Conducting Clinical Studies in Low Incidence/Rare Conditions:

Scientific Challenges and Study Design Considerations

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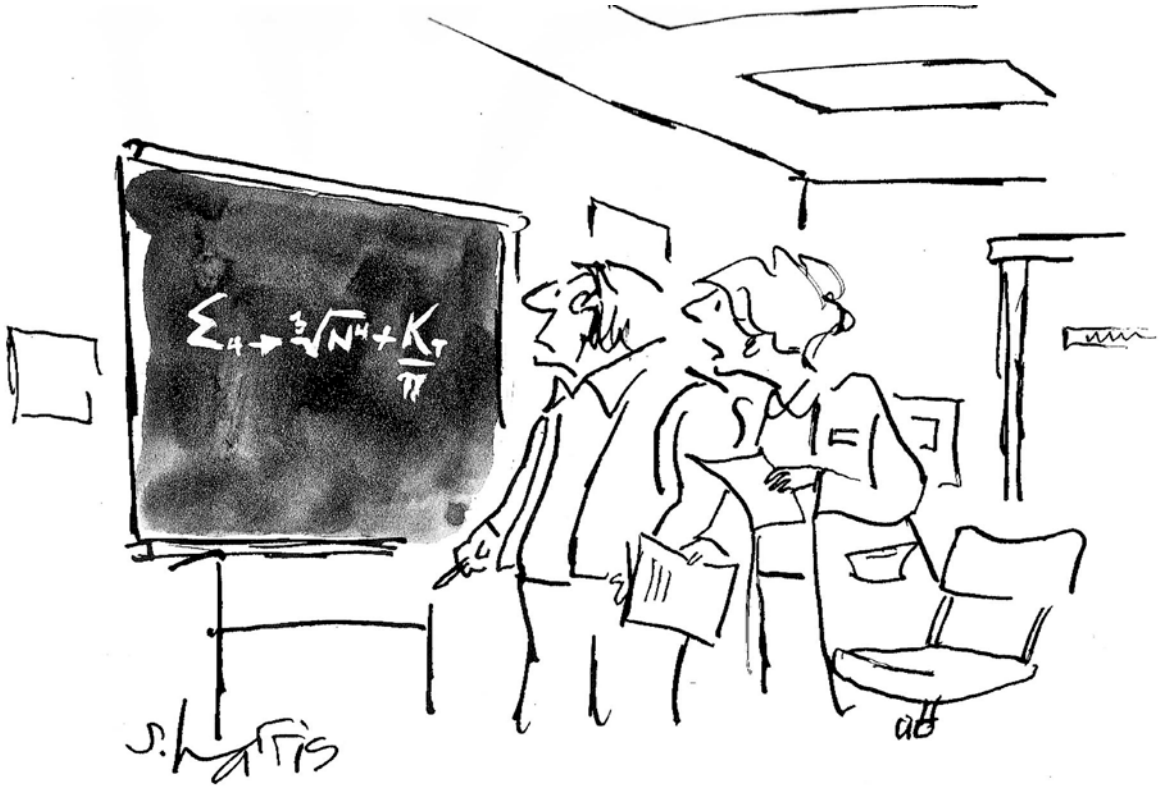
Disclosure

- I am a full time employee of CTI Clinical Trial and Consulting Services, an international contract research organization that delivers a full spectrum of clinical trial and consulting services to the pharmaceutical and biotechnology industry.

Further Disclosure …



Scientific Challenges

- Very few epidemiologic studies have been performed describing the occurrence of AMR
- Reported incidence varies depending on:
  - Type of organ transplanted
  - Local practice
    - diagnostic criteria & clinical protocol
  - Period studied
  - Patient population/Geographic region
  - Clinical follow-up and management

Scientific Challenges (cont'd)

- Requires multi-center, multi-country participation
  - Inherently different healthcare systems, treatment options, and management approaches
- Study design and analysis complexity
- Prevention versus treatment
  - What defines success?
  - What defines enrollment criteria?

