Response adaptive platform trials for navigating in uncharted territory

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Integration of research and clinic to advance treatment

Built-in innovation

Platform trials

vs.

Platform trials

- Open ended – new hypotheses can be tested perpetually
- Master protocol, ideally a central IRB and approval process
- Leverage design, statistical engine, infrastructure, logistics, IT, …
- Universal consent process
- New hypotheses described in amendments
- Enables a common control arm → increased efficiency
- Standing infrastructure for research

STAMPEDE

ProBio

- Open since 2005 for men with high-risk prostate cancer
- More than 10,000 patients joined
- 4000 people involved in running the trial
- Practice changing results

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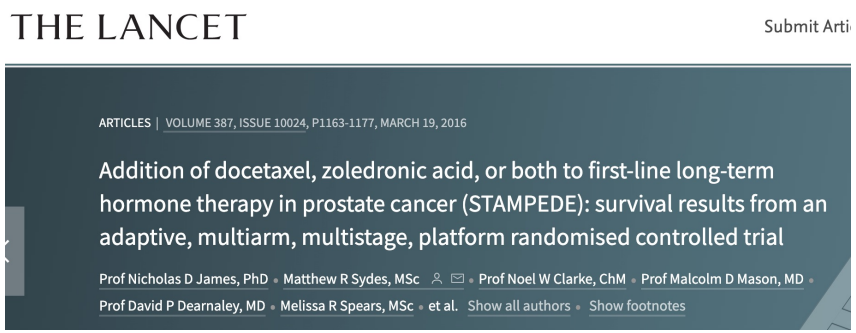
THE LANCET

Submit Arti

ARTICLES | VOLUME 387, ISSUE 10024, P1163-1177, MARCH 19, 2016

Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial

Prof Nicholas D James, PhD • Matthew R Sydes, MSc • Prof Noel W Clarke, ChM • Prof Malcolm D Mason, MD • Prof David P Dearnaley, MD • Melissa R Spears, MSc • et al. Show all authors • Show footnotes

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Abiraterone for Prostate Cancer Not Previously Treated with Hormone Therapy

N.D. James, J.S. de Bono, M.R. Spears, N.W. Clarke, M.D. Mason, D.P. Dearnaley, A.W.S. Ritchie, C.L. Amos, C. Gilson, R.J. Jones, D. Matheson, R. Millman, G. Attard, S. Chowdhury, W.R. Cross, S. Gillessen, C.C. Parker, J.M. Russell, D.R. Berthold, C. Brawley, F. Adab, S. Aung, A.J. Birtle, J. Bowen, S. Brock, P. Chakraborti, C. Ferguson, J. Gale, E. Gray, M. Hingorani, P.J. Hoskin, J.F. Lester, Z.I. Malik, F. McKinna, N. McPhail, J. Money-Kyrle, J. O'Sullivan, O. Parikh, A. Protheroe, A. Robinson, N.N. Srihari, C. Thomas, J. Wagstaff, J. Wylie, A. Zarkar, M.K.B. Parmar, and M.R. Sydes, for the STAMPEDE Investigators*

STAMPEDE

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ProBio

RECOVERY

Randomised Evaluation of COVID-19 Therapy

ProBio

- We push this envelope further

ProBio

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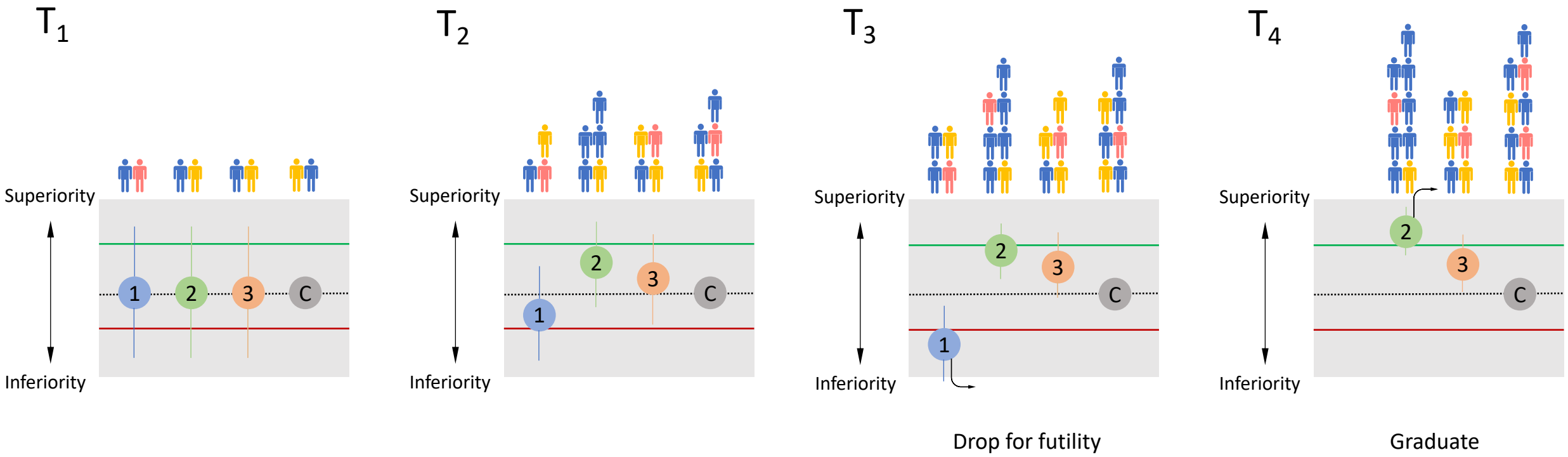
- **Individualization!**

