Promoting Effective Drug Development Programs: Opportunities and Priorities for FDA's Office of New Drugs

Master protocols: One solution for CKD drug development

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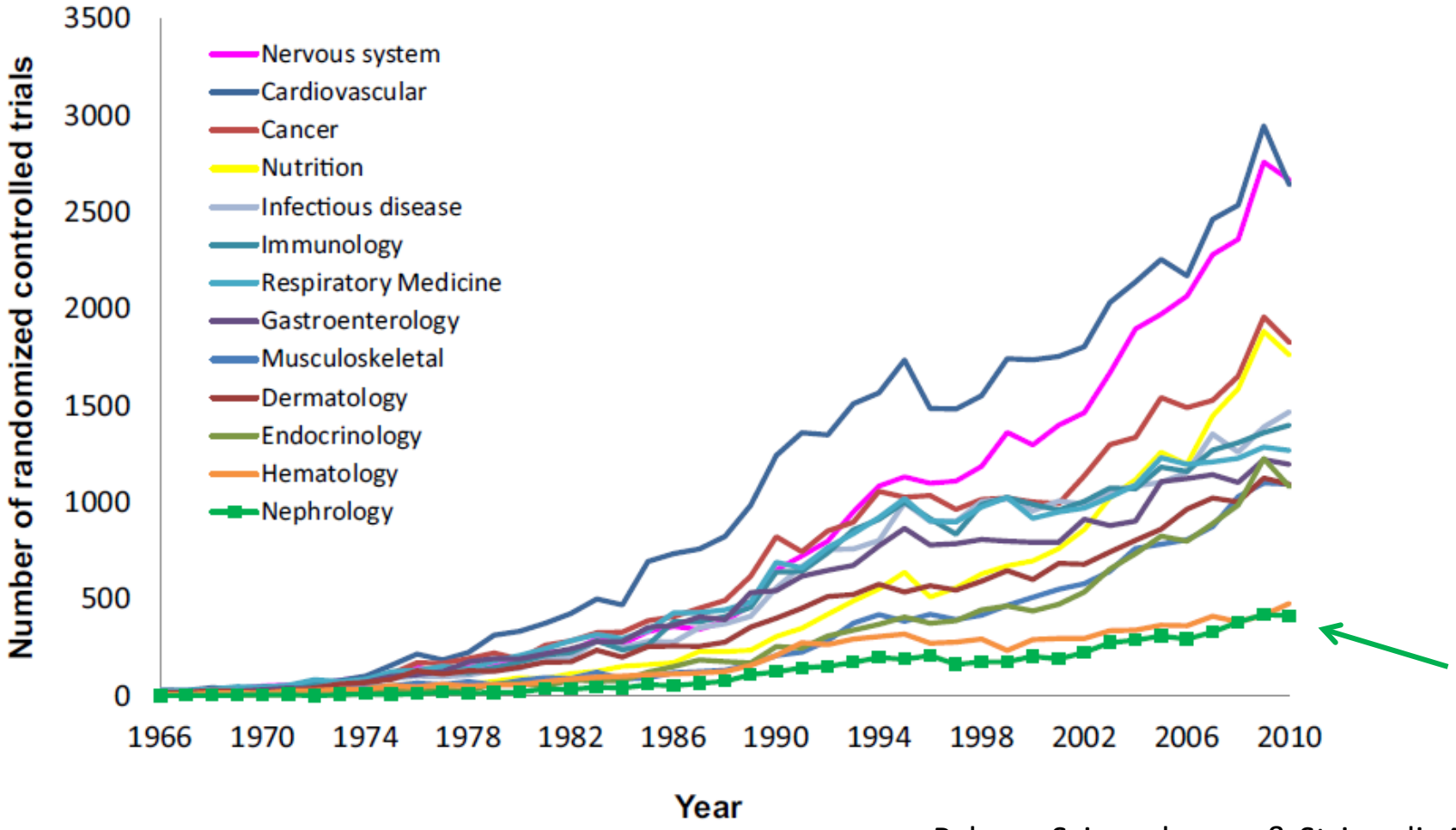
Disclosures