Regulatory Challenges

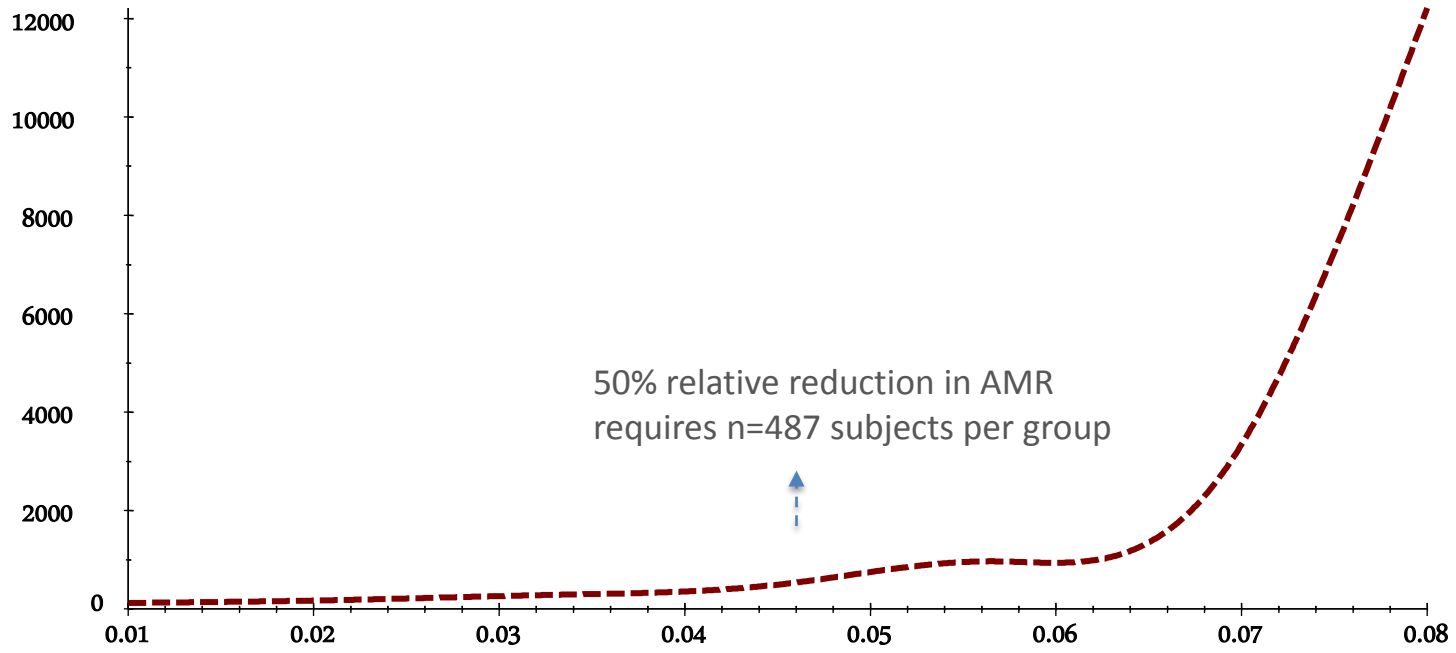
- No special methods for designing, carrying out or analyzing clinical trials in low incidence/rare conditions
  - Guidelines relating to common diseases are also applicable to rare conditions
- Choice of endpoints
  - Reliable & assessed consistently
  - Surrogate endpoints may be applicable but need to be fully justified
- Choice of comparator group
  - Ethics of randomization (Clinical equipoise/Uncertainty principle)
  - Historical controls
- Sufficient sample size
  - Minimize noise-to-effect ratio

Incidence of AMR

Author/Year	Location/setting	Number/Type of Patients	AMR Incidence
Marlo et al., 2011	Multicenter systematic review, 2000-2010 studies	725 patients in 21 studies	AMR 28% at 2-year median follow-up
Naesens et al., 2012	RCT Multicenter (US)	130 pediatric KTx	AMR 6.8% at 3-years post-transplant
Lefaucheur et al., 2013	Cohort (consecutive patients) Paris, FR 1998-2008	2,079 All ABOc and XM- Biopsies for indication in course of clinical care	Acute AMR 6.6%, occurring at median of 3.1 months post-transplant
Djamali et al., 2013	Cohort (consecutive patients) Madison, WI 2009-2011	146 “Moderately sensitized” (XM-, undergoing desensitization)	AMR 12% and mixed rejection 6% at mean follow-up 18 months
Malheiro et al., 2015	Cohort (consecutive patients) Single-center (Portugal)	462 (40 DSA+)	AMR 4% at 1-year post-transplant AMR in DSA+ KTx=35%
Vo et al., 2015	Cohort Single-center (US)	226 highly sensitized; desensitization with IVIG + rituximab	AMR 20% at mean follow-up 36 months
Burkhalter et al., 2016	RCT Single-center	35 patients DSA+, XM-	AMR (clinical/subclinical) 27% at 1-year post-transplant
Ferrandiz et al., 2016	Cohort Multicenter (France)	390 Non-HLA-sensitized, ABOc	AMR 4.4% at 1-year post-transplant
Calp-Inal et al., 2016	Cohort (consecutive patients) Single-center (US)	284, DSA-	AMR 45% at median follow-up of 2.5 years