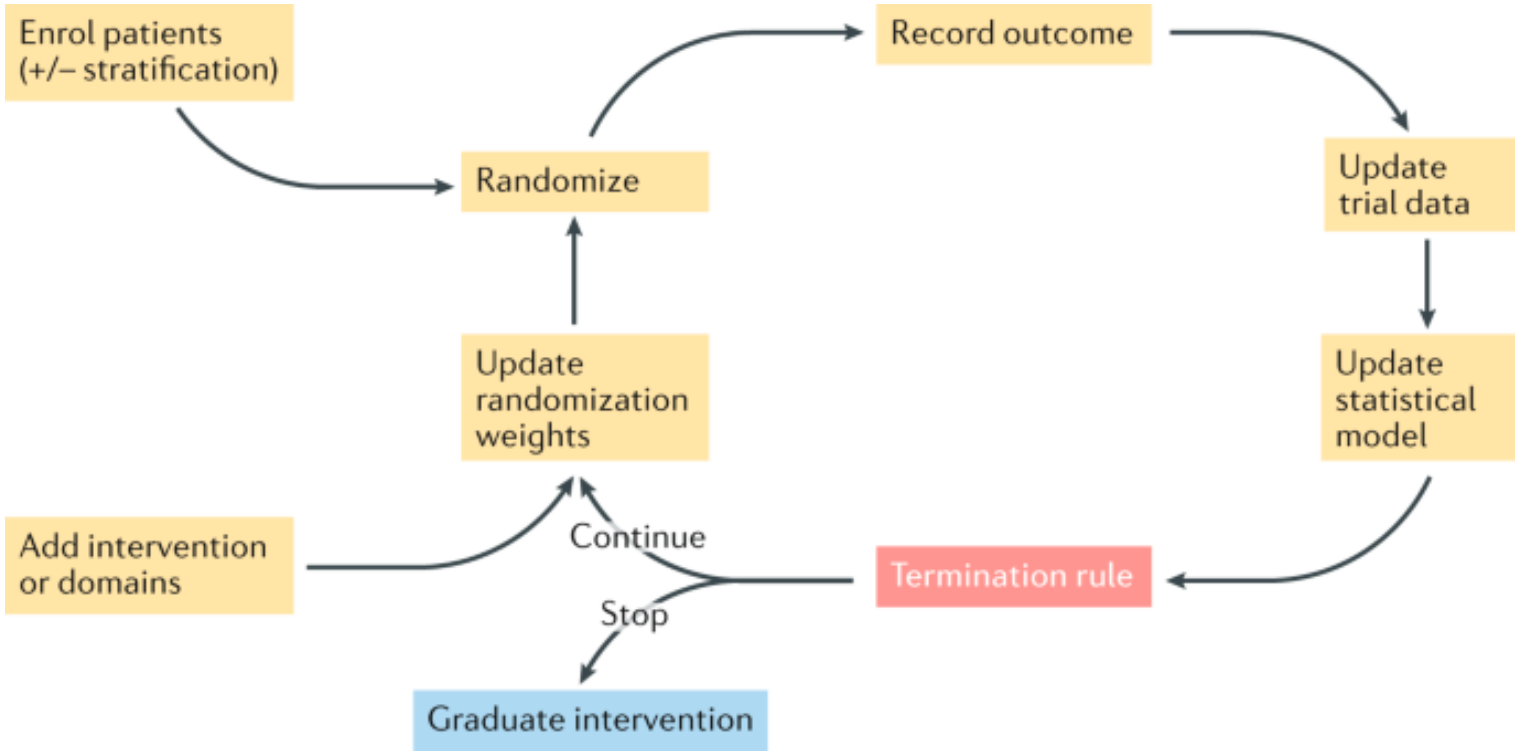
ProBio

- We push this envelope further
- **Individualization!**
- Treatment predictive genomics, measured with ctDNA
- Explosion of hypotheses to test
- We need to allocate patients as efficiently as possible
- Response adaptive randomization

Response adaptive randomization



Learning engines



Still – accrual is everything!

https://stweb.meb.ki.se/

ProBio Automatic Report

Accessibility level: Public
Report issued: 2023 January, 12
Data cut-off date: 2023 January, 11

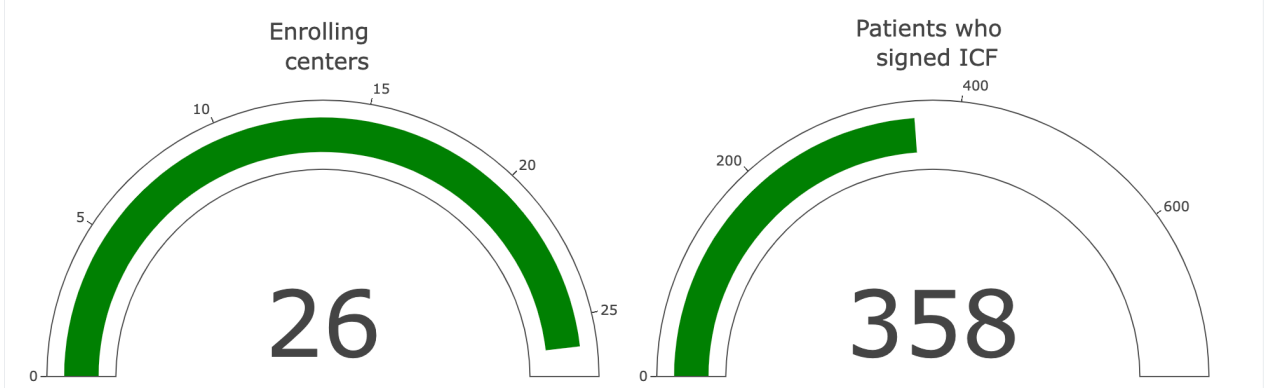
This report contains summary information of the enrollment and follow-up of patients in ProBio. All the data are anonymized and blinded on both the subjects' biomarker profile and randomized therapy.
Information in the "Evaluation of therapies" and "Efficacy of therapies" is based on simulated data which don't reflect the accumulated outcome data in ProBio.

This is a computer-generated document. Contact the author Alessio Crippa for any question.

Summary details of the ProBio study are reported in the Home. Separate information for metastatic Hormone-Sensitive Prostate Cancer (mHSPC) and metastatic Castration-Resistant Prostate Cancer (mCRPC) patients are reported in dedicated tabs.

