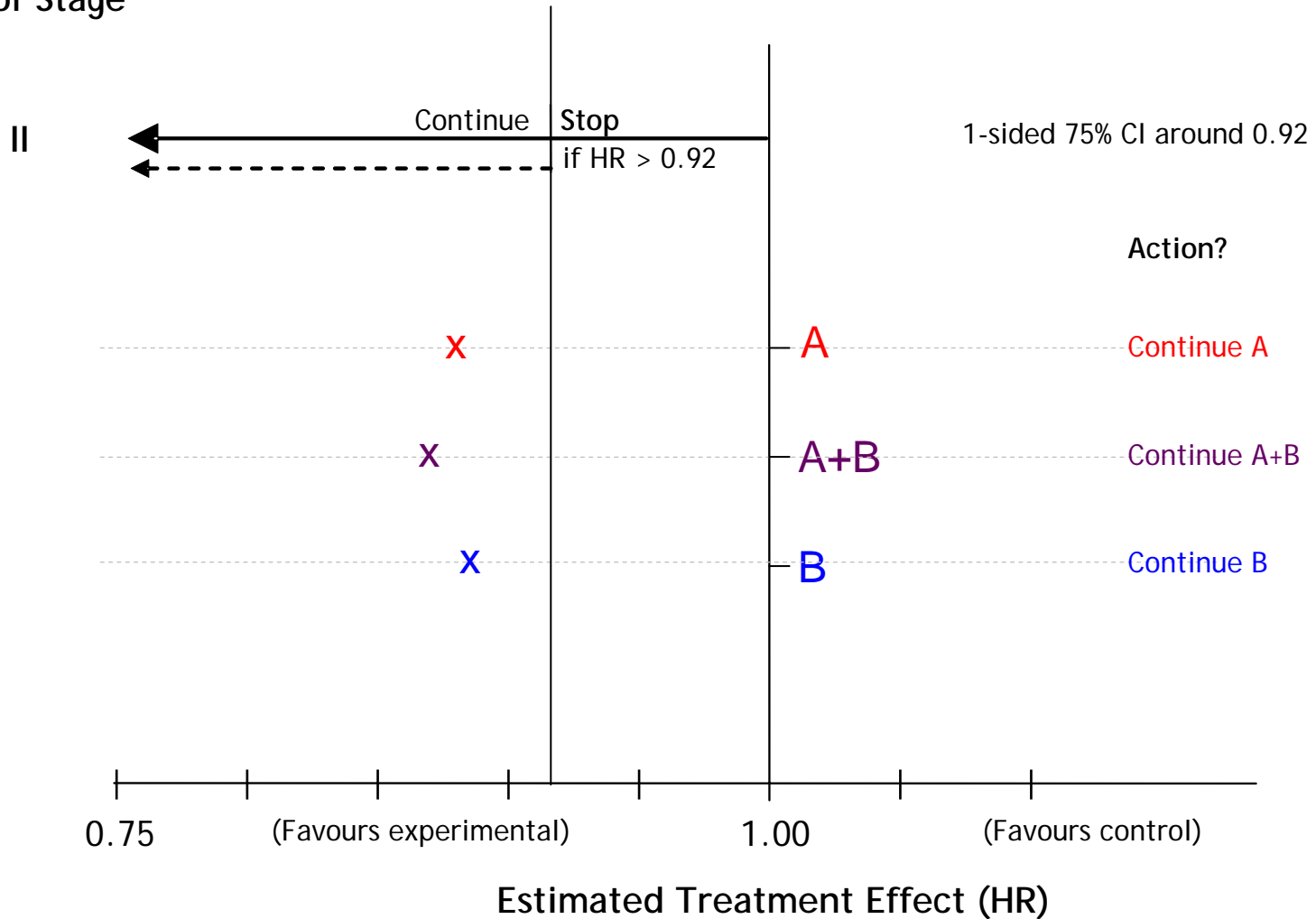
# Example

End of Stage