Conventional Phase III Trial
Fixed Design

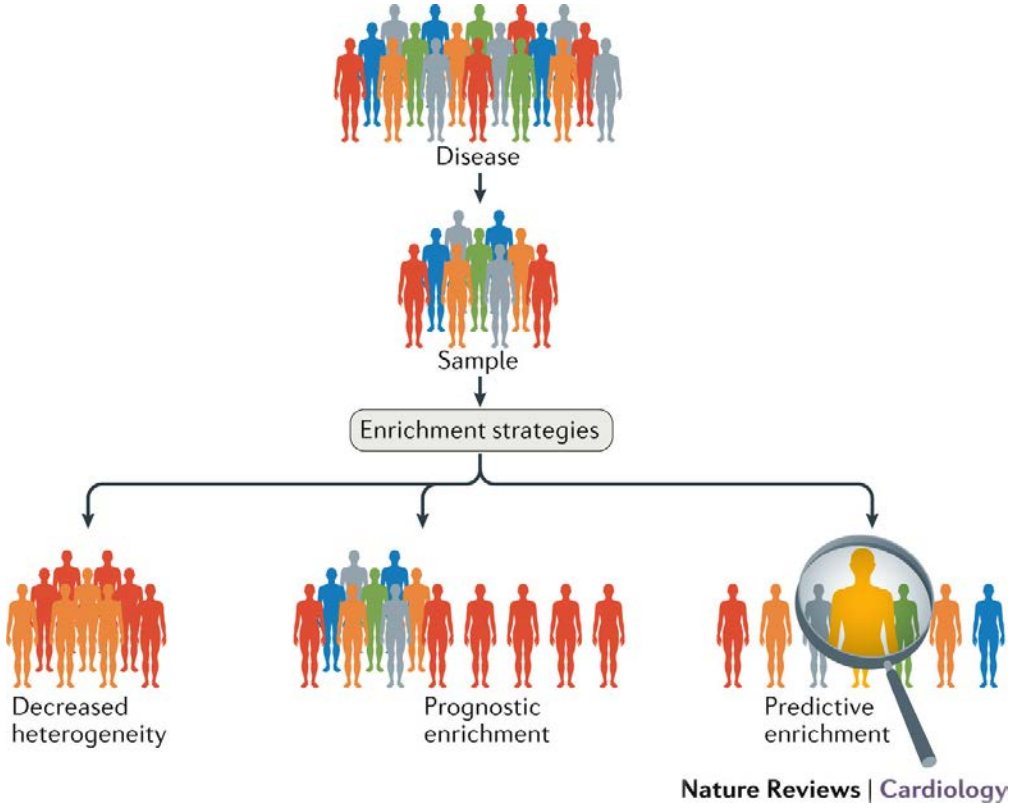
Anticipated proportion of first occurrence of AMR at one-year post-KTx in Control: 9.0%; 95% CI=4.7%,16.5%
Anticipated proportion of first occurrence of AMR at one-year post-KTx in Experimental: 1% to 8.0%
Power=80%
Type I error=0.05 (two-sided)
Test statistic: Chi-square



Key Considerations in Overcoming Challenges

- Goal: Design a trial with an acceptable compromise between (i) level of scientific evidence and (ii) feasibility in terms of trial size and duration
- Key considerations at the design stage:
  - Enrichment strategies
  - Adaptive Designs
  - Surrogate endpoints
  - Composite endpoints
  - Bayesian methods

Design Stage
Enrichment Strategies



Antman, E. M. & Loscalzo, J. (2016) Precision medicine in cardiology
Nat. Rev. Cardiol. doi:10.1038/nrcardio.2016.101

Design Stage
Decrease Heterogeneity

- Include subjects that have certain characteristics that put them at risk
  - Example:
    - Class II HLA epitope mismatch
    - Patients likely to be medication compliant
- Characteristics need to be agreed to by the regulatory agency:
  - Example:
    - Quantitative measures of pre-transplant DSA levels
    - > pre-determined threshold value
- Limit the number of sites

Design Stage
Prognostic Enrichment

- Select subjects with a greater likelihood of occurrence of AMR (event-driven study) or a substantial worsening of renal function (for continuous measurement endpoints e.g., change in estimated GFR)
- Characteristic or measurement process needs to be validated and agreed to by the regulatory agency

Risk of Antibody Mediated Rejection
Highly Sensitized Patient

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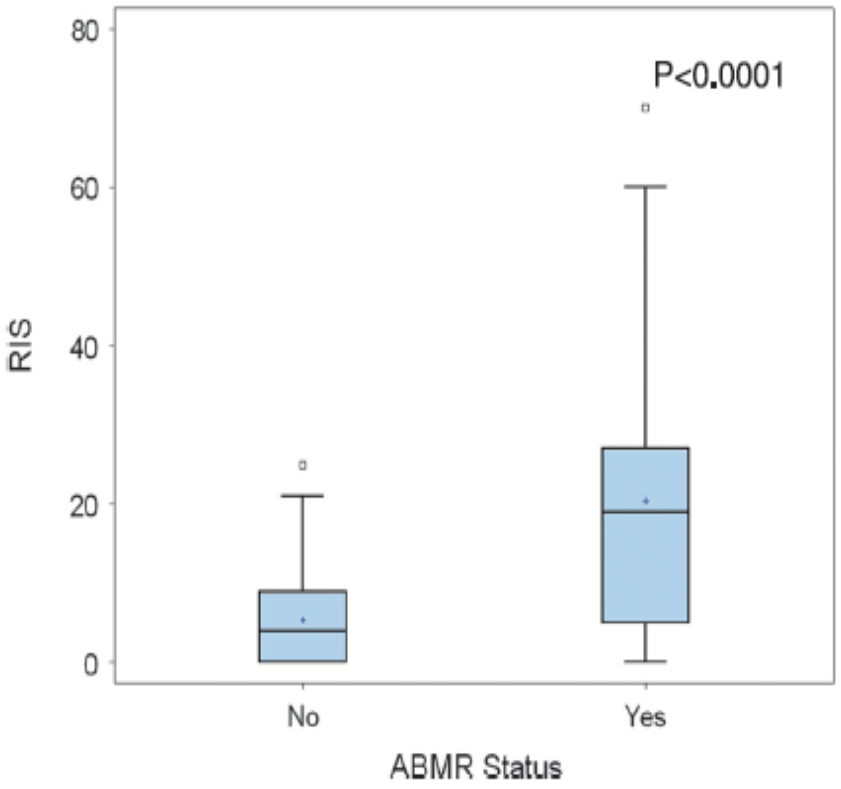