Home | mHSPC | mCRPC

Outline | Enrollment | Follow-up | Baseline variables | Biomarkers (first randomization) | Number of progressions | Evaluation of therapies | Efficacy of therapies | Serious Adverse Events



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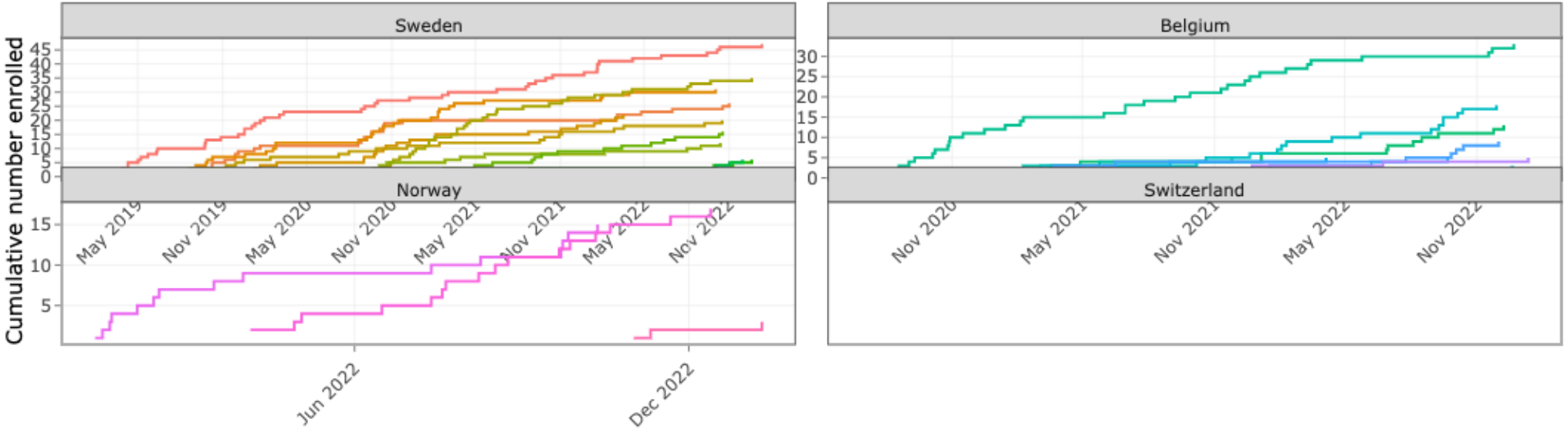
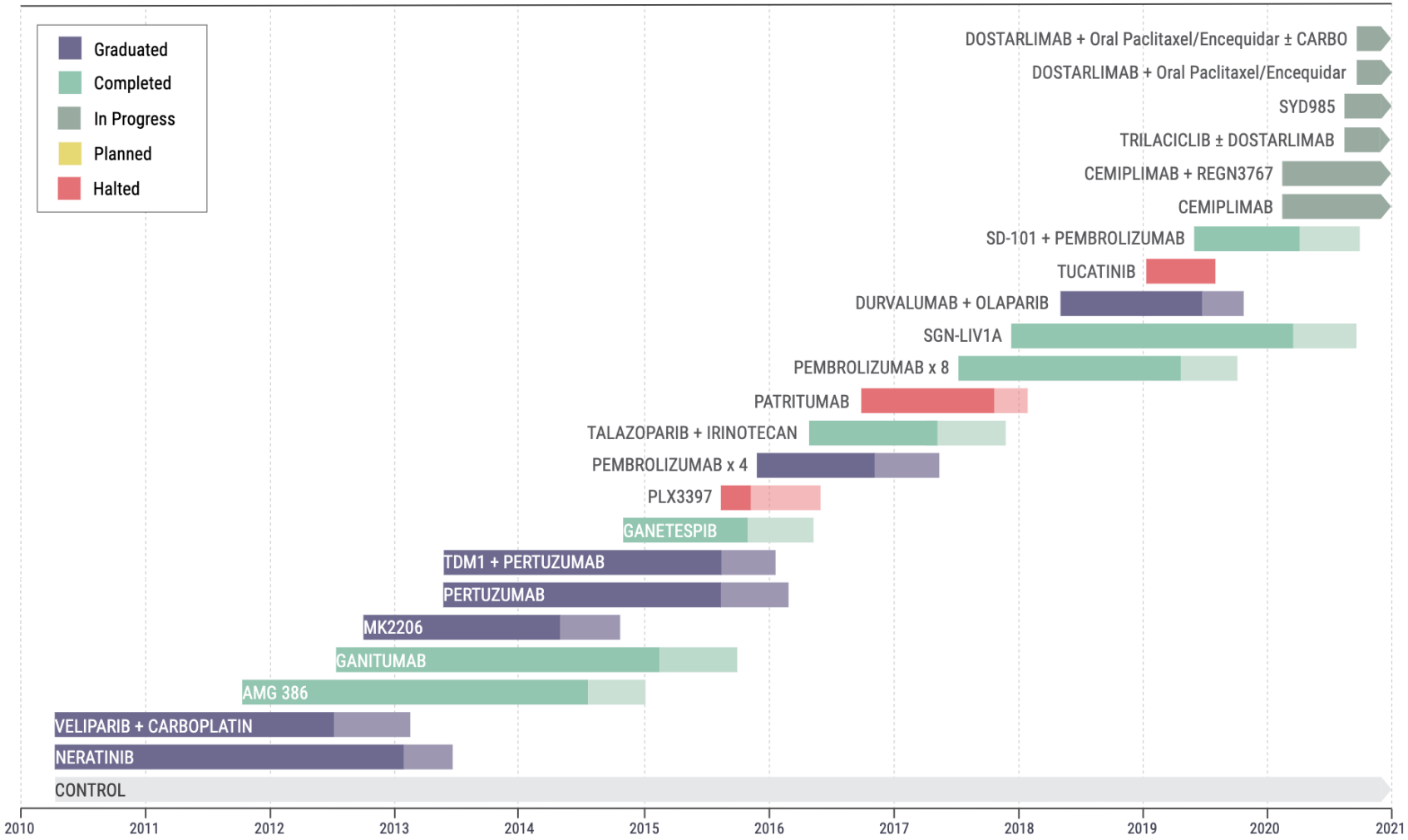


Center — Capio S:t Görans Sjukhus — Karolinska Universitetssjukhuset — Akademiska Sjukhuset — Norrlands Universitetssjukhus — Länssjukhuset i Sundsvall — Länssjukhuset i Ryhov — Växjö lasarett — Centralsjukhuset Karlstad — Länssjukhuset i Kalmar — Falu lasarett — AZ St-Jan Brugge — UZ Gent — AZ Groeninge — OLV Aalst — AZ Damiaan — Ziekenhuis Oost-Limburg (ZOL) — AZ St-Lucas Brugge — CHU Liège — Jessa Ziekenhuis — AZ Nikolaas — GZA Sint-Augustinus — Akershus Universitetssykehus (Ahus) — Stavanger universitetssjukehus — Universitetssykehuset Nord-Norge Tromsö — Ålesund Sjukehus — University Hospital Basel