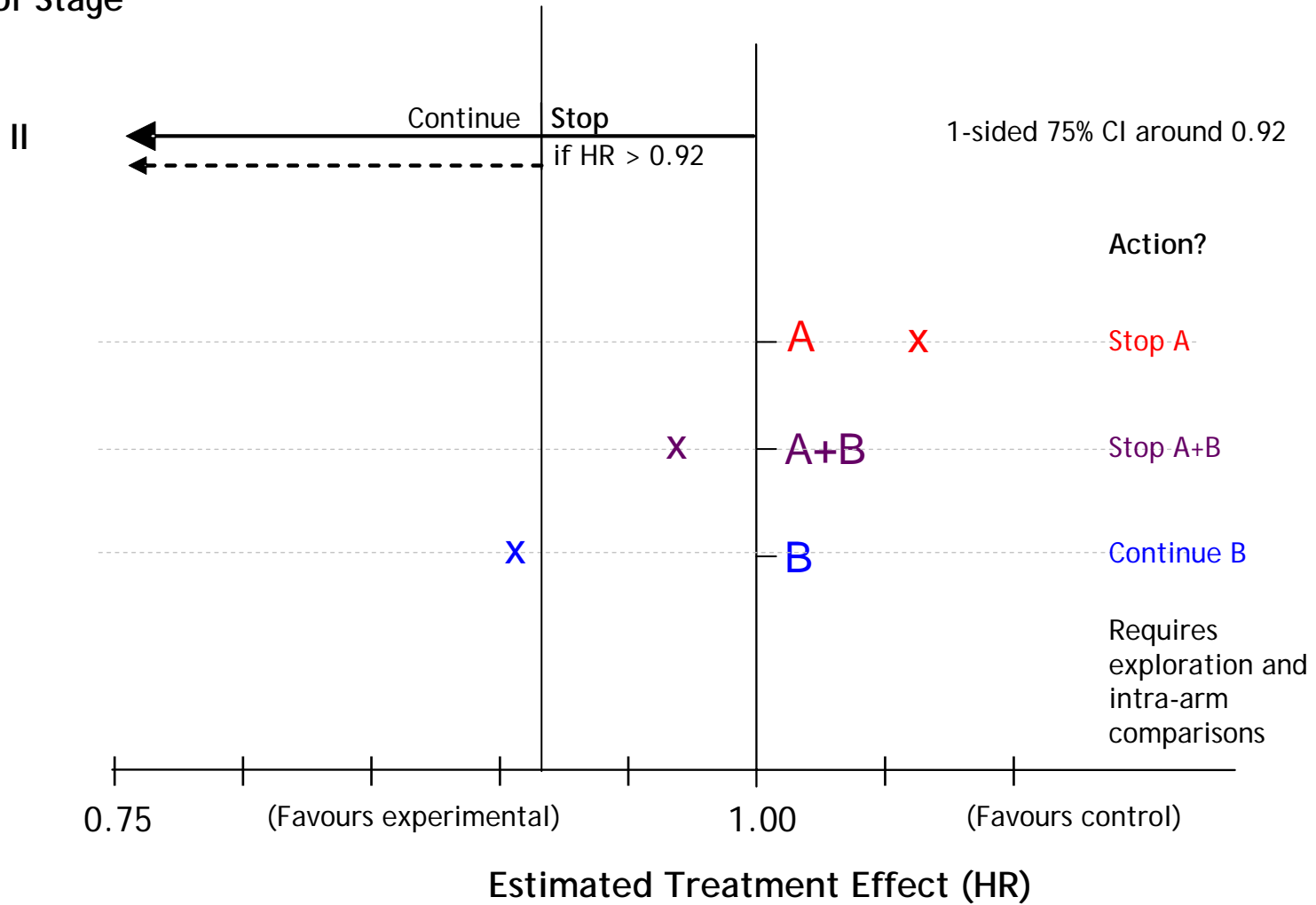
# Example

End of Stage



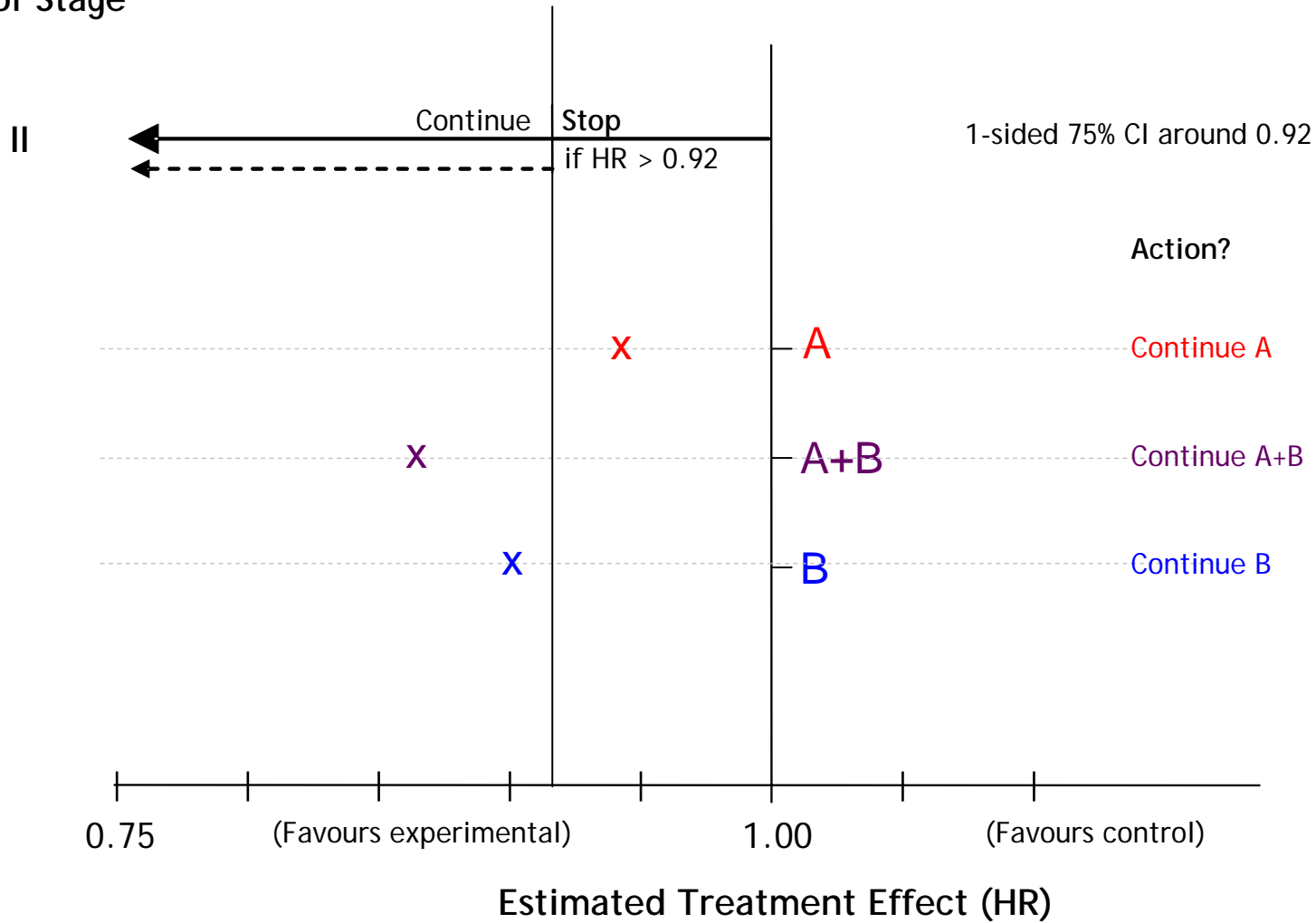
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End of Stage



