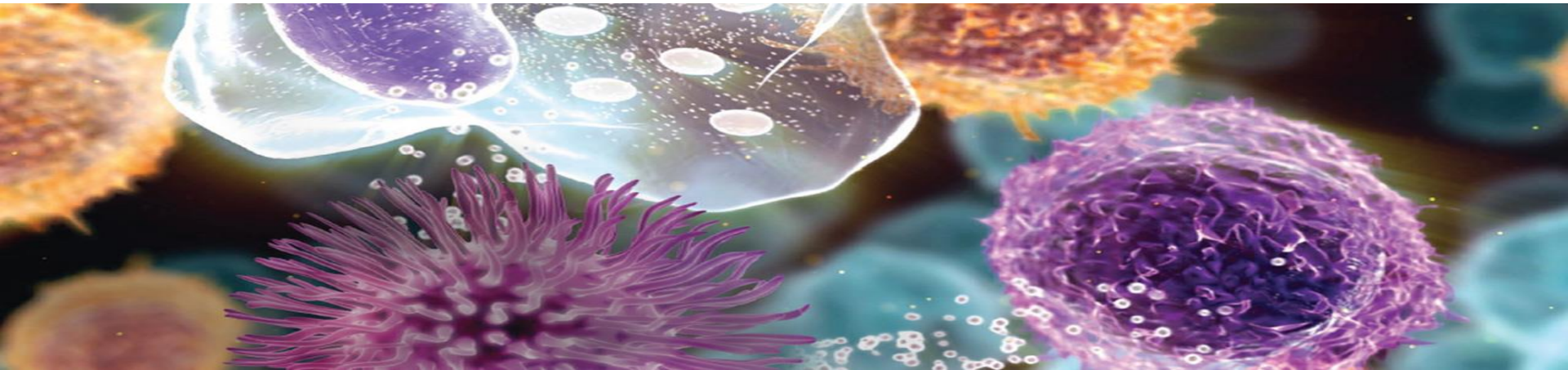
Innovative statistical approaches for studies in drug combination development to treat infectious diseases

Alun Bedding, Roche Products



Work in Progress……..

- Conceptual
- Accepted by senior management
- Now go away and work up the design – details, simulations, operating characteristics

The Infectious Disease Problem

Traditional Development

Adaptive Platform Trial

Next Steps

Problem with Infectious Diseases

- Single agent treatment of some infectious diseases (such as HCV, HBV, HEV etc….) are sub-optimal ~ 0-5% functional cure
- Also have to be administered for a sustained period
- Once patients treatment is withdrawn a rebound occurs
- Question – can combination strategies work towards an absolute cure?
- But what molecules do we combine?
  - New molecular entities
  - Existing molecules

What can we learn from oncology?

- Oncology uses many combinations to treat specific cancers
- But these tend to be an NME on top of an existing therapy, which then have a potential interaction which lead to better therapy

- In many infectious diseases this may not be possible.
- Looking for absolute cure and not just functional cure
  - Absolute means eradication of the disease
  - Functional cure means controlling the disease

Take Hepatitis B infection as an example

The unmet medical need

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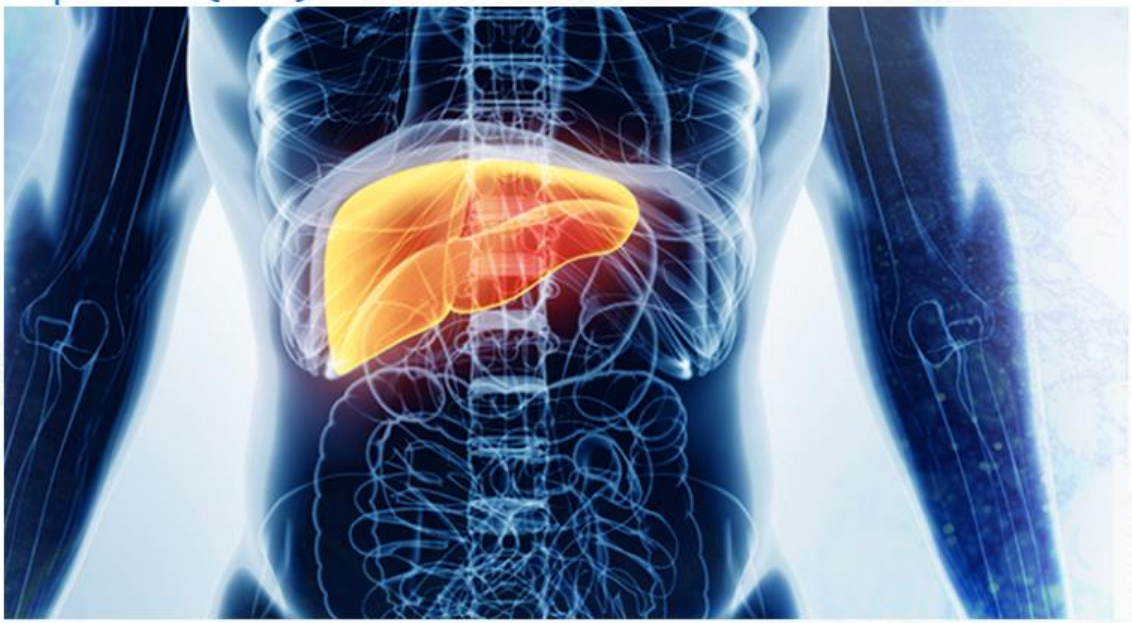
Solutions > Disease Areas > **Hepatitis B (HBV)**

Hepatitis B (HBV)



A commitment to innovative diagnostics and treatment

A silent, yet life-threatening infection

Contact us

Have a question? Get in touch with us here and we'll work to get you the answers you need from one of our experts.

> Contact

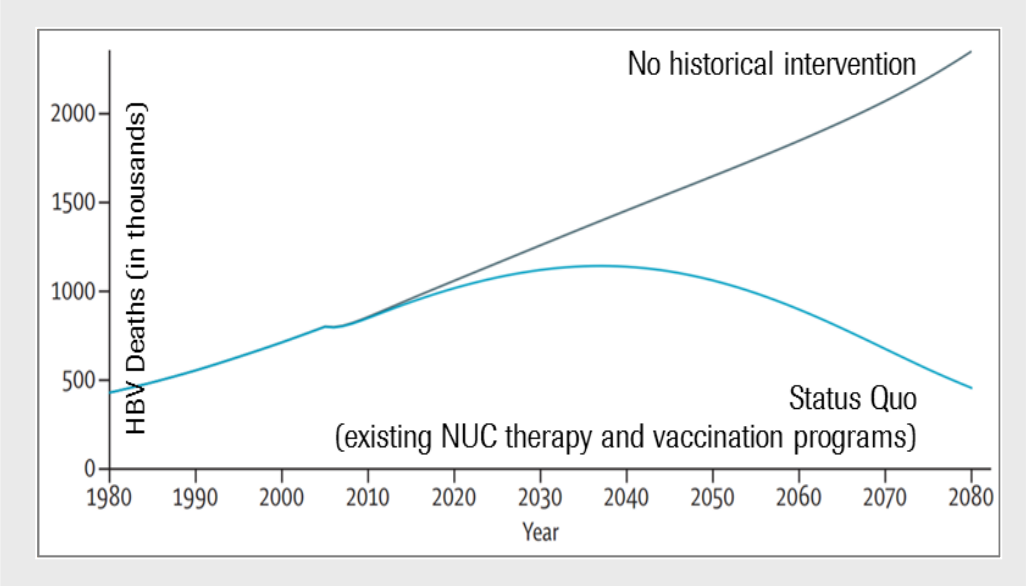
Related content

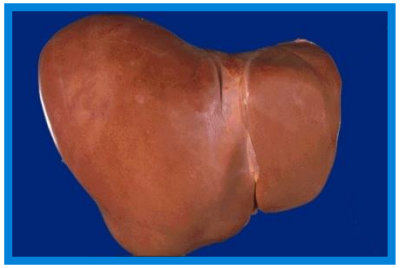
> Committed to Hepatology

Take Hepatitis B infection as an example

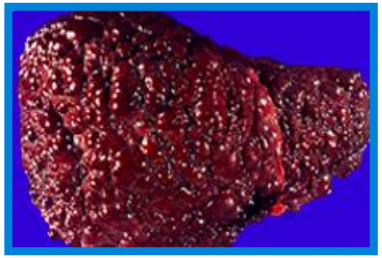
The unmet medical need

- CHRONIC HEPATITIS B (CHB) IS A MAJOR GLOBAL HEALTH PROBLEM
- IN SPITE OF VACCINATION, >250 million people are chronically infected with Hepatitis B, 1/3 in china
- CHB patients at high risk of developing cirrhosis and hepatocellular carcinoma (HCC)
- 15%-25% OF CHB PATIENTS DIE OF CIRRHOSIS OR HEPATOCELLULAR CARCINOMA (HCC) WITH ~700,000 DEATHS ANNUALLY WORLDWIDE