- Fellowship
  - Medical Research Future Fund Next Generation Clinical Researchers Program Career Development Fellowship
- Research funding
  - Gambro, Baxter, CSL, Amgen, Eli Lilly, and Merck
- Scientific presentations/Advisory boards
  - Akebia, Baxter, Boehringer Ingelheim, CSL, Vifor, Janssen, Amgen, Roche
- CREDENCE Trial
  - Global Scientific Lead, Steering Committee member
- Any consultancy, honoraria, or travel support are paid to my institution

Insufficient evidence in kidney disease

Number of RCTs published in 13 internal medicine specialities: 1966-2010



Palmer, Sciancalepore & Strippoli, *Am J Kidney Dis*. 2011

… but our ambition is big

ISN ACT CLINICAL TRIALS

Global kidney health 2017 and beyond: a roadmap for closing gaps in care, research, and policy

International Society of Nephrology summit report

"At least 30% of people with CKD globally should be involved in a clinical trial"

A Levin, *Lancet* 2017; 390: 1888–917

Master protocol trials for chronic kidney disease

- Ongoing trial
- Common endpoint
- Shared infrastructure
- Multiple agents
- Shared control arm
- Adaptive randomization
- Potential Bayesian statistics

Ongoing trial

Common endpoint

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Prostate cancer

- 2005 – ongoing
- Over 10,000 participants

Neoadjuvant treatment for locally advanced breast cancer

- 2010 - ongoing

REMAP-CAP

- Community-acquired pneumonia in critical care
- 2016 – Ongoing

…and others

- Woodcock, N Engl J Med 2017; 377:62-70

Ongoing trial

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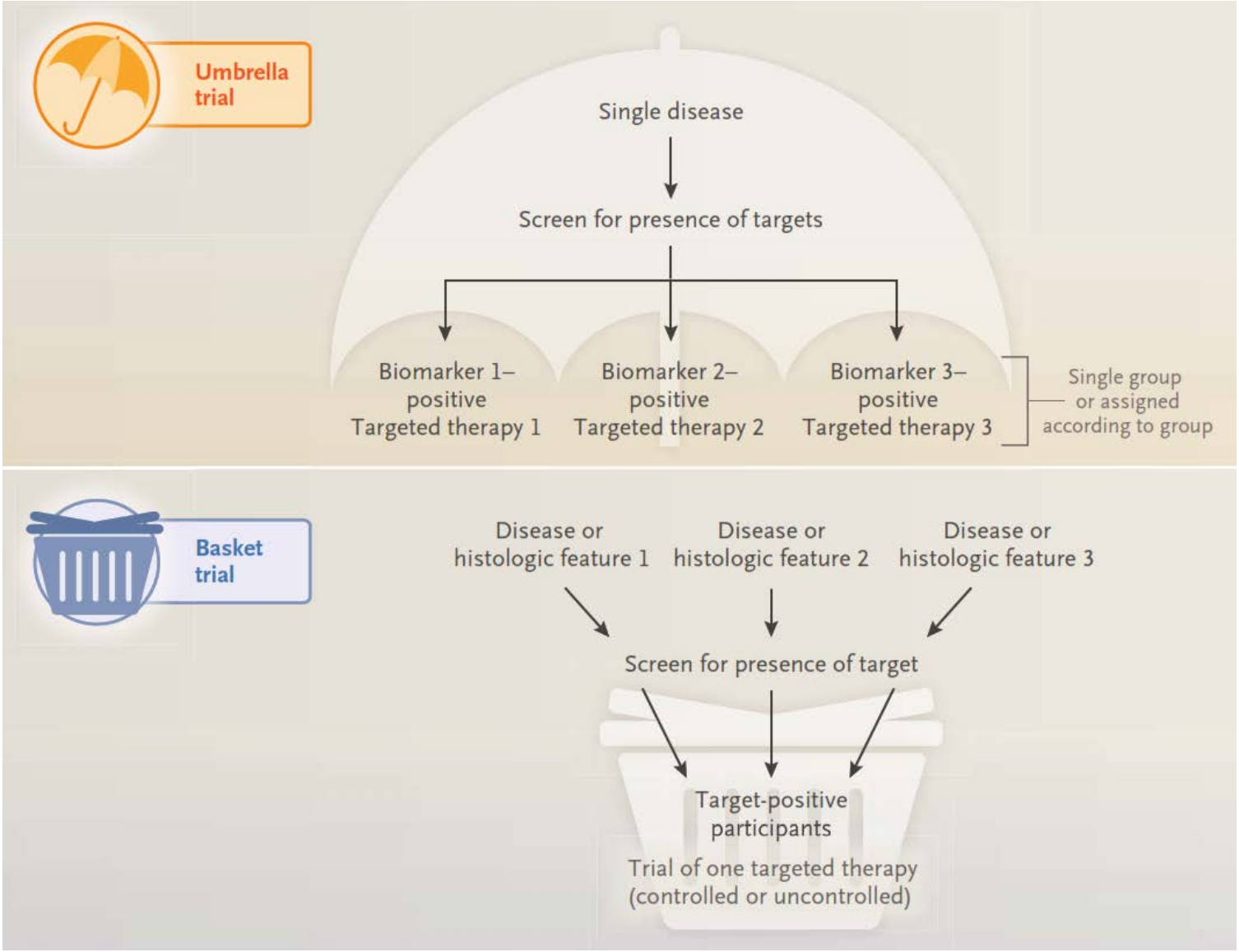