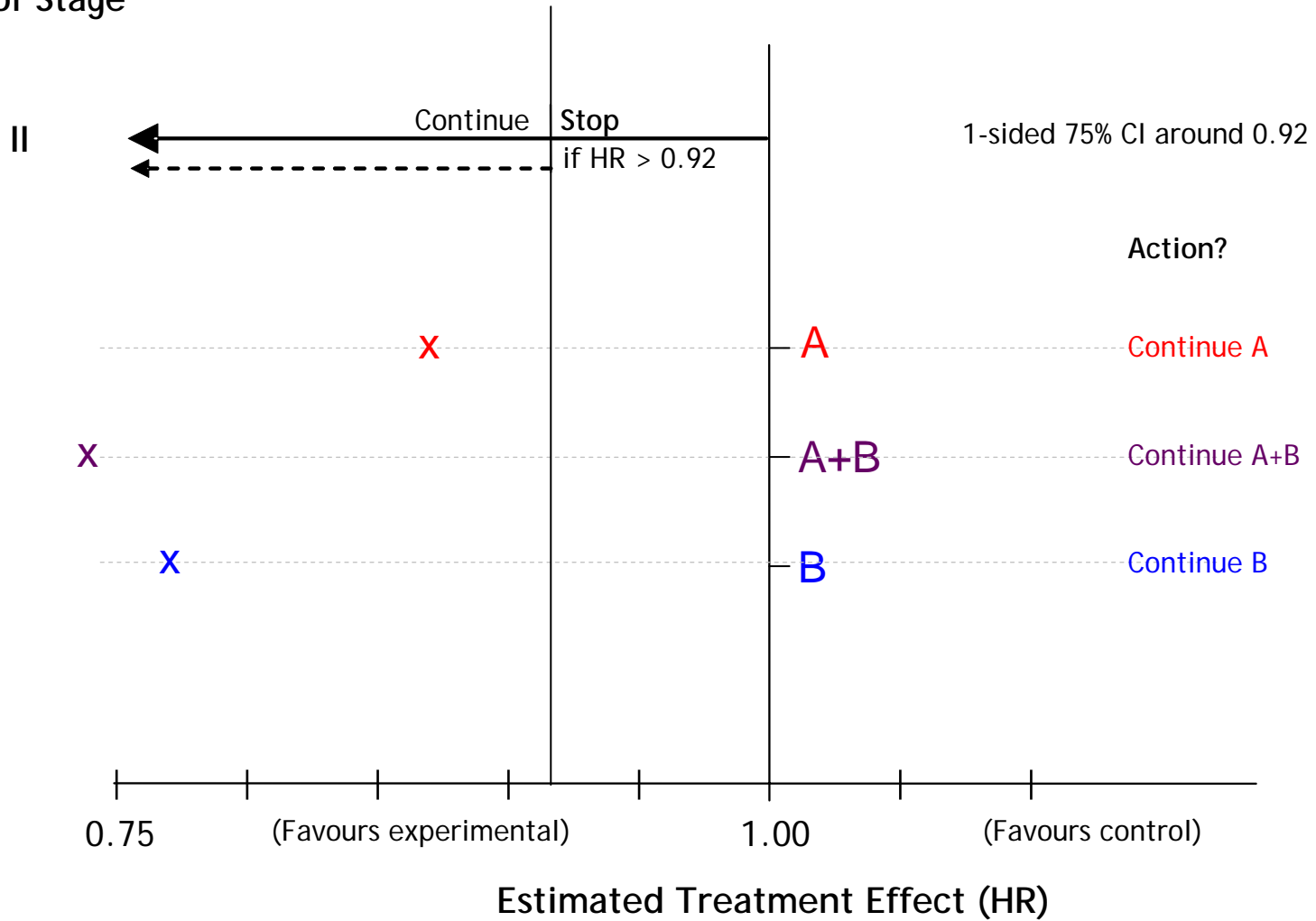
# Example

End of Stage



# Example

End of Stage



# Design Assumptions: for all stages

- Pairwise comparison of each research arm against control
- Hazard ratios for design