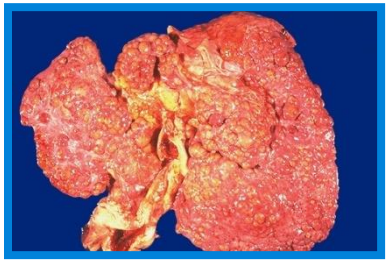




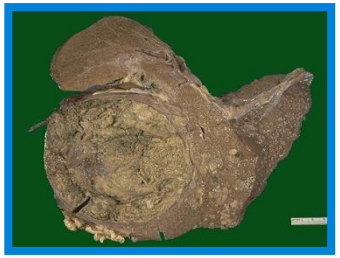
Normal liver



Cirrhosis



End-stage liver disease

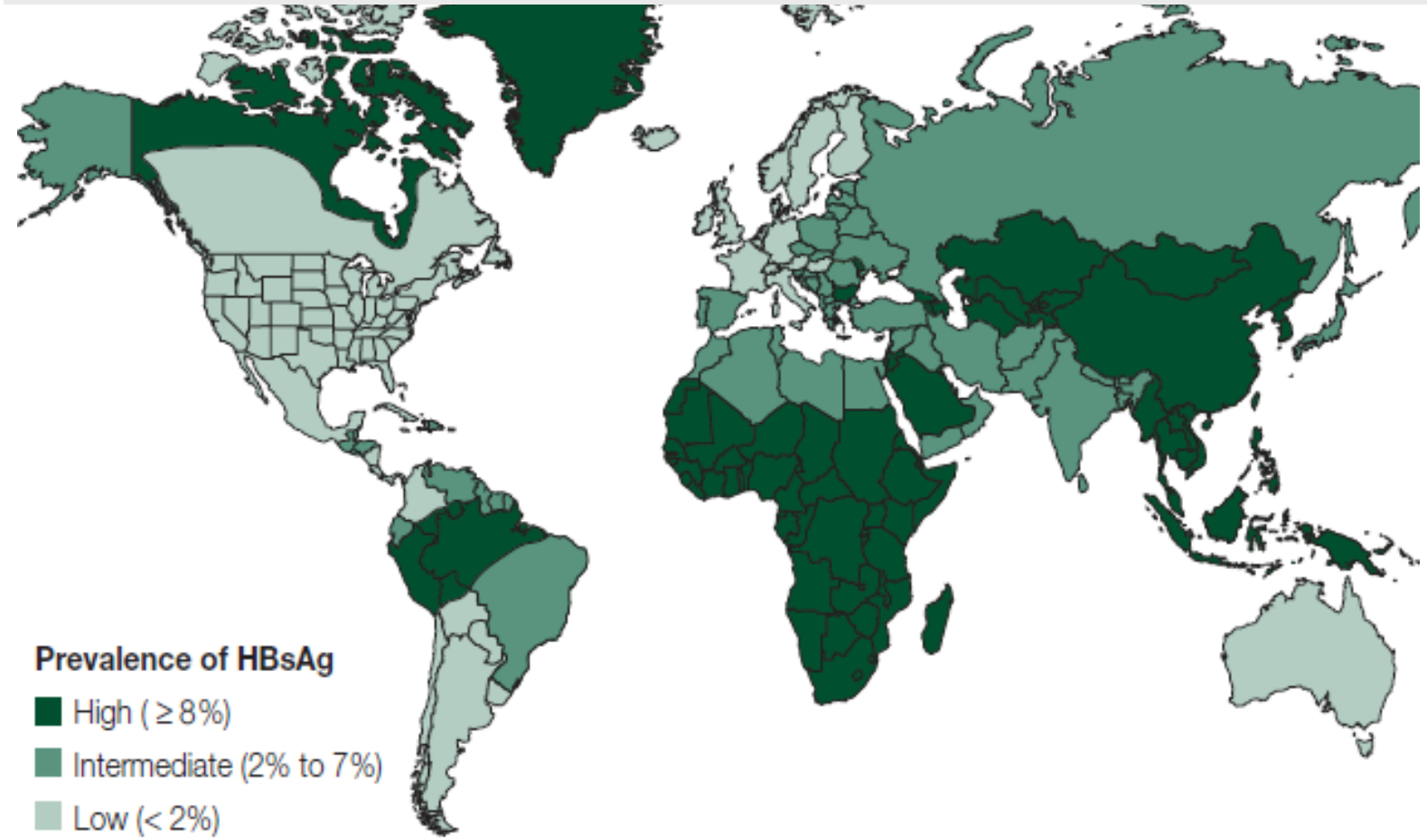


HCC

Source: www.who.com, www.thelancet.com, http://dx.doi.org/10.1016/S1473-3099(16)30204-3 (CDC estimates 2016)

Prevalence of HBV

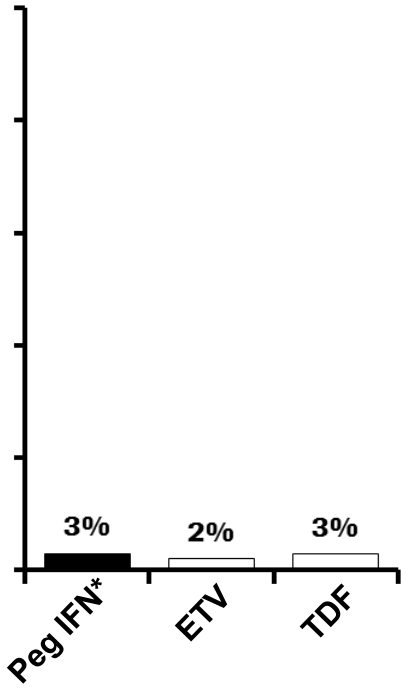
75% of long-term carriers live in Asia-pacific



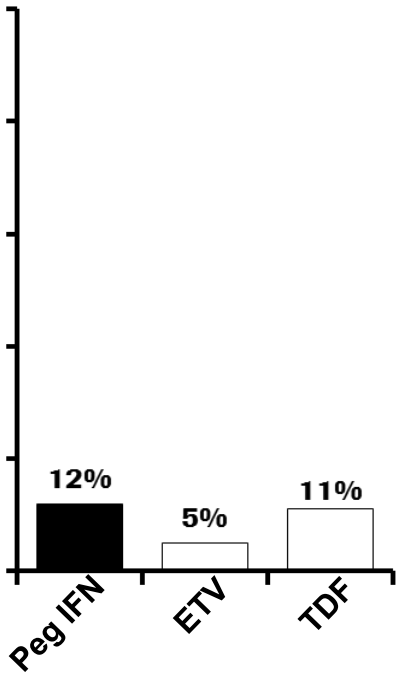
CDC. 2010; DHHS Public Health Service. 2009

Currently available therapies result in low rates of Functional Cure

Maximum reported (after 1 year)