Response adaptive randomization – success story



Response adaptive randomization – success story

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ORIGINAL ARTICLE

Adaptive Randomization of Veliparib–Carboplatin Treatment in Breast Cancer

H.S. Rugo, O.I. Olopade, A. DeMichele, C. Yau, L.J. van 't Veer, M.B. Buxton, M. Hogarth, N.M. Hylton, M. Paoloni, J. Perlmutter, W.F. Symmans, D. Yee, A.J. Chien, A.M. Wallace, H.G. Kaplan, J.C. Boughey, T.C. Haddad, K.S. Albain, M.C. Liu, C. Isaacs, Q.J. Khan, J.E. Lang, R.K. Viscusi, L. Pusztai, S.L. Moulder, S.Y. Chui, K.A. Kemmer, A.D. Elias, K.K. Edmiston, D.M. Euhus, B.B. Haley, R. Nanda, D.W. Northfelt, D. Tripathy, W.C. Wood, C. Ewing, R. Schwab, J. Lyandres, S.E. Davis, G.L. Hirst, A. Sanil, D.A. Berry, and L.J. Esserman, for the I-SPY 2 Investigators*

ABSTRACT

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 7, 2016 VOL. 375 NO. 1

Adaptive Randomization of Neratinib in Early Breast Cancer

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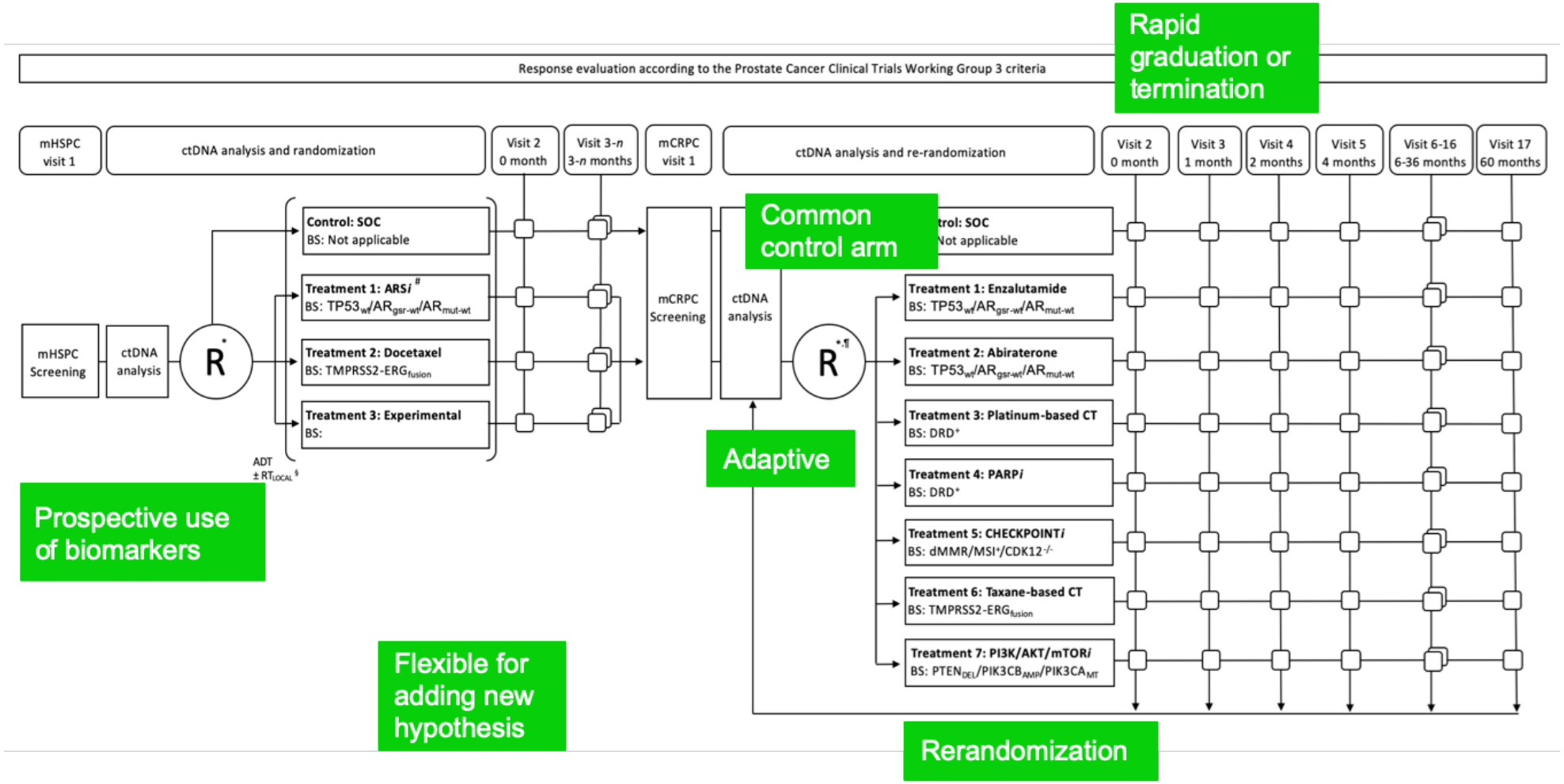
ProBio response adaptive design