Woodcock *NEJM* 2017; 377:62-70

Ongoing trial

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Trials for many ‘diseases’ currently use common endpoints

	Albuminuria	Proteinuria	eGFR
C3 Glomerulopathy	0	6	2
Chronic Kidney Disease	65	62	114
Diabetic Nephropathy	115	48	60
End-Stage Renal Disease	16	19	19
FSGS	1	25	7
IgA Nephropathy	8	58	24
Minimal Change Disease	0	4	0
Nephrotic Syndrome	0	14	1
SLE Nephropathy	0	41	5

Trials of ‘Glomerular diseases’: snapshot from clinicaltrials.gov, Oct 18, 2019

Ongoing trial

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Primary proteinuria endpoint in FSGS trials

	Trial Identifier	Units	Complete Remission
Multiple Tests	NCT02592798	g/g	≤0.3
	NCT02896270	g/d g/g	<0.3
	NCT03298698	g/d g/g	<0.3
	NCT02000440	g/d	<0.3
	ChiCTR-TRC-10001024	g/d	<0.4
UP:Cr Ratio	NCT03493685	g/g	<1.5
	NCT00550342	g/g	<0.2
	NCT00135811	g/g	<0.2
	NCT01613118	g/g	<0.3
	NCT00098020	g/g	<0.3
	NCT01665391	g/g	<0.3
	NCT02633046	g/g	≤0.3
24-Hour Protein Excretion	NCT00981838	g/d	<0.3
	NCT00040508	g/d	<0.3
	NCT01573533	g/d	<0.5

Proteinuria in remission definitions: International Clinical Trials Research Platform (ICTRP) 2001 - July 20th 2019

Ongoing trial

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Potential Bayesian statistics

Master protocol trials shared infrastructure

- Endpoint assessment, Endpoint evaluation
- Monitoring, DSMB, Oversight
- Contracting, Site staffing