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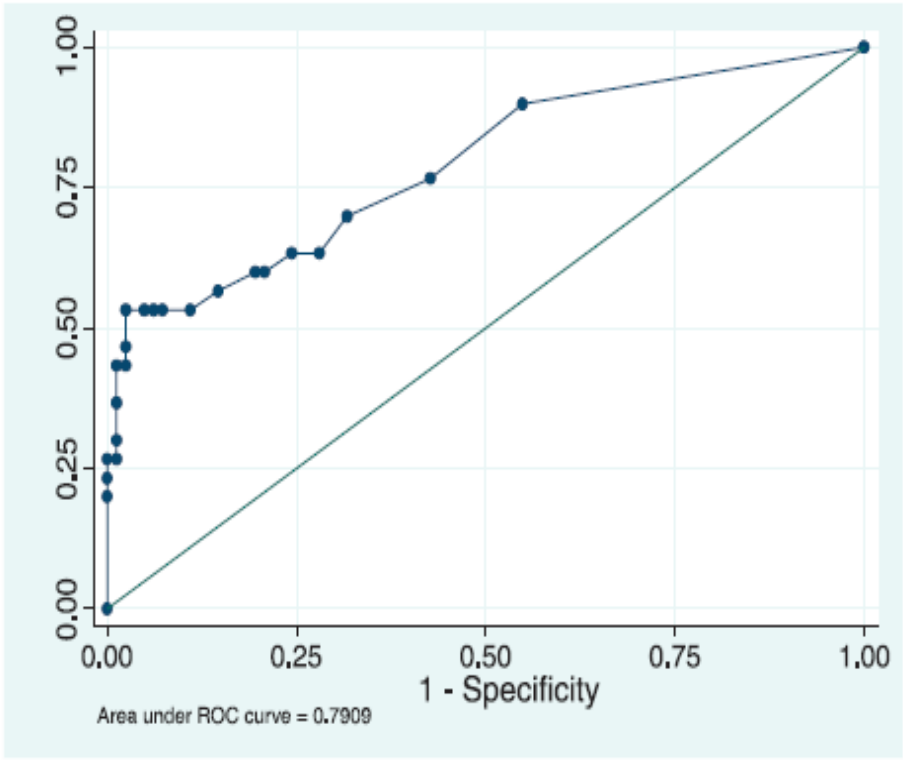
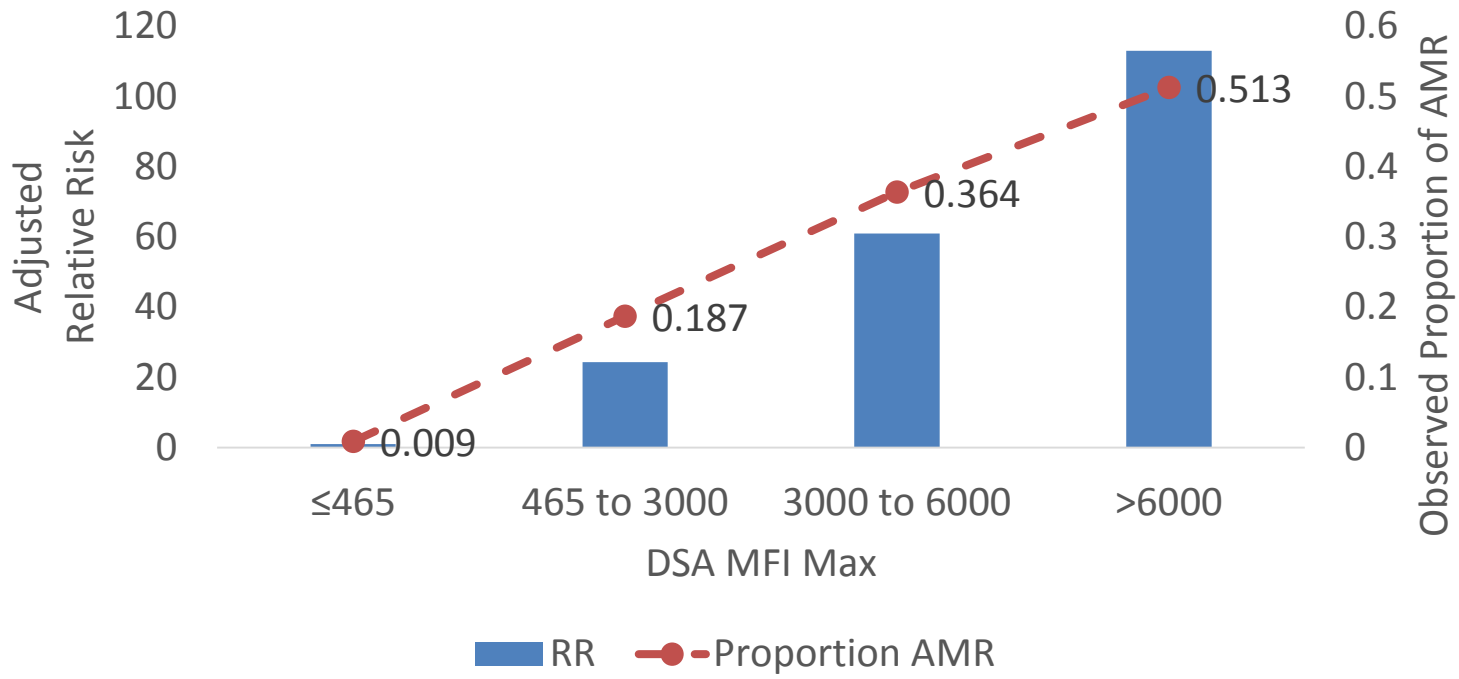