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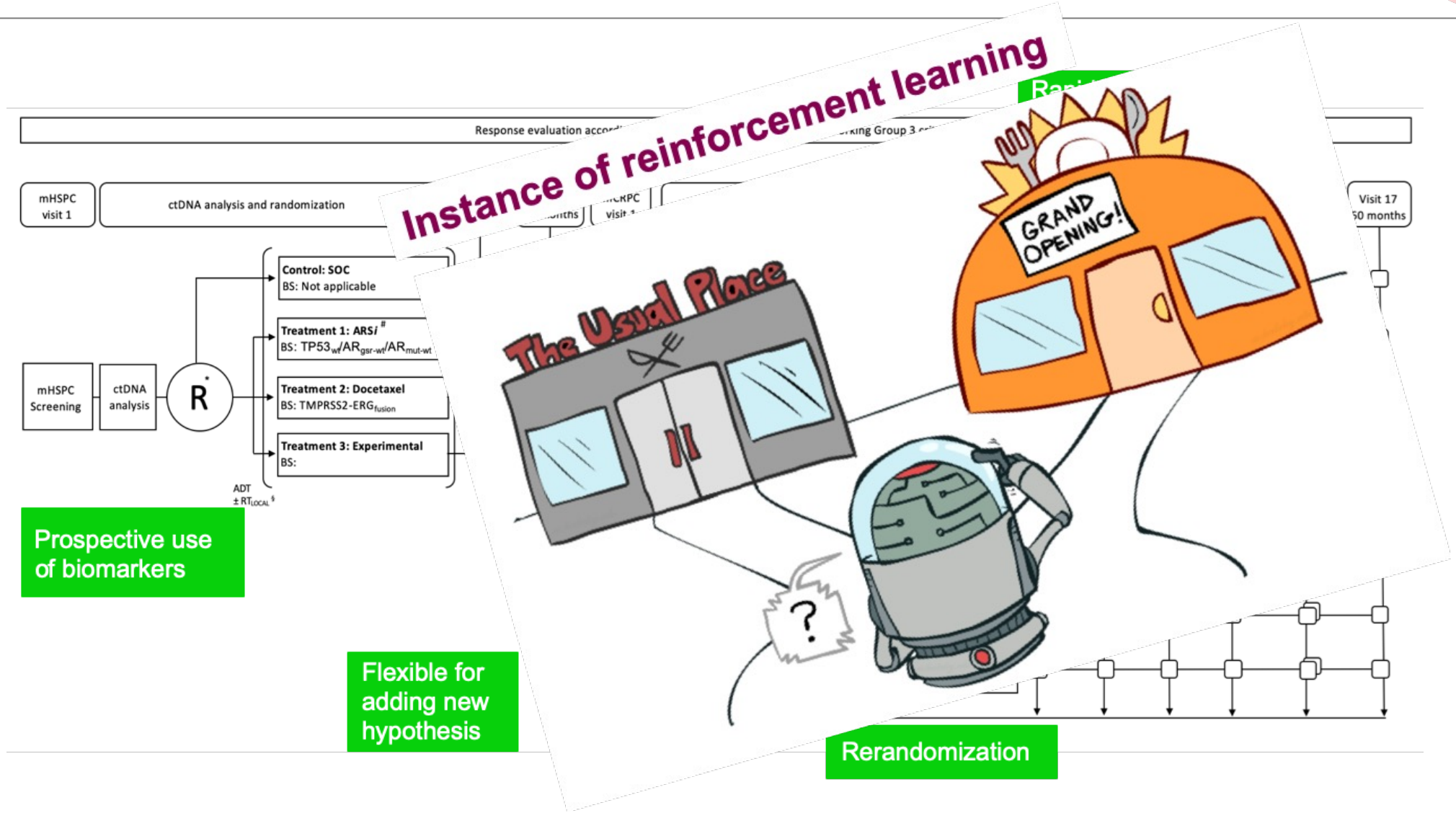

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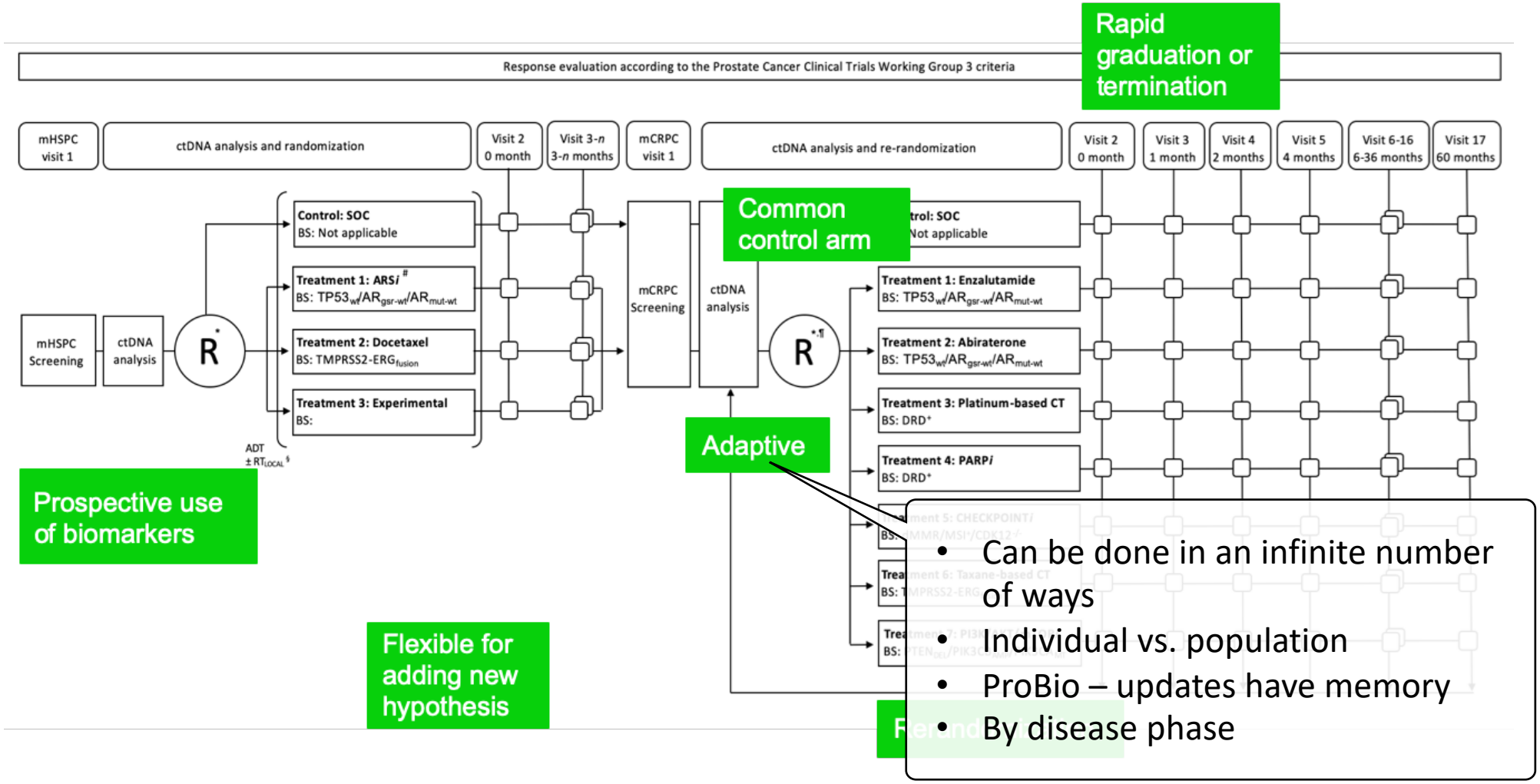
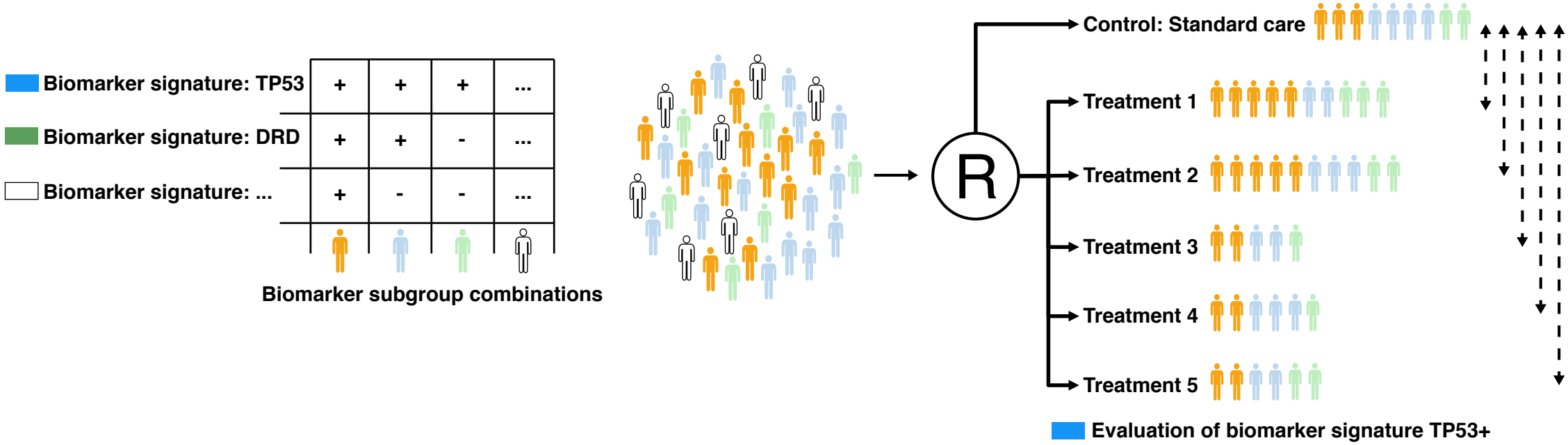