Ongoing trial

Common endpoint

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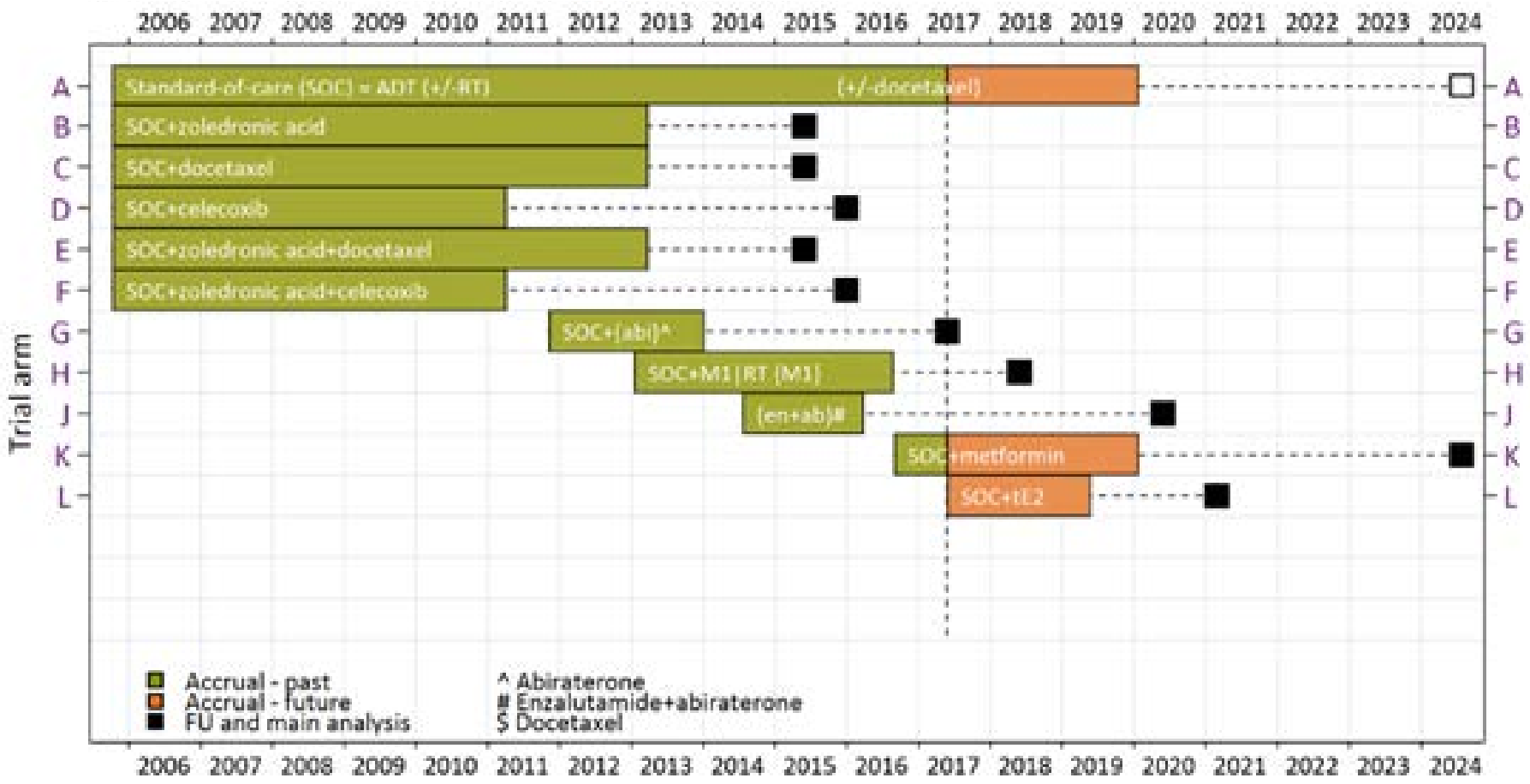
Adaptive randomization