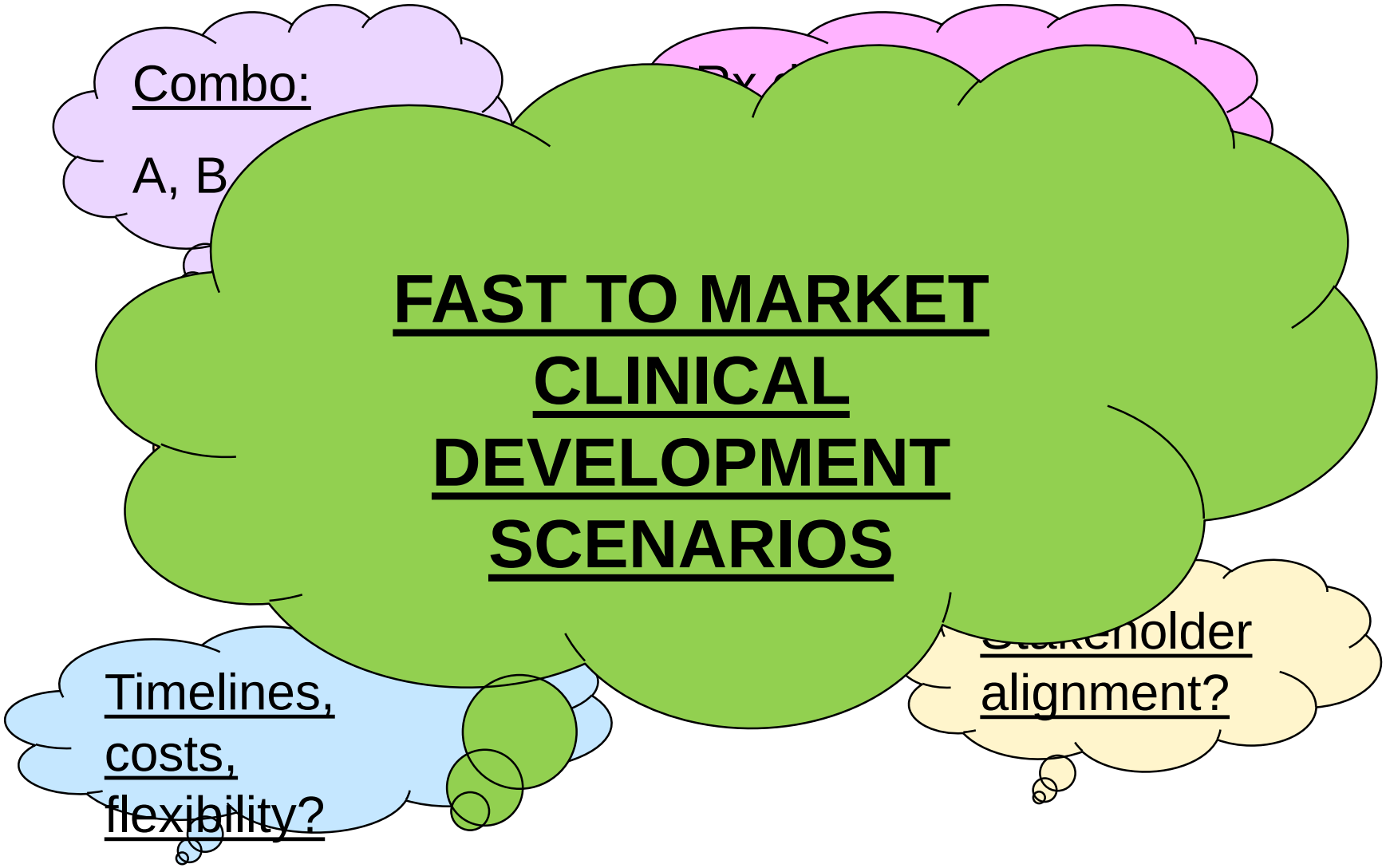


Maximum reported (after 5 years)



ETV = Entecavir , TDF = Tenofovir Peg IFN = Peg Interferon

Drug development in anti-infectives - Questions



The Infectious Disease Problem

Traditional Development

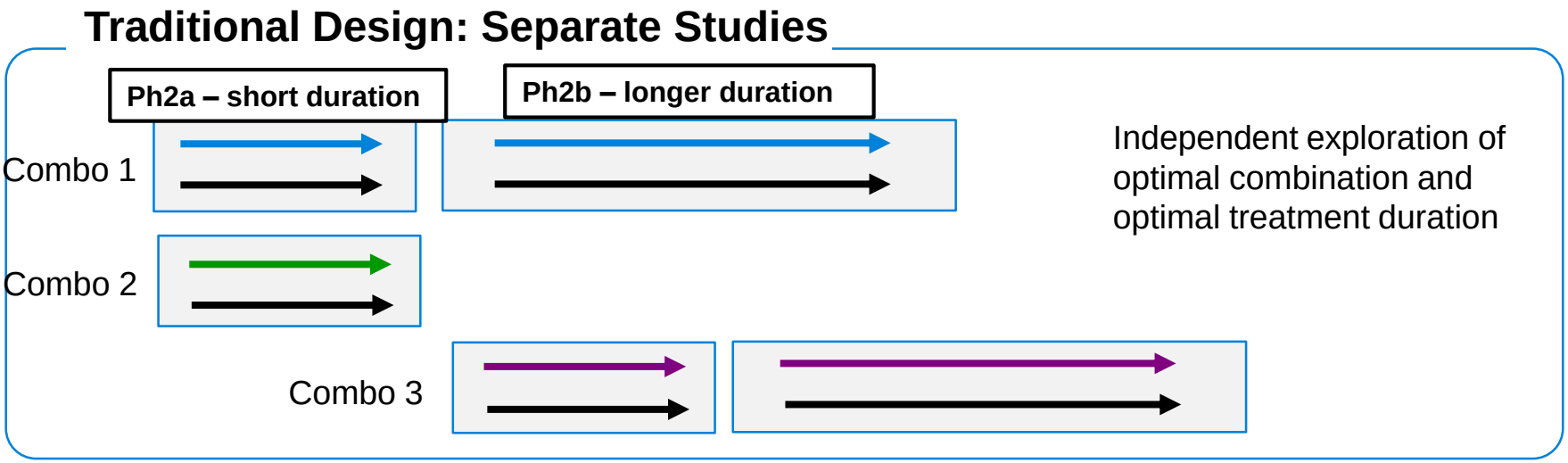
Adaptive Platform Trial

Next Steps

Traditional Study Development

- Three molecules (A, B, C)
    - All can be combined with each other
        - Combo 1 (A+B), Combo 2 (B+C), Combo 3 (A+C)
- Phase 1 has been completed and a single dose has been selected
- Phase 2a will look at the shortest treatment duration – say 12 weeks
- Phase 2b might then look at a longer treatment duration
- 1:1 randomisation - experimental:control

Traditional Study Development



Some Issues:

- Common Control – 1:1 experimental:control
- Separate study teams
- Resource and patient intensive
- Easy to analyse (but more difficult to compare combos)