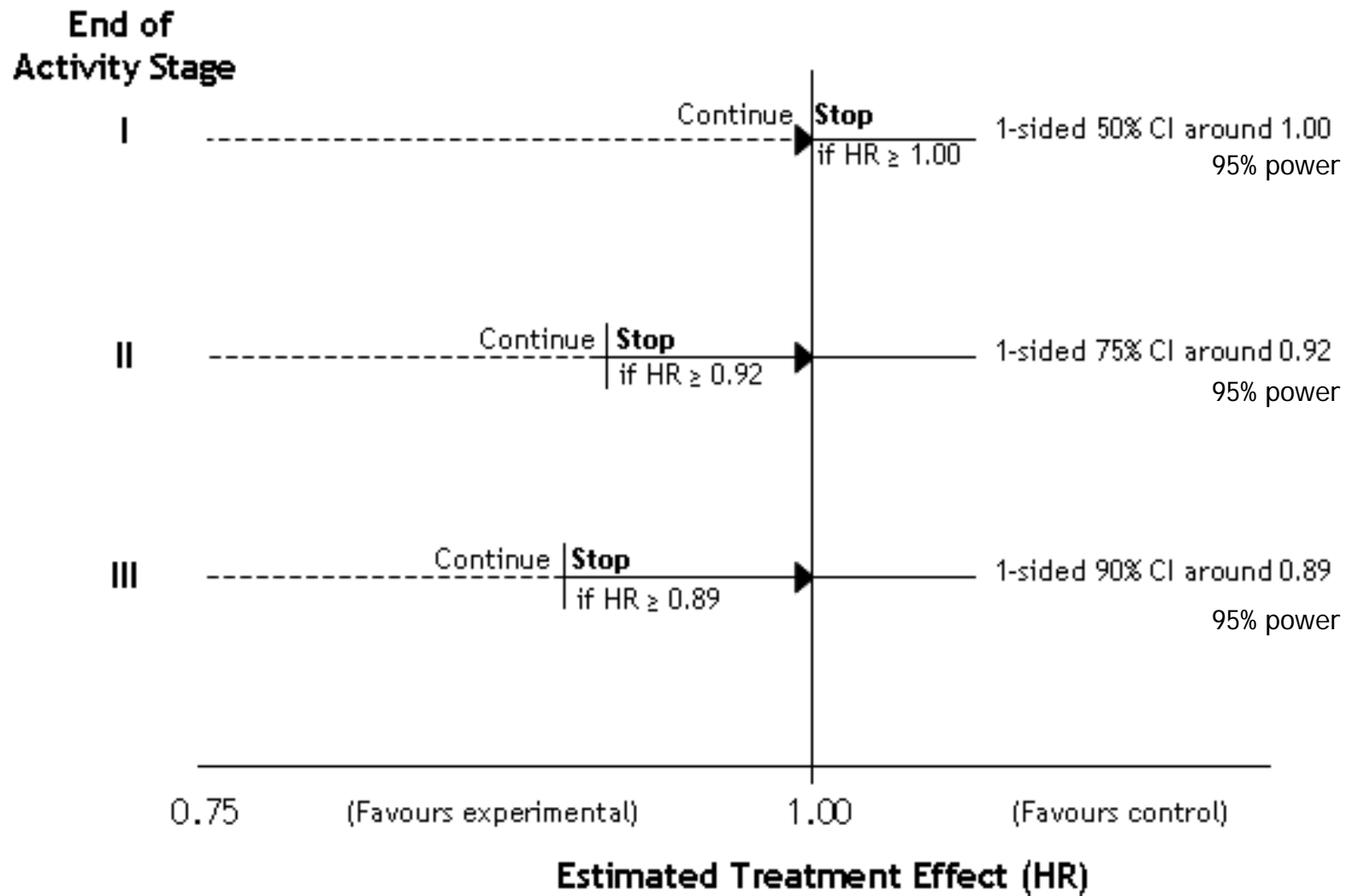
	Overall survival	Failure-free survival
Null ( $H_0$ )	1.0	0.75
Alternative ( $H_A$ )	1.0	0.75