Potential Bayesian statistics

STAMPEDE

Indication: newly diagnosed advanced prostate cancer



http://www.stampedetrial.org/

Ongoing trial

Common endpoint

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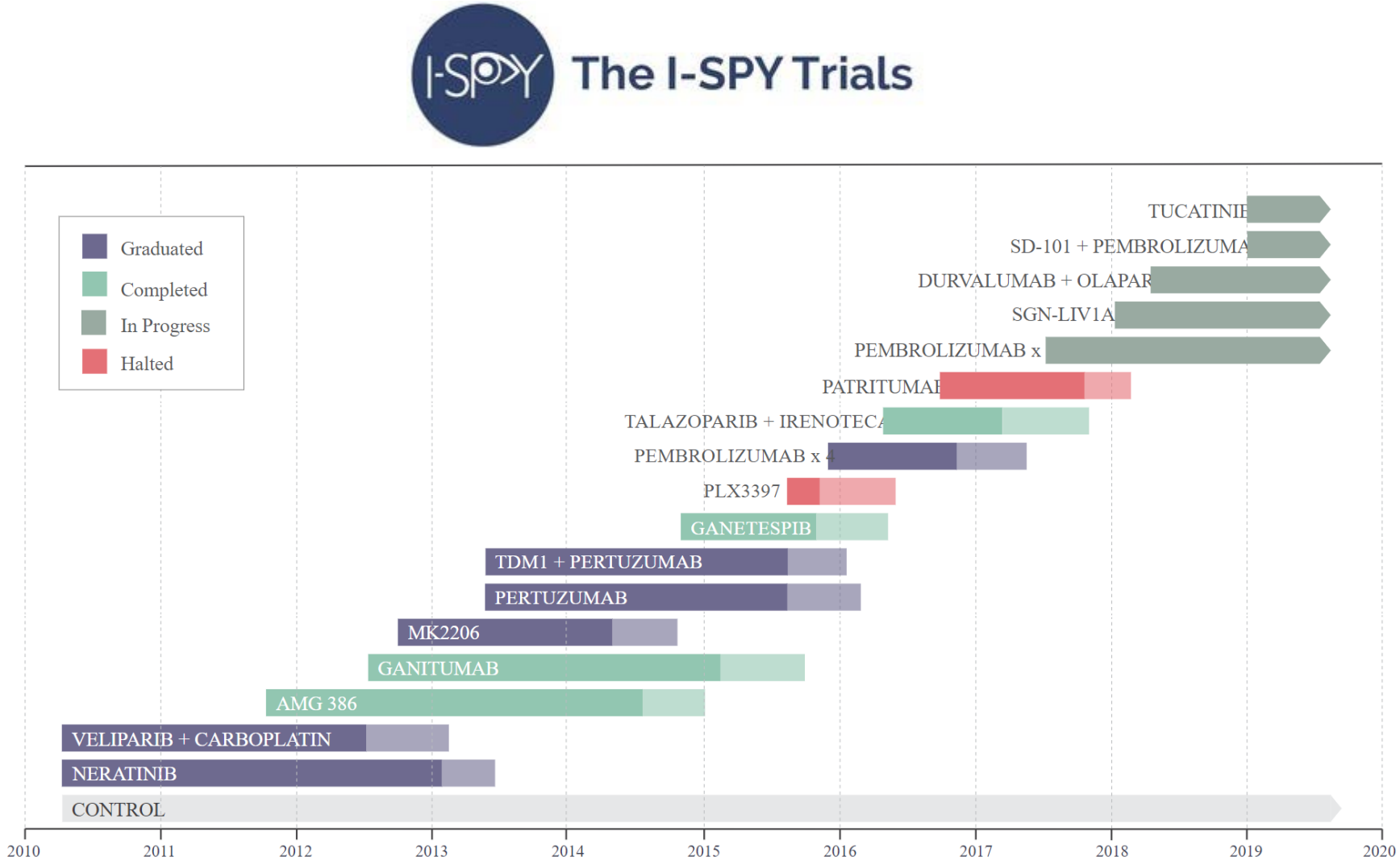
Shared control arm

Adaptive randomization

Potential Bayesian statistics



https://www.ispytrials.org/results/past-agents

Ongoing trial

Common endpoint

Shared infrastructure

Multiple agents

Shared control arm

Adaptive randomization

Potential Bayesian statistics

- Reduces sample size
- Participants have increased likelihood of receiving an active agent

Incidence of primary glomerulonephritis (GN)