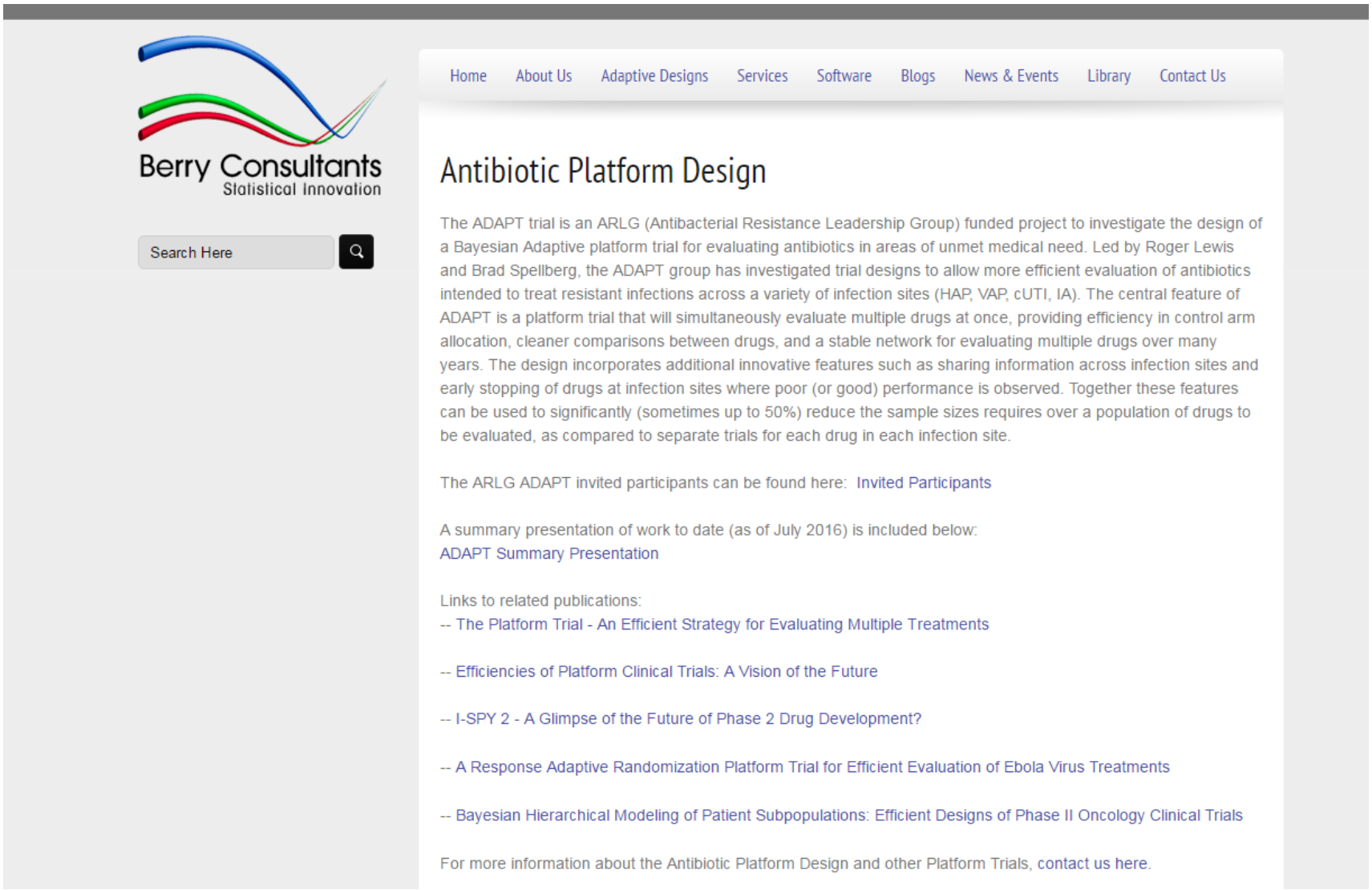
The Infectious Disease Problem

Traditional Development

Adaptive Platform Trial

Next Steps

Work by ARLG



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Antibiotic Platform Design

The ADAPT trial is an ARLG (Antibacterial Resistance Leadership Group) funded project to investigate the design of a Bayesian Adaptive platform trial for evaluating antibiotics in areas of unmet medical need. Led by Roger Lewis and Brad Spellberg, the ADAPT group has investigated trial designs to allow more efficient evaluation of antibiotics intended to treat resistant infections across a variety of infection sites (HAP, VAP, cUTI, IA). The central feature of ADAPT is a platform trial that will simultaneously evaluate multiple drugs at once, providing efficiency in control arm allocation, cleaner comparisons between drugs, and a stable network for evaluating multiple drugs over many years. The design incorporates additional innovative features such as sharing information across infection sites and early stopping of drugs at infection sites where poor (or good) performance is observed. Together these features can be used to significantly (sometimes up to 50%) reduce the sample sizes requires over a population of drugs to be evaluated, as compared to separate trials for each drug in each infection site.

The ARLG ADAPT invited participants can be found here: Invited Participants

A summary presentation of work to date (as of July 2016) is included below:
ADAPT Summary Presentation

Links to related publications:
-- The Platform Trial - An Efficient Strategy for Evaluating Multiple Treatments

-- Efficiencies of Platform Clinical Trials: A Vision of the Future

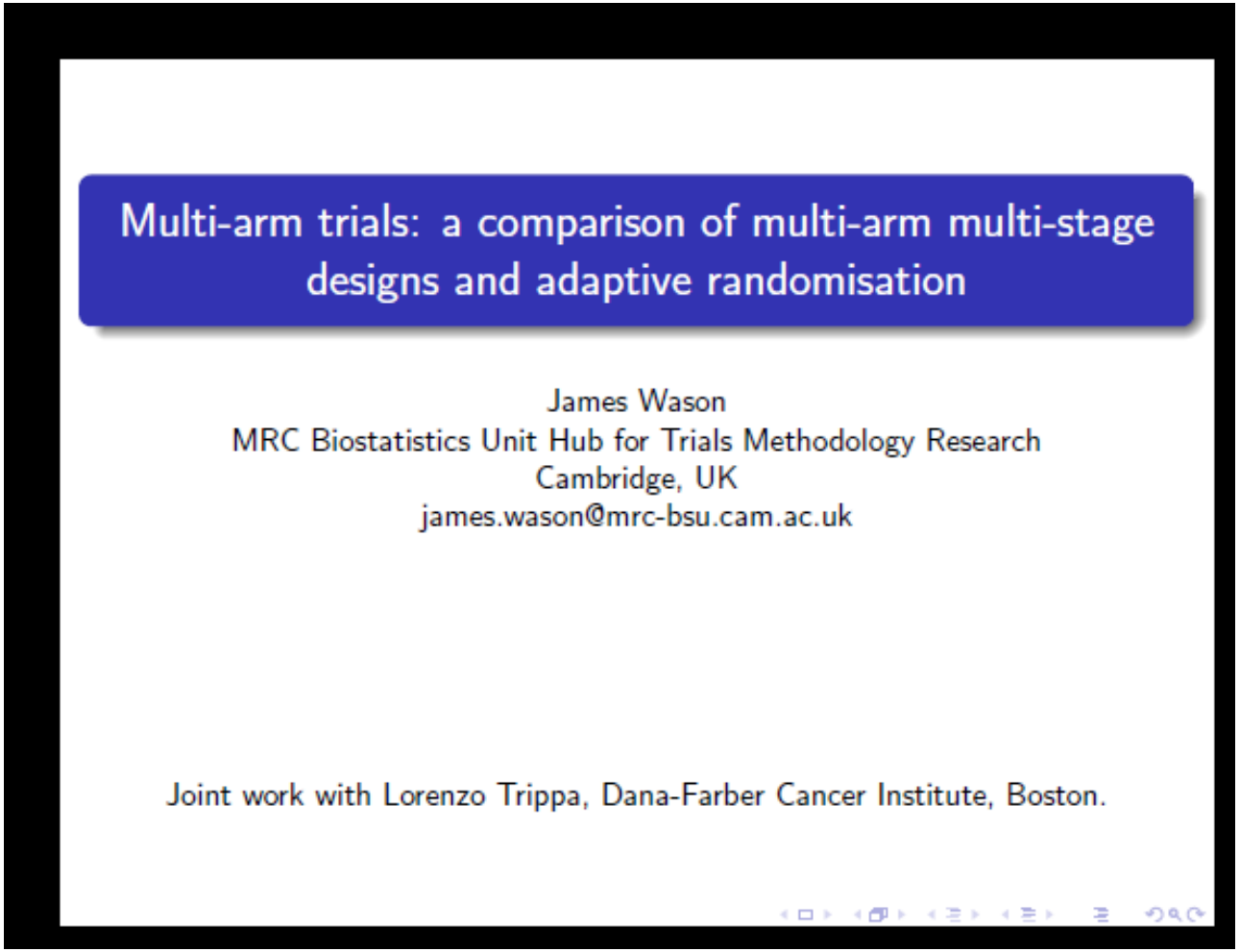
-- I-SPY 2 - A Glimpse of the Future of Phase 2 Drug Development?

-- A Response Adaptive Randomization Platform Trial for Efficient Evaluation of Ebola Virus Treatments

-- Bayesian Hierarchical Modeling of Patient Subpopulations: Efficient Designs of Phase II Oncology Clinical Trials

For more information about the Antibiotic Platform Design and other Platform Trials, contact us here.