- 10% improvement in FFS: 50 to 60% at 2 yr

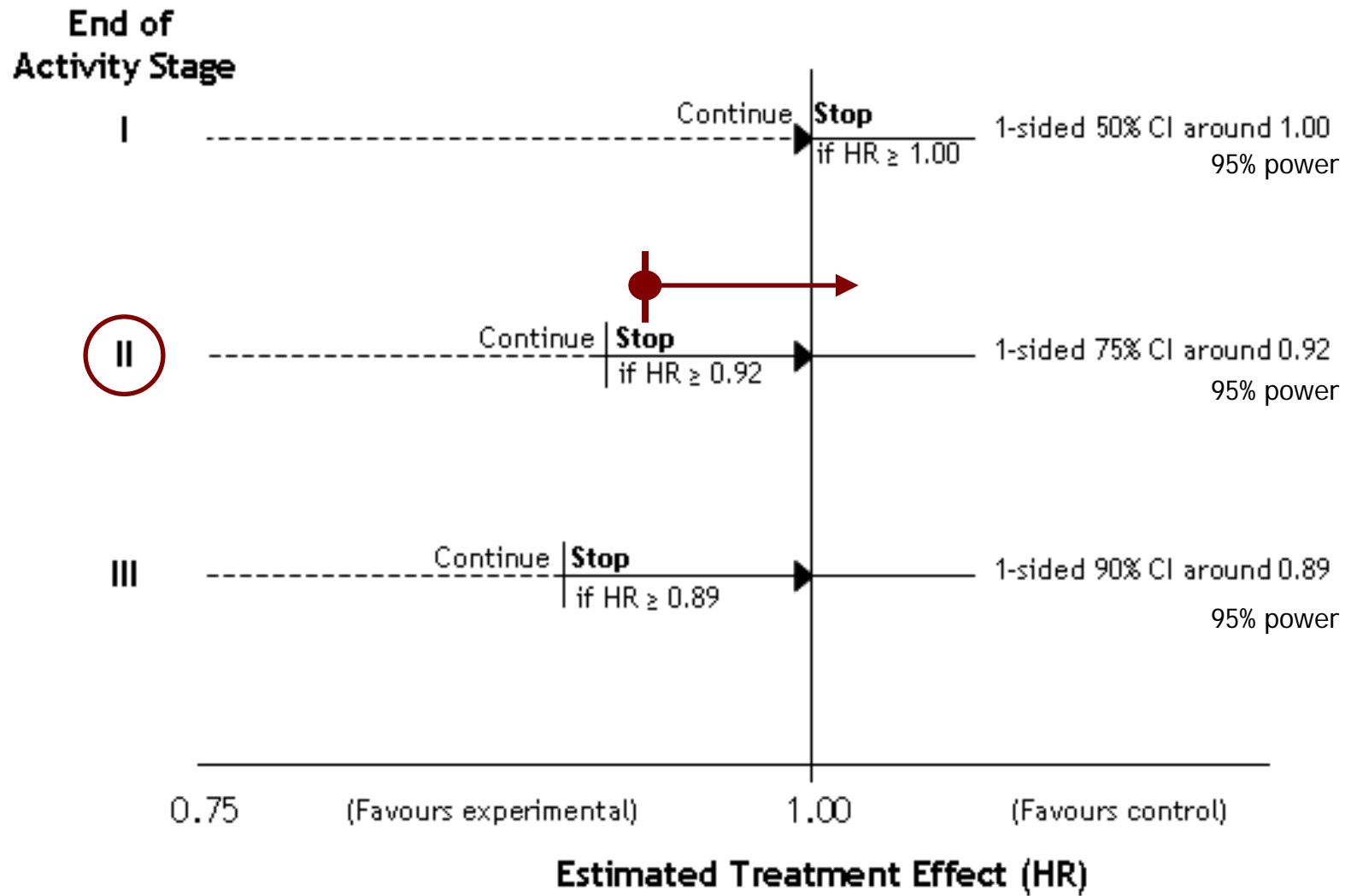
# Significance level and power

Stage	Primary Outcome	Significance Level	Power
I	FFS	0.50	95%
II	FFS	0.25	95%
III	FFS	0.10	95%
IV	OS	0.025	90%
Overall	-	0.013	85%