Vo et al., Transplantation 2015; 99: 1423-1430

Risk of Antibody Mediated Rejection
Peak HLA DSA Risk Stratification



Lefaucheur et al., J Am Soc Nephrol 2010; 21: 1398-1406

Sample Size Under Prognostic Enrichment

Background Rate AMR	Relative Reduction in AMR with Treatment	Sample Size per Group[1]	Ratio
0.09	50%	487	1
0.20	50%	200	0.41
0.30	50%	121	0.25
0.40	50%	82	0.17
0.50	50%	58	0.12

1. Test statistic=Chi square; Power=80%; type I error=0.025 (one-sided significance)

Sample Size Under Prognostic Enrichment Peak Pre-transplant HLA-DSA[1]

Figure 1

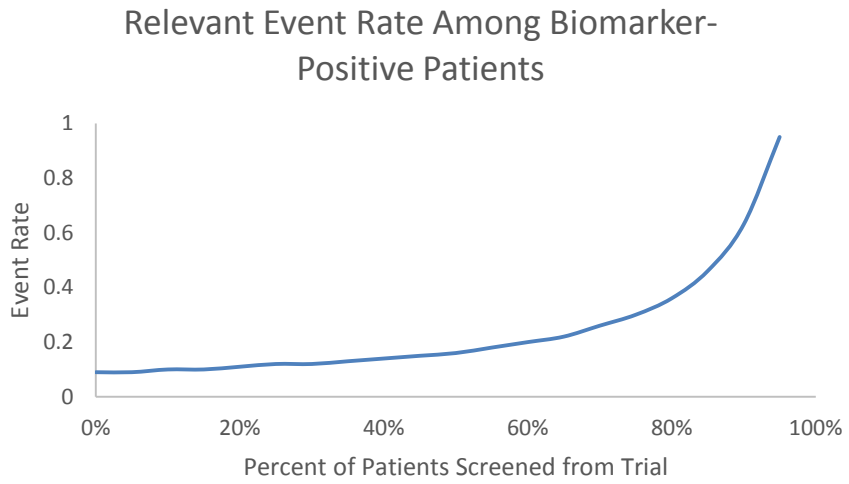
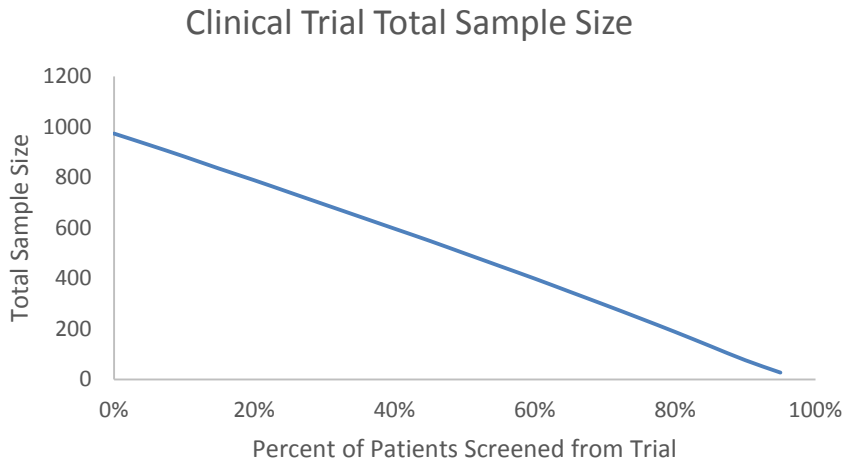


Figure 2



Input Name[2]	Input Value
Background rate of any type of AMR	0.09
Percent reduction in AMR rate under treatment	50
Form of alternative hypothesis	one.sided
Type I error rate	0.025
Power	0.8
AUC	0.9