Work by James Wason



Multi-arm trials: a comparison of multi-arm multi-stage designs and adaptive randomisation

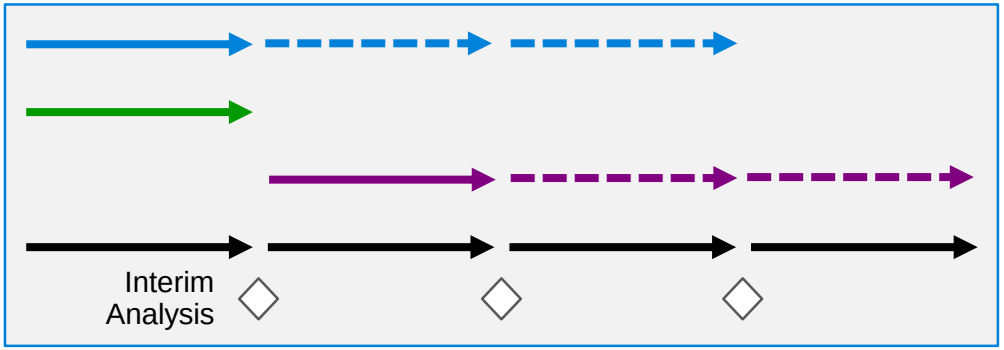
James Wason
MRC Biostatistics Unit Hub for Trials Methodology Research
Cambridge, UK
james.wason@mrc-bsu.cam.ac.uk

Joint work with Lorenzo Trippa, Dana-Farber Cancer Institute, Boston.

Adaptive Platform (Multi-arm, Multi-stage) Design for Phase 2

Nimble design to save time and reduce costs

Adaptive Platform Design: Single study



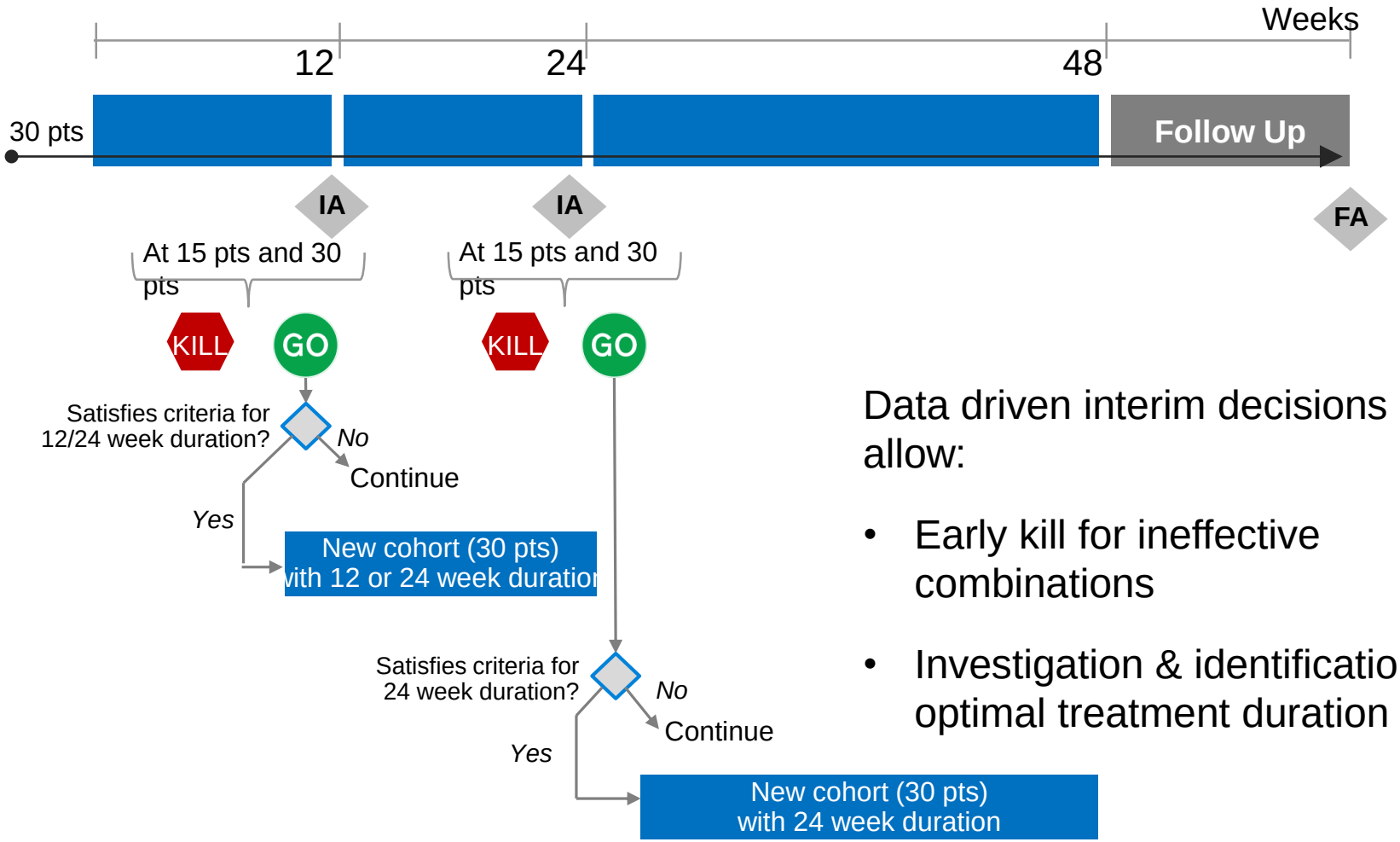
1) **Platform** - multiple combinations in single study with master protocol
2) **Adaptive** – data driven flexible design
3) **Multi-stage** – combine phases (2a/2b and possibly 3)

Some Issues:

- Less control patients required.
- 2:1 randomisation - experimental:control
- Attractive to patients (better chance of active drug)
- One common master protocol – combos come in and out of the platform trial
- Adjustments need to be made for time effects (combos come in later)

Adaptive Data Driven Design for Phase 2

Decisions based on evolving data to select winning combinations



Data driven interim decisions allow:

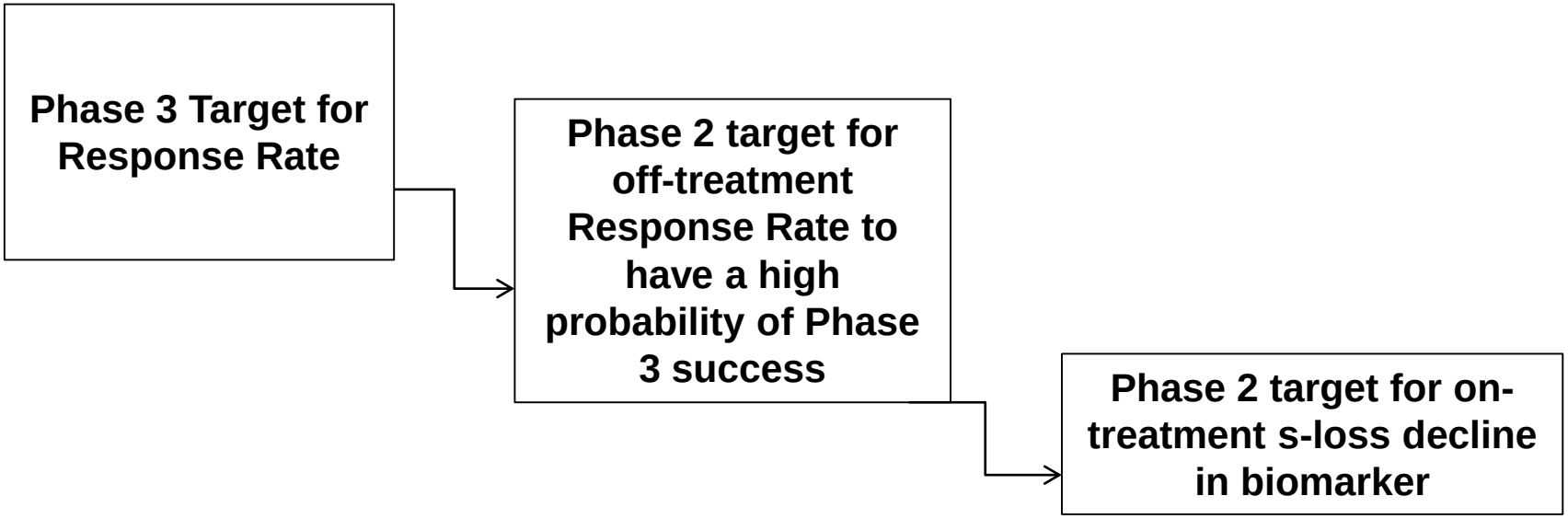
- Early kill for ineffective combinations
- Investigation & identification of optimal treatment duration