Adults	rate/100 000/year
• Membrano-proliferative GN	0.2
• Mesangio-proliferative GN	0.2
• Minimal change disease	0.6
• Focal segmental glomerulosclerosis	0.8
• Membranous nephropathy	1.2
• IgA nephropathy	2.5
Children	
• In general	~ 0.1
• Minimal change disease	2.0 – 15.6

McGrogan *NDT* 26(2), 2011; 414–430

- Ongoing trial
- Common endpoint
- Shared infrastructure
- Multiple agents
- **Shared control arm**
- Adaptive randomization
- Potential Bayesian statistics

Finding participants is challenging

Focal Sclerosing Glomerulosclerosis trials

All trials

- n=2168 participants

Active trials

- n=1404 participants (65% total recruitment target ever)

Completed /terminated trials

- Targeted n=764
- Actual n=605 (79%)

Source: International Clinical Trial Registry Platform (ICTRP)
Search criteria: condition FSGS, Trial Phase 2-4, Interventional trials
Search interval: 2001 to July 20th, 2019

T Bradbury, draft

Ongoing trial

Common endpoint

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Potential Bayesian statistics

Finding participants is challenging even for ‘common’ conditions

Diabetic Kidney Disease trials

CREDENCE

- 6.4 pt/site

SONAR

- 6.8 pt/site

EVOLVE

- ~7.8 pt/site

Cardiovascular trials

EMPA-REG

- 11.9 pt/site

CANVAS

- 15.2 pt/site

DECLARE

- 19.5 pt/site

Ongoing trial

Common endpoint

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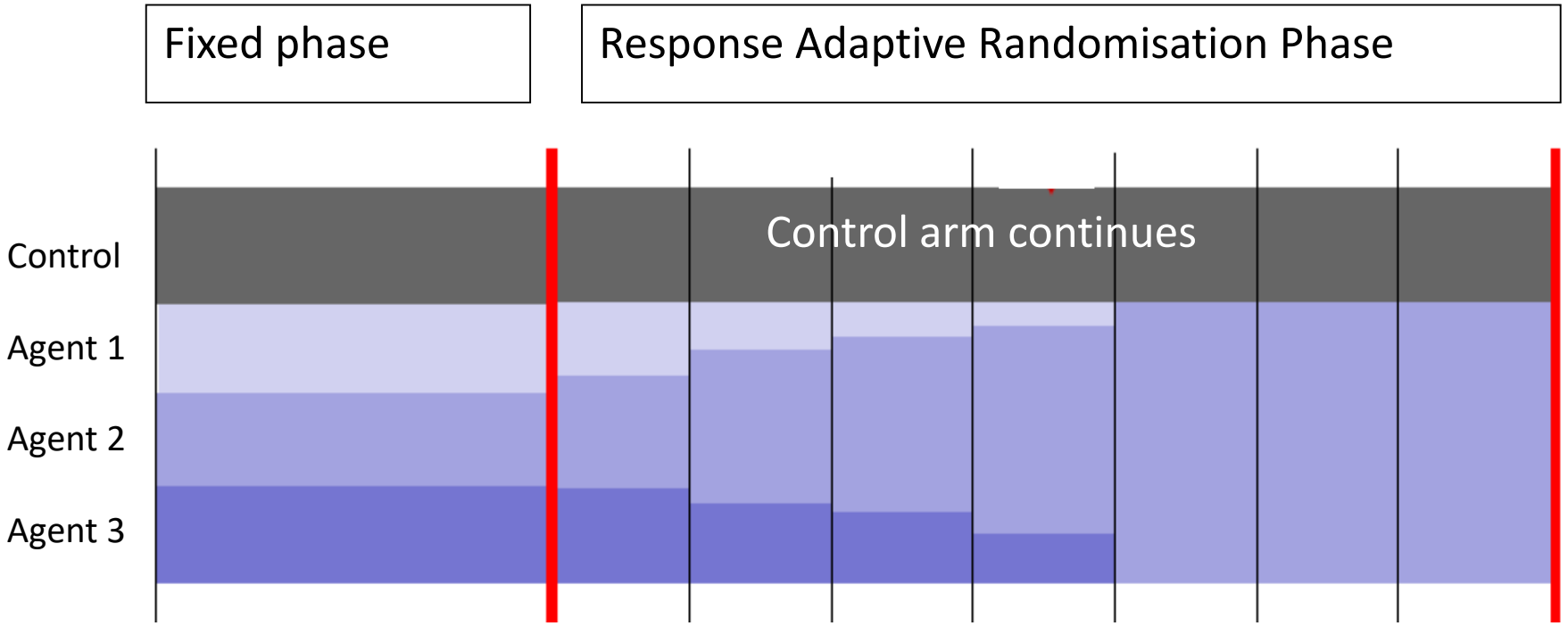
Adaptive randomization