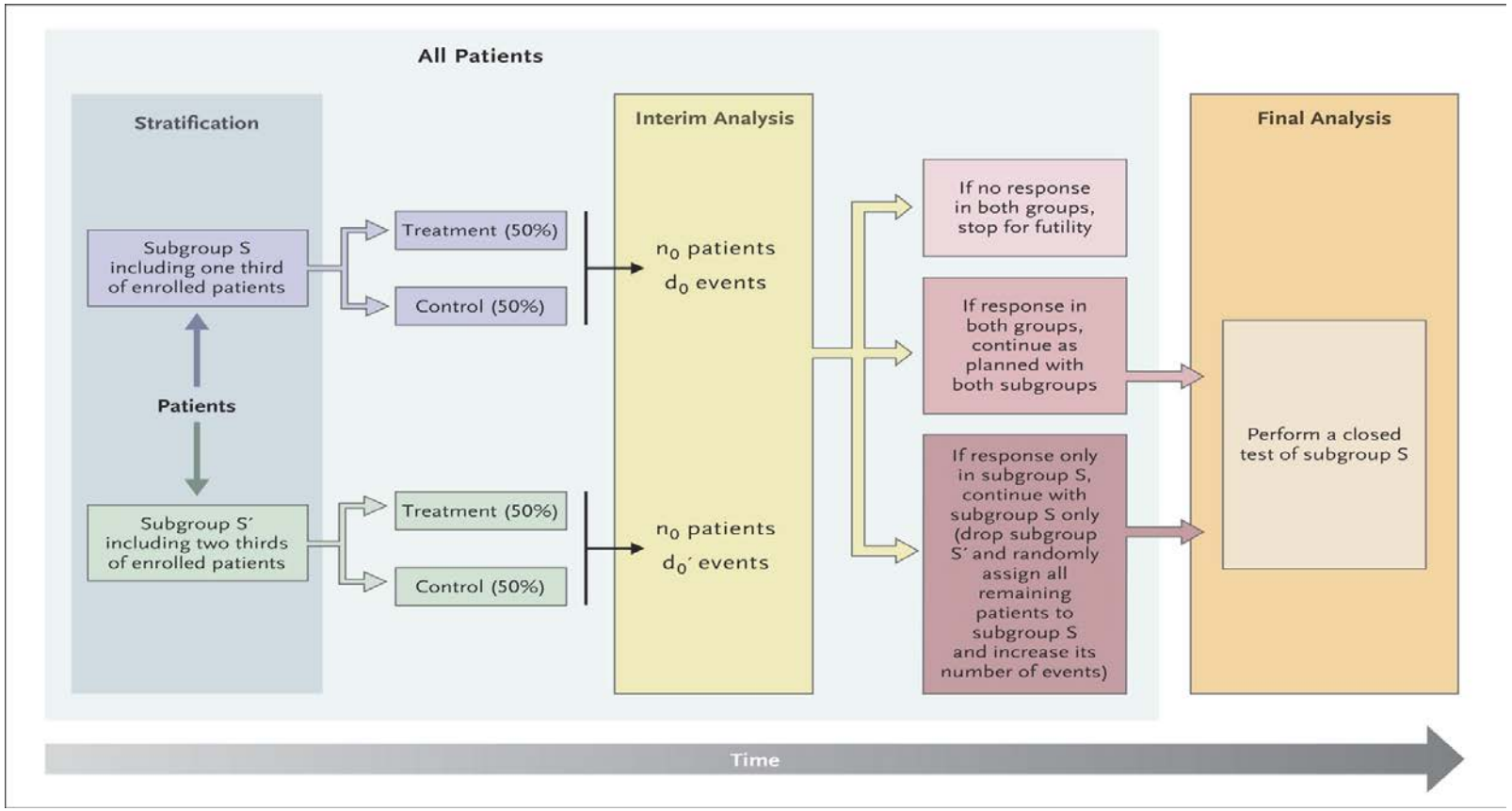
1. Lefaucheur et al., J Am Soc Nephrol 2010; 21: 1398-1406
2. Package 'BioPET' in R

Design Stage
Predictive Enrichment

- Choosing people more likely to respond to treatment (probable responders)
- Based on:
  - patient characteristics related to a study drug's mechanism (pathophysiology, proteomic/genomic)
  - response of a biomarker
  - past response to the test drug (e.g., randomized withdrawal study)

	Response in Marker-negative Patients (0% of marker positive response)	
Prevalence of Marker Positive Patients	0%	50%
	Sample Size Ratio	Sample Size Ratio
100%	1.0	1.0
75%	1.8	1.3
50%	4	1.8
25%	16	2.6