IA = interim analysis

Comparability of the Control Data

- Large database of control data
- Use this to enrich the control arm
- Also, need to add a small number of controls whenever a new combo is added to the platform – this takes into account the time aspect
- Use methods such as a hierarchical model to assess the comparability of the control data
- Historical studies with effect $\theta_0,\theta_1,\theta_2$ with θ_3 being the effect of the current study
- $\theta_0,\theta_1,\theta_2$, $\theta_3 \sim N(\mu,\tau)$ with μ and τ having prior distributions.
- Creates dynamic borrowing through τ – borrow more when data are consistent with common treatment effects, less when one treatment effect looks different than the others

Deriving the decisions for the Interim Analyses



Interim Analysis Decisions

Kill versus Go Decision

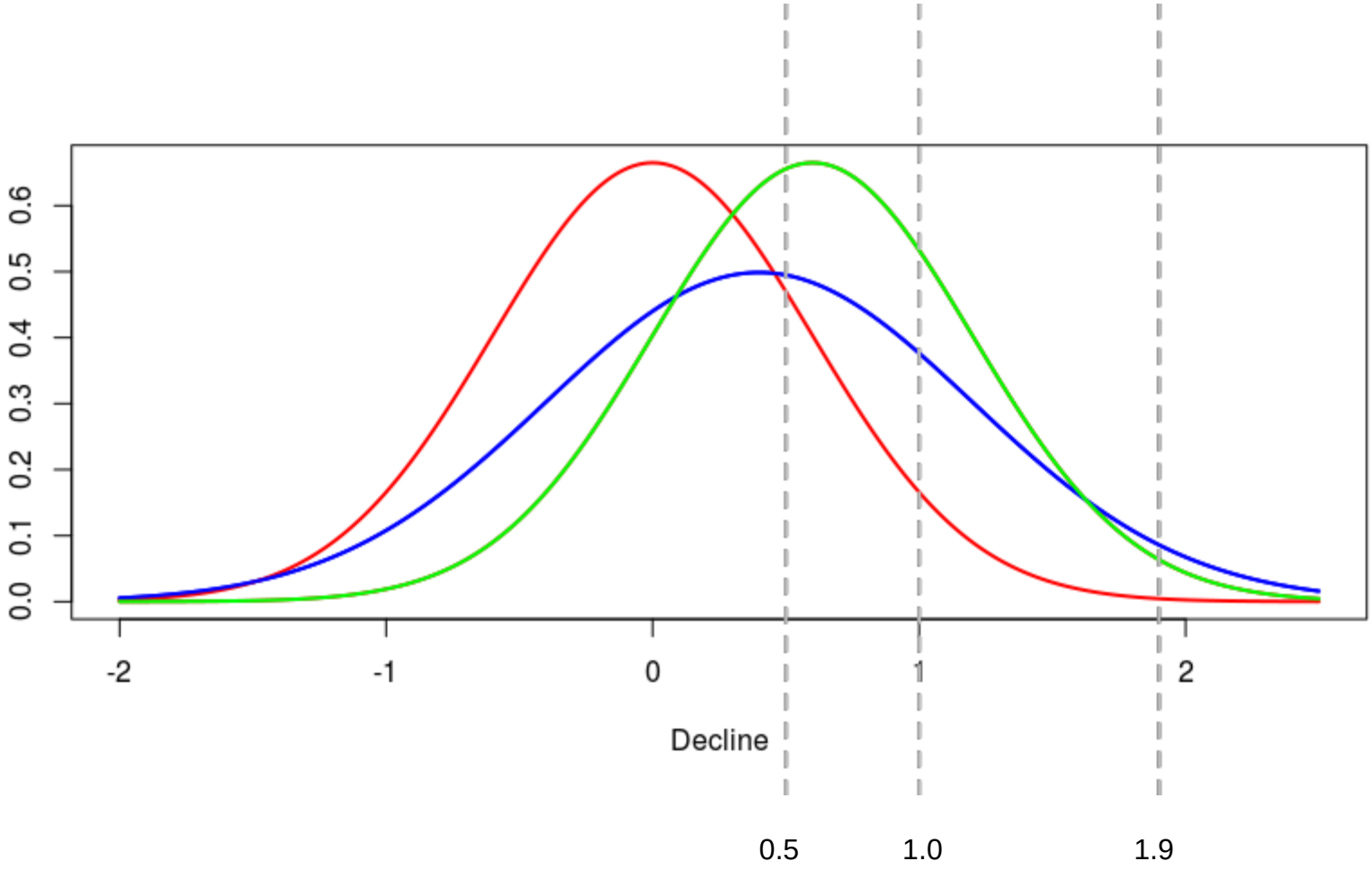
	Week 12	Week 24
Kill	0/3 criteria	0/3 criteria
Evaluate	1/3 criteria	1/3 criteria
Go	Criterion A + 1 or 2 other	Criterion A + 1 or 2 other

Criteria	Decline on treatment	Decline on treatment
A	50% of patients ≥ 0.5	50% of patients ≥ 1.2
B	30% of patients ≥ 1.0	30% of patients ≥ 1.8
C	10% of patients ≥ 1.9	10% of patients ≥ 2.8

Criteria for activating an additional cohort

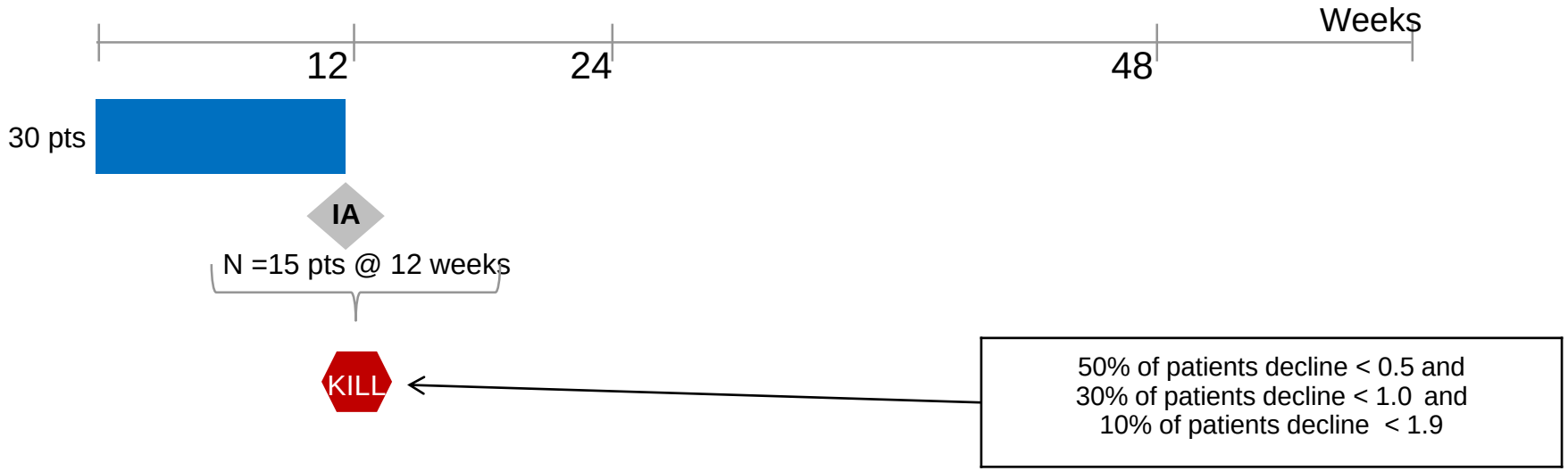
Week 12	Week 24
Loss rate ≥ 50% of patients – Activate 12 week treatment cohort	Loss rate ≥ 50% of patients – Activate 24 week treatment cohort
Loss rate < 50% of patients, but patients have a similar profile to a 24 week comparator– Activate 24 week treatment cohort	Loss rate < 50% of patients – no extra cohorts