- Can be done in an infinite number of ways
- Individual vs. population
- ProBio – updates have memory
- By disease phase

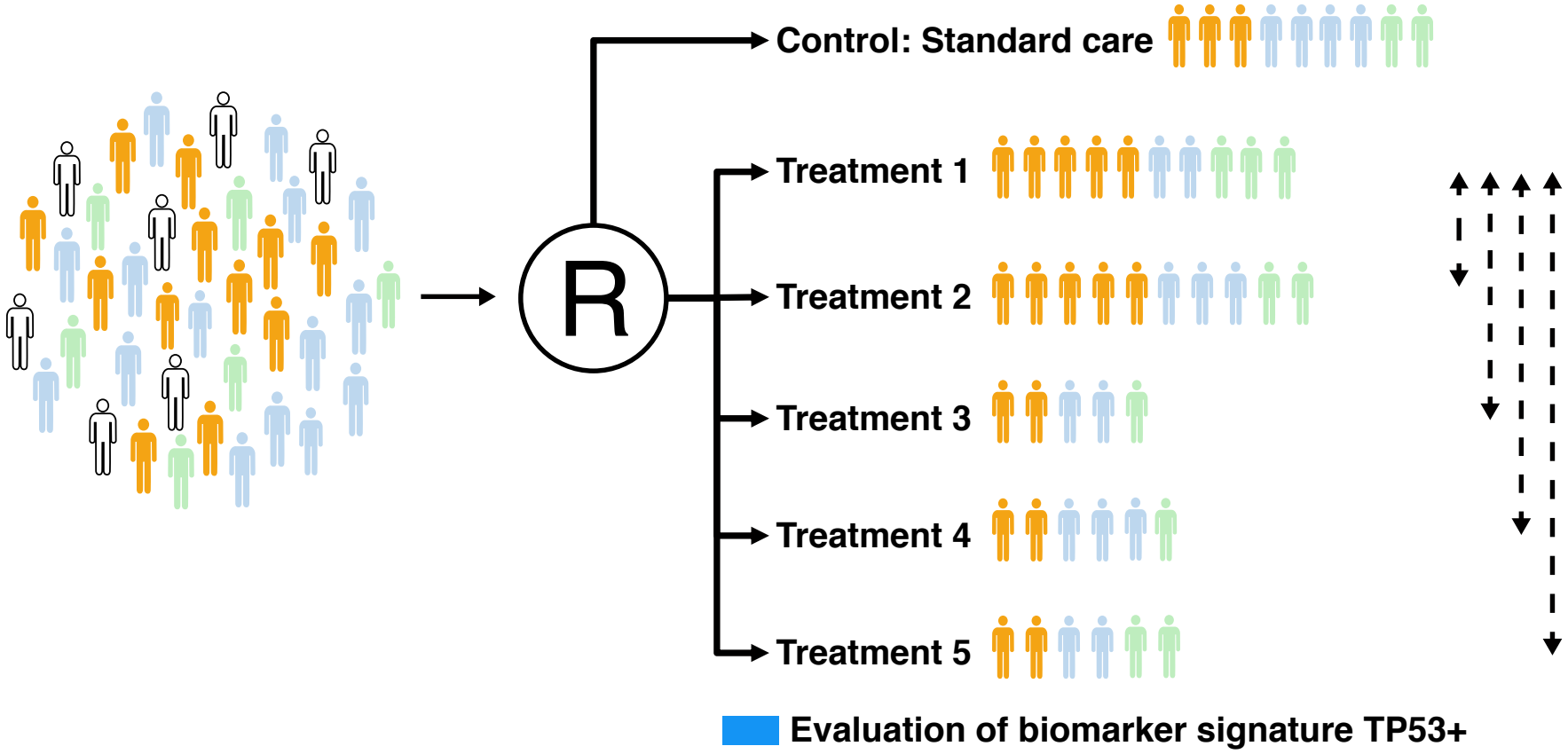
Key questions the design can answer

Primary efficacy analysis



Key questions the design can answer

Secondary efficacy analysis



Key questions the design can answer

Can ctDNA dynamics predict time to no longer clinically benefiting?