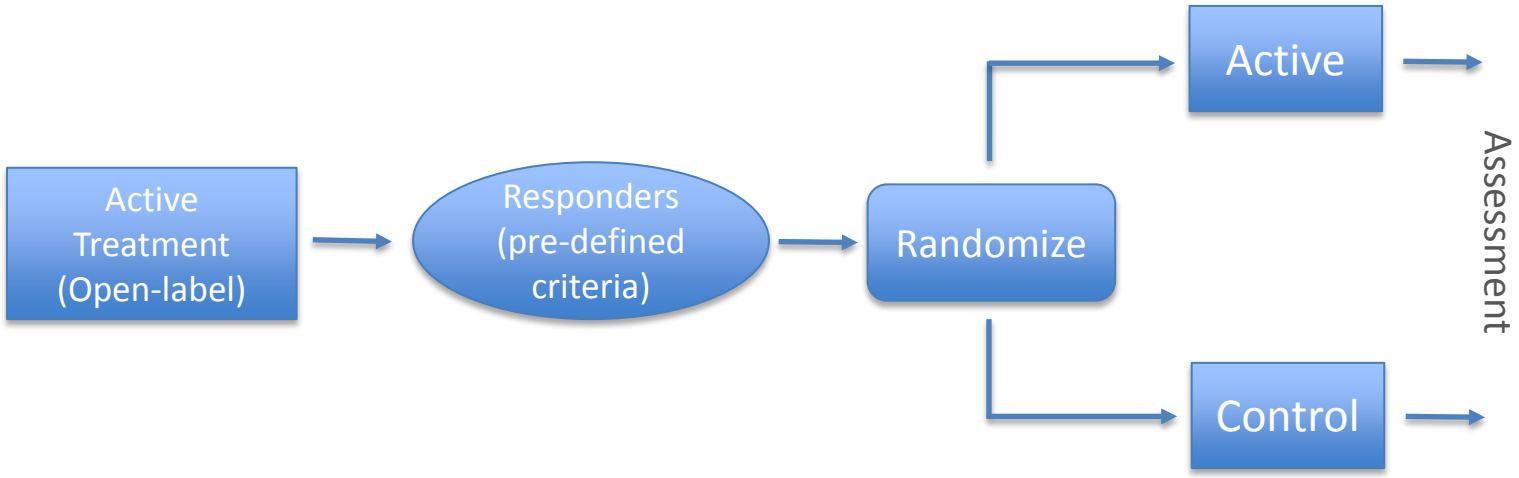
Predictive Enrichment
Adaptive population-enrichment



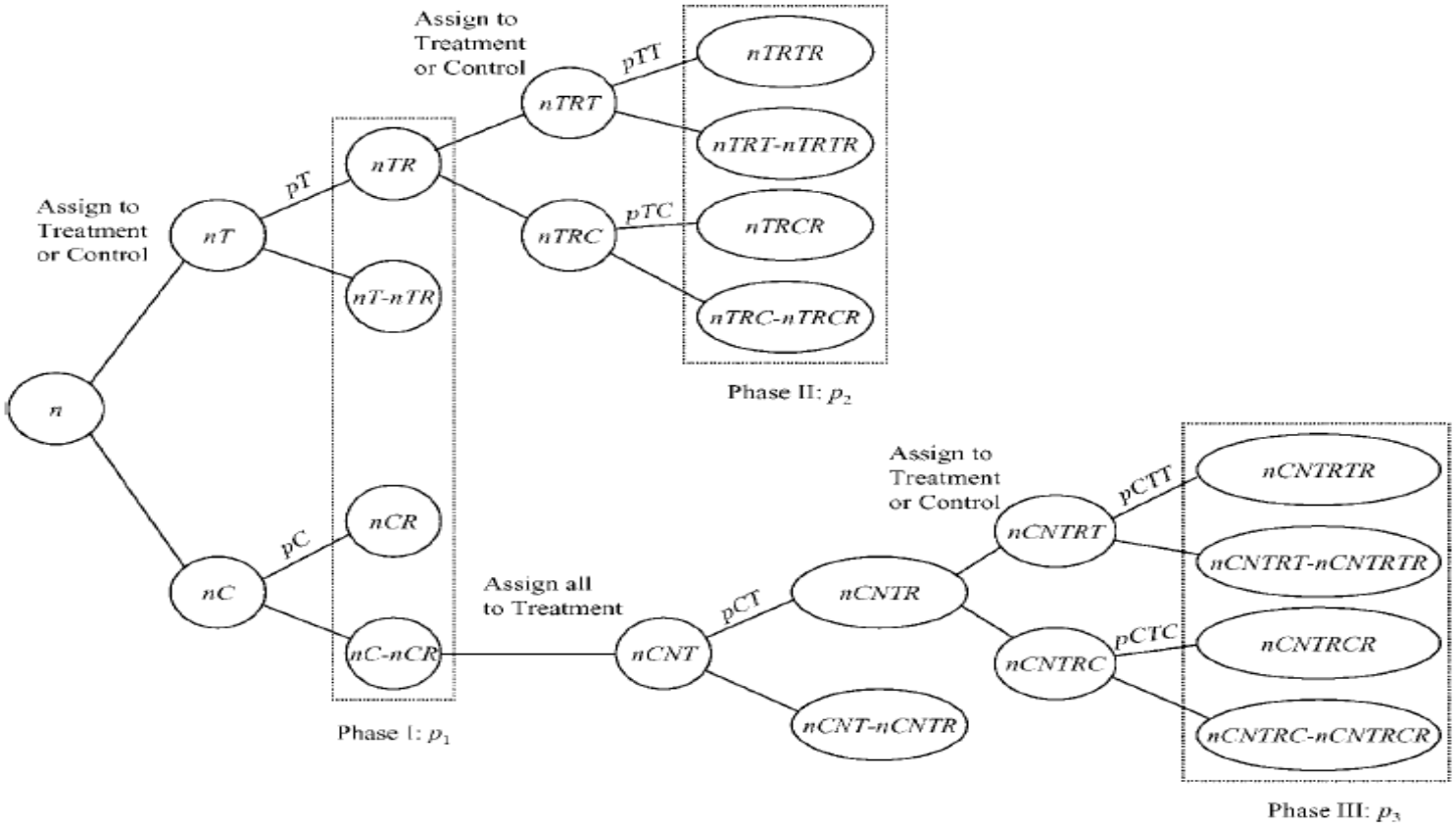
Bhatt DL, Mehta C. N Engl J Med 2016;375:65-74..