What this looks like in terms of distribution (not drawn to scale)



Adaptive Data Driven Design for Phase 2

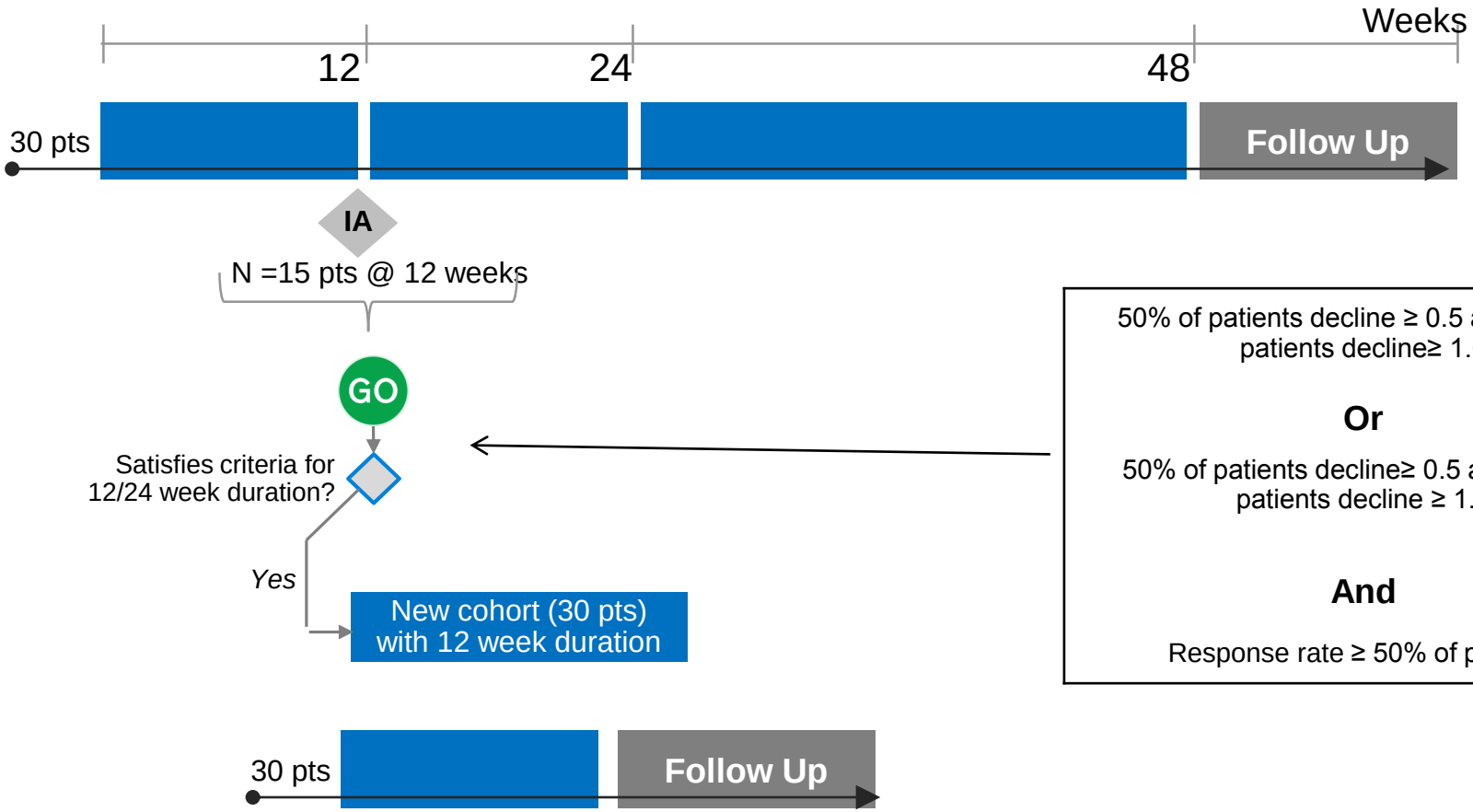
1st Interim – Kill



IA = interim analysis

Adaptive Data Driven Design for Phase 2

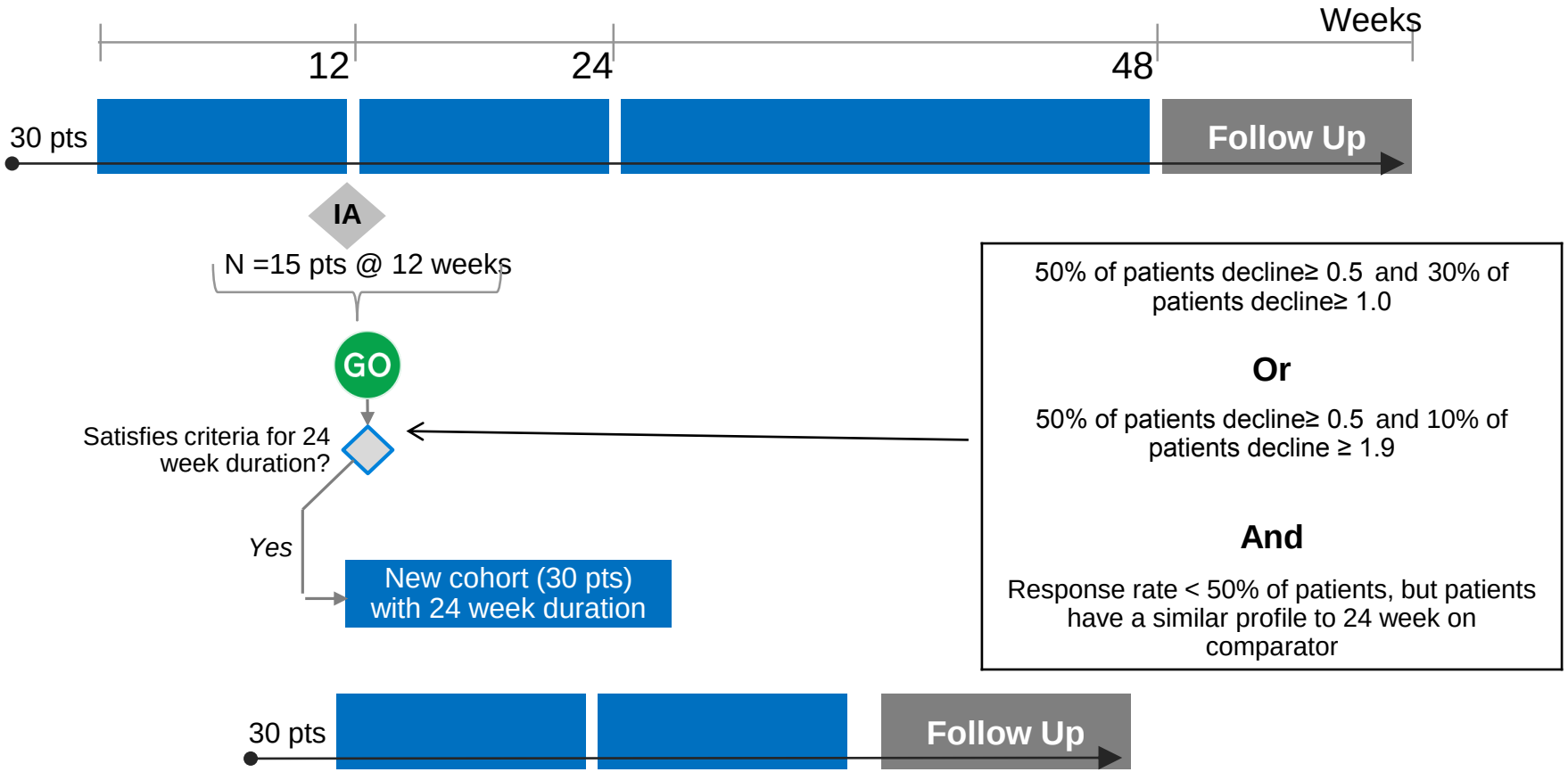
1st Interim – new 12 week duration cohort