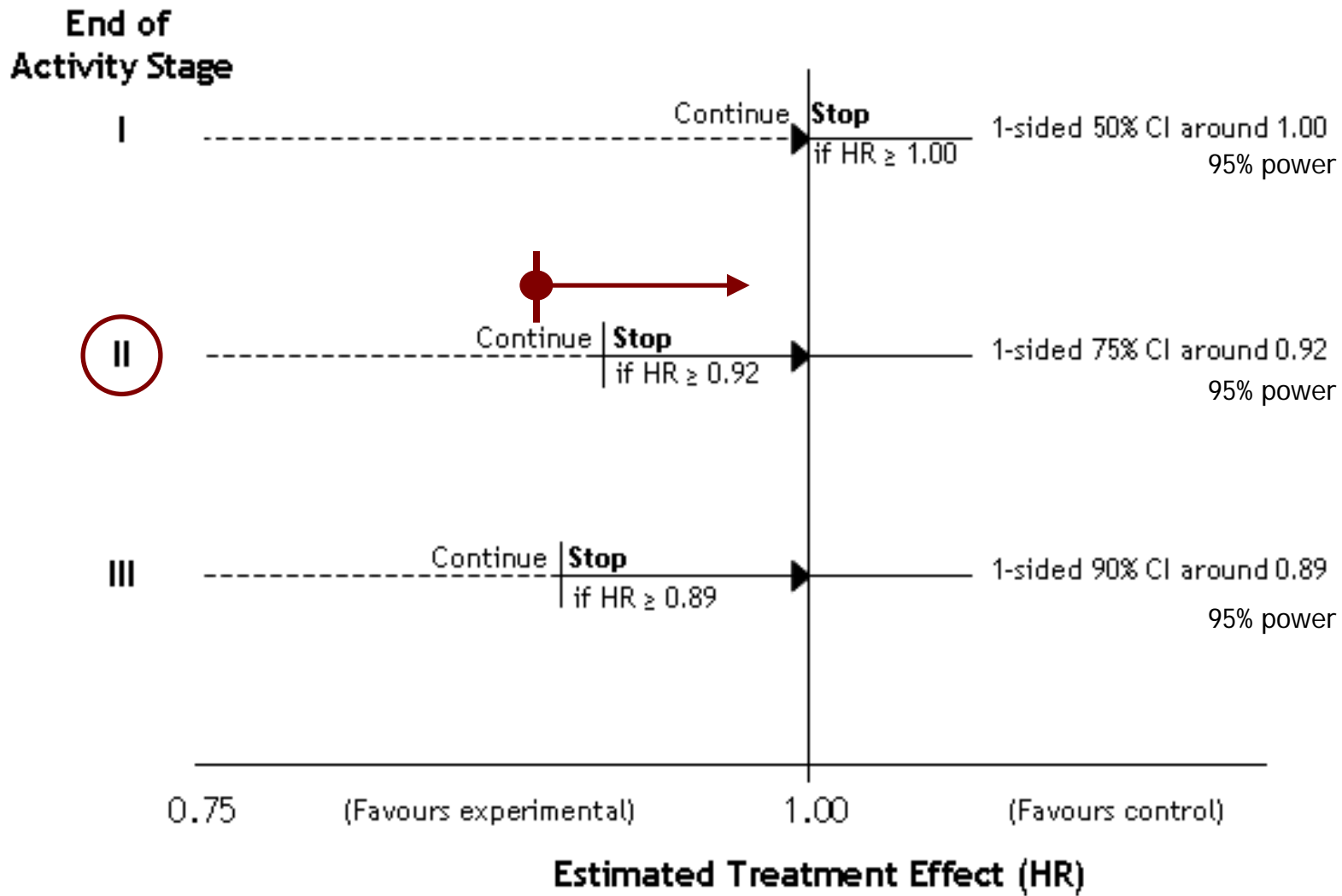
# Cutpoints in STAMPEDE



# Cutpoints in STAMPEDE



# Cutpoints in STAMPEDE



# Pilot Phase

- Assessing safety & feasibility
  - Particularly for the combination arms
- Target: 210 patients in 18 months
  - Limited centres
- Completed: Oct-2005 to Spring-2007
  - On schedule
- IDMC recommended continuing all arms
  - None stopped because of clear safety signals

# Groups to convince

- Medical community
- Would it appear complex in clinics?
  - Or in MDT meetings?
- Previous multi-arm trials
  - Excellent recruitment to:
  - FOCUS – colorectal cancer – 5 arms
  - ICON5 – ovarian cancer – 5 arms

# Groups to convince

- Men with prostate cancer
  - Involved patient groups
  - Two patients on Trial Management Group
  - Very positive opinions
  - Patient involvement good for trial
- Two-part PIS
  - General information – prior to randomisation
  - Arm-specific information
    - -- all before randomisation or
    - -- relevant one after randomisation
    - Patient choice

# Groups to convince

- Funding bodies
- Regulatory and ethical committees
- Hospital governance
  
- Potential for conservative reviewers
  - No precedent for such approaches
  
- Approved

# Groups to convince

- Industry partners
  - 3 partners in STAMPEDE
  - Keen on design
  - Efficient
  - Early “get-out” if agent not so beneficial
- More companies = more negotiations
  - More contracts
  - More time
  - ...but true for many two arm trials

# Recruitment rates

- How many patients are required?