Design Stage
Randomized Withdrawal Study

- Subjects receiving a test treatment for a specified time are randomly assigned to continued treatment or to placebo (i.e., withdrawal of active therapy)



Design Stage
Three-stage Trial Design



Honkanen et al. Statist Med 2001; 20: 3009-3021

Biomarker/Surrogate Endpoints

- A biomarker intended to substitute for a clinical endpoint (patient and graft survival) and expected (is reasonably likely) to predict clinical benefit/outcome
- Easy to quantify and measure, reproducible, not subject to wide variation in the general population and unaffected by co-morbid factors
- Composite surrogate endpoints:

Biomarker/Surrogate Endpoints

Potential Surrogate Endpoints[1]	Issues
– Change in GFR – GFR < 30 ml/min	– Timing? 1, month, 6 months or 1 year post-transplant – Near term change may not be a good correlate with long-term allograft survival (5-,10-years?)
– Post-transplant DSA	– Measurement - Reliability/Validity? – Timing? – Variable incidence – Non-adherence potential confounder
– Cd4 positive stain plus TG+ – Banff CG score	– May not correlate with long-term allograft survival – Prognostic significance not clearly elucidated

1. Archdeacon P et al., Am J Transpl 2011; 11:896-906.

What about a Composite Surrogate Endpoint?

- Assumptions:
  - Individual components of the composite are clinically meaningful and of similar importance to the patient
  - The expected effects on each component are similar, based on biological plausibility
  - The clinically more important components of composite endpoints should at least not be affected negatively

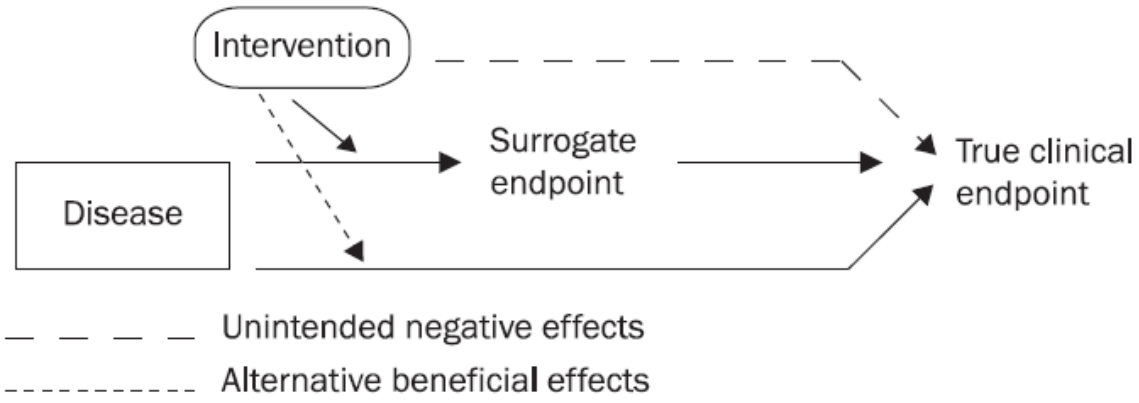
Advantages	Limitations
– Statistical precision and efficiency	– Individual components are not always clinically meaningful
– Trial are smaller and less costly	– Problems of non-validated surrogate endpoints
– Results of promising therapies could be available earlier	– Differential distribution of the individual components makes interpretation difficult
	– Including a component that is insensitive to treatment increases variability
	– Potential bias due to competing risks between endpoints

Kleist P. Applied Clinical Trials 2006

The Problem of Surrogate Endpoints

EXHIBIT 2

Additional Reasons For The Unreliability Of Proposed Surrogates: Disease Processes Having Multiple Causal Pathways And Interventions Having Mechanisms Of Action Independent Of The Disease Process



SOURCE: T.R. Fleming and D.L. DeMets, "Surrogate End Points in Clinical Trials: Are We Being Misled?" *Annals of Internal Medicine* 125, no. 7 (1996): 605–613.

Fleming TR. Health Affairs 2005; 24(1):67-78.

Summary

- Therapeutic development in AMR present many challenges:
  - Incomplete understanding of AMR to inform trial design
  - Need for alternatives to the traditional randomized controlled clinical trial
  - Requirement for more sensitive and creative outcome measures
    - Biomarkers/surrogate endpoints
    - Non-biologic measures such as time-off dialysis or Quality of Life
  - Difficulties of recruiting a small sample to participation:
    - Due to unpredictable occurrence of AMR
    - Recruiting a control group

Summary – cont'd

- Solutions require:
  - Multi-collaboration among stakeholders (Transplant community, Sponsors, Regulatory agency)
  - Regulatory acceptance of biomarkers
  - Creative or non-traditional endpoints
  - Alternative trial designs e.g., adaptive, withdrawal, historical controls
  - Leveraging existing resources (e.g., transplant registry, clinical trial data)