Mind the gap

vs.

Mind the gap

- Multiplicativity – many drugs and many genomic subgroup combinations
- Signatures
- Errors are more challenging to define than in a standard trial
- Example: PARP inhibitors

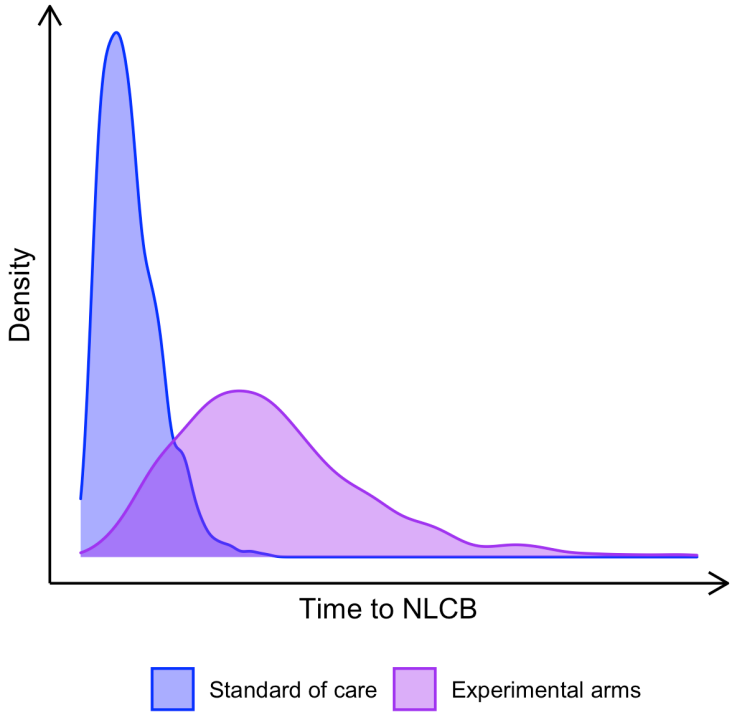
Biomarker	----	---+	--+-	--++	-+--	-+-+	-++-	-+++	+---	+--+	+-+-	+-++	++--	++-+	+++-
AR	-	-	-	-	-	-	-	-	+	+	+	+	+	+	+
HRD	-	-	-	-	+	+	+	+	-	-	-	-	+	+	+
TP53	-	-	+	+	-	-	+	+	-	-	+	+	-	-	+
TEfus	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-
Prevalence	32%	7%	17%	11%	7%	5%	2%	1%	5%	4%	1%	4%	3%	1%	1%

Signature	----	---+	--+-	--++	-+--	-+-+	-++-	-+++	+---	+--+	+-+-	+-++	++--	++-+	+++-	Prevalence
all	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	100%
TP53- & AR-	X	X			X	X										50%
TP53+			X	X			X	X			X	X			X	37%
DRD+					X	X	X	X					X	X	X	19%
TEfus+		X		X		X		X		X		X		X		32%

Mind the gap

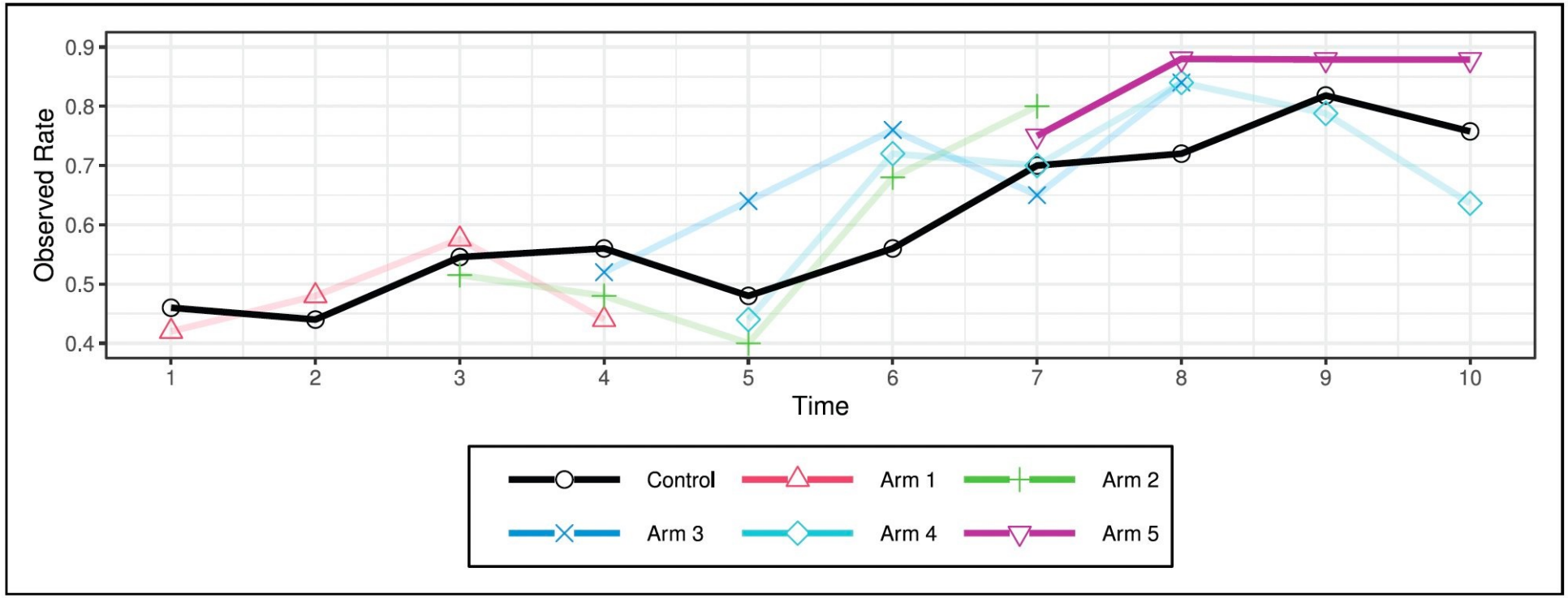
https://stweb.meb.ki.se/

- Adaptiveness ≠ arbitrariness
- **Prespecification**
- Simulations to estimate operating characteristics
- ProBio is a screening trial for finding signature-treatment combinations that are likely to be superior to standard of care
- Validation trial (frequentist, using O'Brian-Fleming alpha spending function)