- Total N dependent on:
  - Observed accrual rates
  - Observed event rates
    - Do we have the predicted mix of patients?
  - N arms recruiting at Activity & Efficacy Stages
- Likely 2300 to 3600 patients
  - Over 5.5 to 7.5 years
- Faster recruitment:
  - Requires more patients
  - Takes less time

## 4. General issues in implementation

1. MAMS Designs
2. MAMS application in STAMPEDE
3. Issues in implementation
4. General issues in implementation
5. Issues in intermediate analyses
6. Conclusions

# No intermediate outcome?

- Design depends on the use of an intermediate outcome
- What happens if no such outcome exists?
- Use the primary outcome, earlier in time
  - Lack-of-benefit analysis
  - Applying this to a number of ongoing trials

# How many arms?

- Could be many arms
  - From 2 to 10 or more
- Consider
  - Accrual rates
  - Rationale for inclusion
  - Adjust randomisation ratio

# Adding new arms

- Considering whether could add extra arm?
  - Promising agents could be added later!
  - Rolling trial or roundabout design
  - Use same rules as for other arms, but delayed
- Exploring in STAMPEDE
- Appealing to companies
  - Pre-existing network of recruiting sites
  - GSK?

# Stopping for efficacy?

- Stopping rules for lack-of-benefit
- No formal stopping rules for efficacy
  - Early data looking for sufficient evidence of activity to support continued investment

# Software

- Free software available
  - Design MAMS trials
  - Available from MRC CTU
  - Implemented in Stata