Potential Bayesian statistics

Potential for adaptive randomisation

- Increases efficiency for identifying effective agents



Ongoing trial

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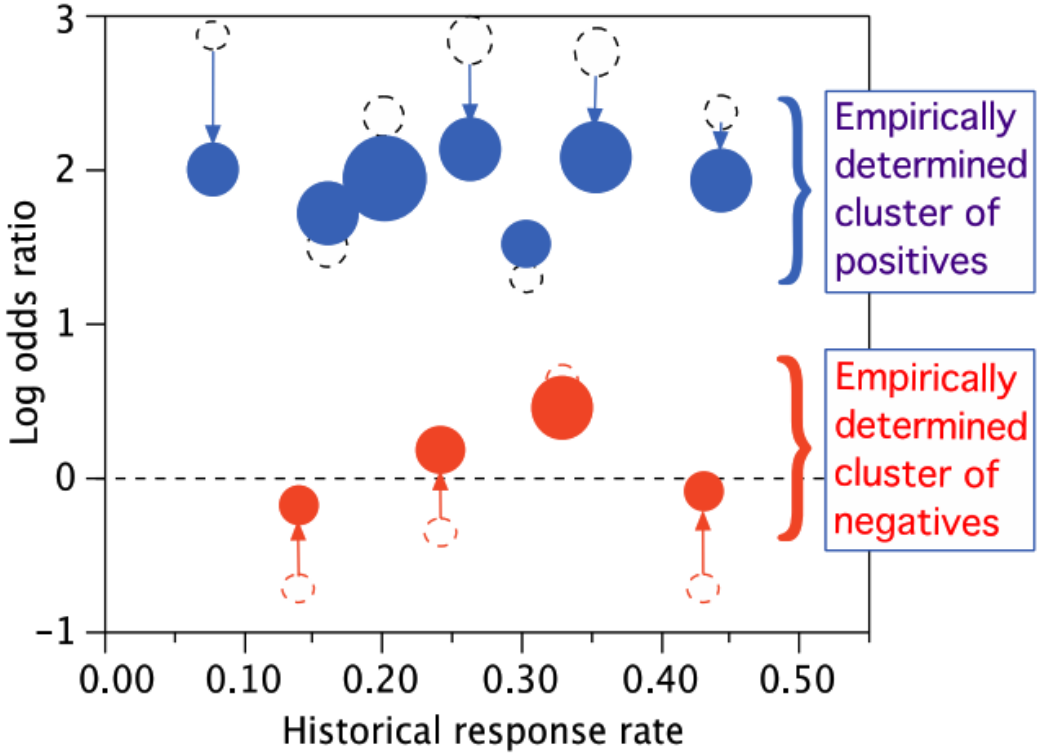
Adaptive randomization

Potential Bayesian statistics

- Capacity to include external knowledge
- Particularly useful for multiple rare but similar conditions

Bayesian heirarchial modelling in which there is “partial borrowing” of results in subtypes (pathologies)



Berry, Molecular Oncology 9(5) 2015, 951-959

Master protocol trials in Nephrology

- Allow patients greater access to research agents
- More efficient for evidence generation
  - Test more agents and more research questions
  - Allow rare conditions to be tested together as ‘subtypes’
  - Lower costs
  - Reduce time
- Can incorporate external learnings

Turn competition into collaboration