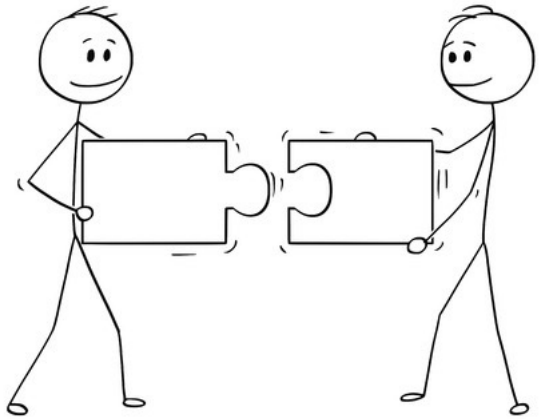
Mind the gap

Concurrent controls



Mind the gap

- Drug specific exclusion criteria in platform trials
- Randomization prior to consent – Niraparib (and Capivasertib)
- Caution in the analytical handling of controls
- Difference in eligibility of controls for different contrasts



Mind the gap

- Complex trial – trial integrity is central to success
- Maintain blinding – who has access to what information
- DSMB plays a central role (even more so than in standard trials)
- Regulated in a charter

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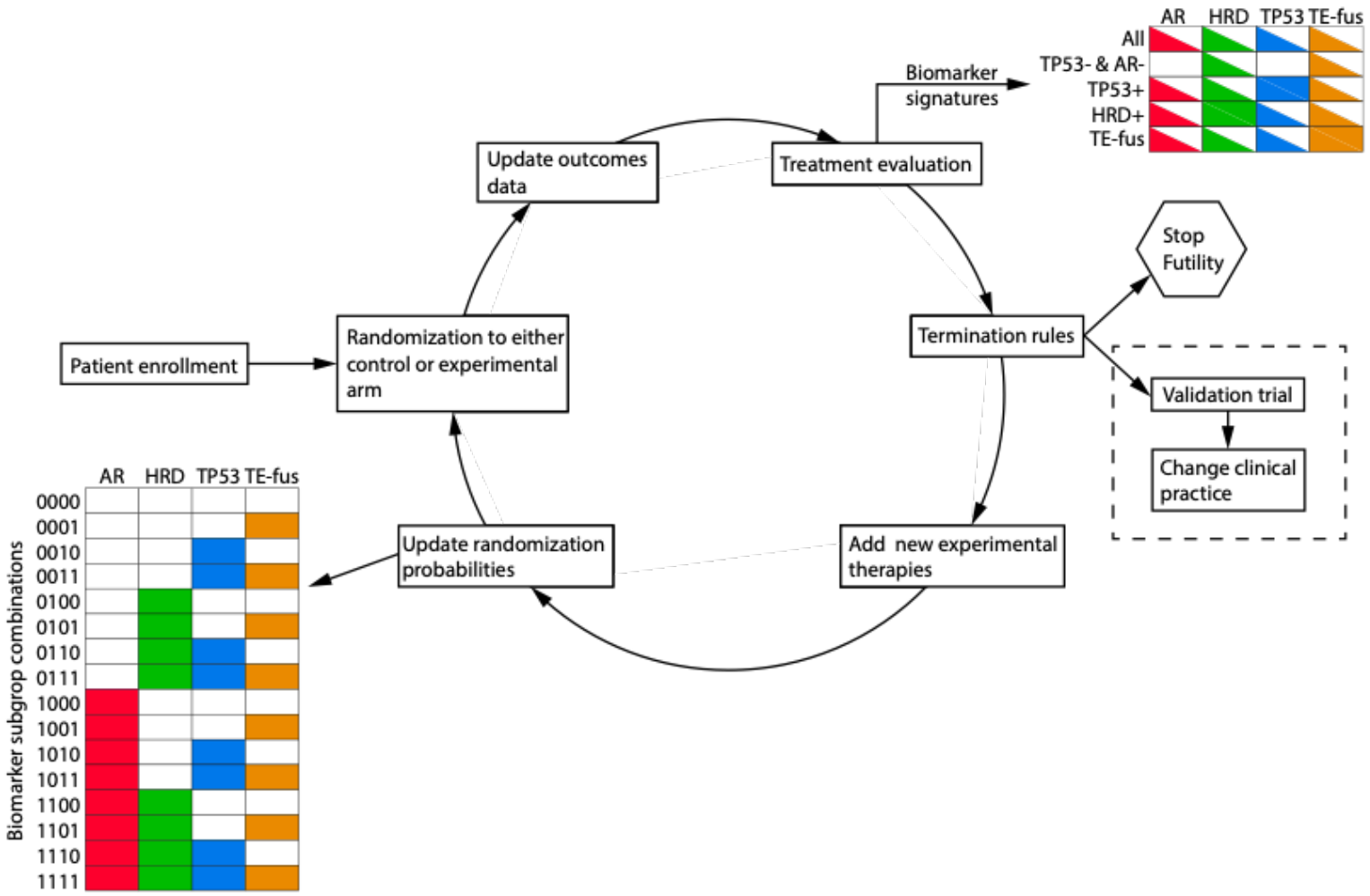
The ProBio learning engine



ProBio

Thank you all!

Karolinska Institutet

AstraZeneca

Janssen

krebsliga beider basel
beraten – unterstützen – informieren

Cancerfonden

Vetenskapsrådet

Kom op tegen Kanker