IA = interim analysis

Adaptive Data Driven Design for Phase 2

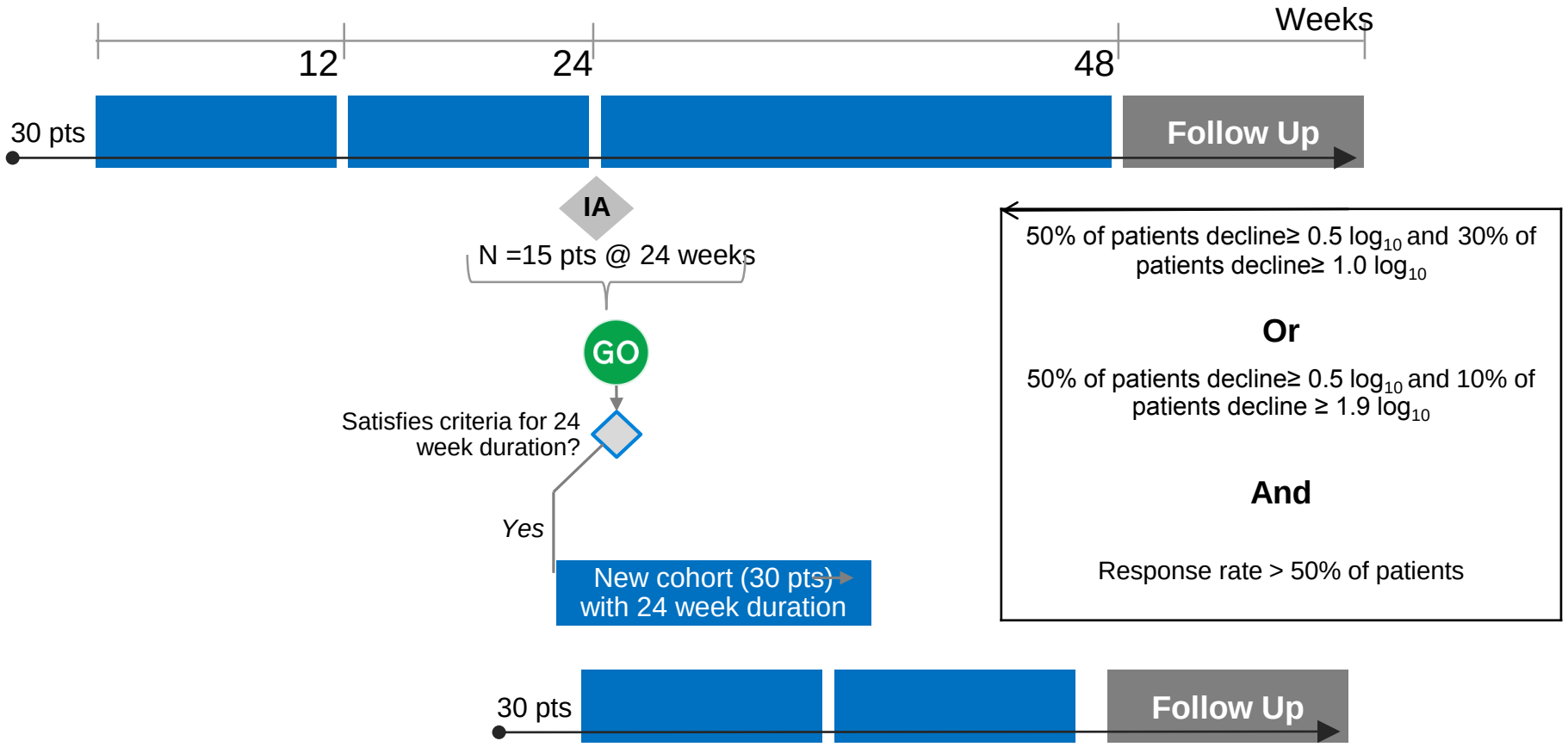
1st Interim – new 24 week duration cohort



IA = interim analysis

Adaptive Data Driven Design for Phase 2

2nd Interim – new 24 week duration cohort

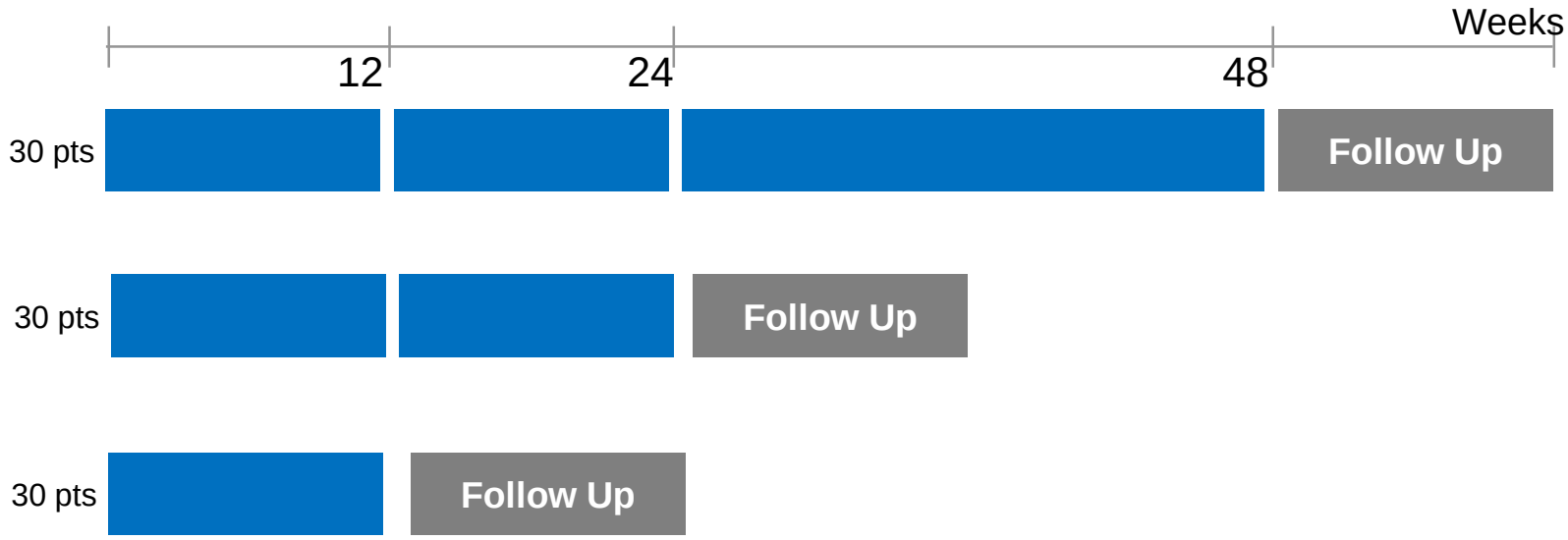


IA = interim analysis

Adaptive data driven Platform Ph2 design: More nimble, de-risking & cost effective

	Platform Design	Traditional – fixed duration, Ph2a shorter duration then Ph2b longer duration
Pros	• Optimal Tx duration currently unknown, adaptive design de-risks uncertainty & will identify optimal Tx duration • Planning for Ph2 adaptive design up to max. 48 wks • Save PVCs cost of 4 separate studies Traditional • Can easily compare combination arms • Saves FTEs costs • One master protocol is designed to support different combinations. • Potential to be more nimble • Re-cycle pts: Controls, potentially killed combos • Potential to be more attractive to pts – increased chance for active Tx	• Starting with shorter Tx duration Ph2a study, with subsequent longer Ph2b study • Simple to design and analyse. • Clear answer from the single trial.
Cons	• More complex, lack of internal experience • HC/EC acceptance is unknown to date in this disease area • Statistical methods more complex.	• Not efficient – uses more patients. • Multiple protocols specific per molecule • Higher cost in PVCs and FTEs • Difficult to compare combination arms due to site/country differences

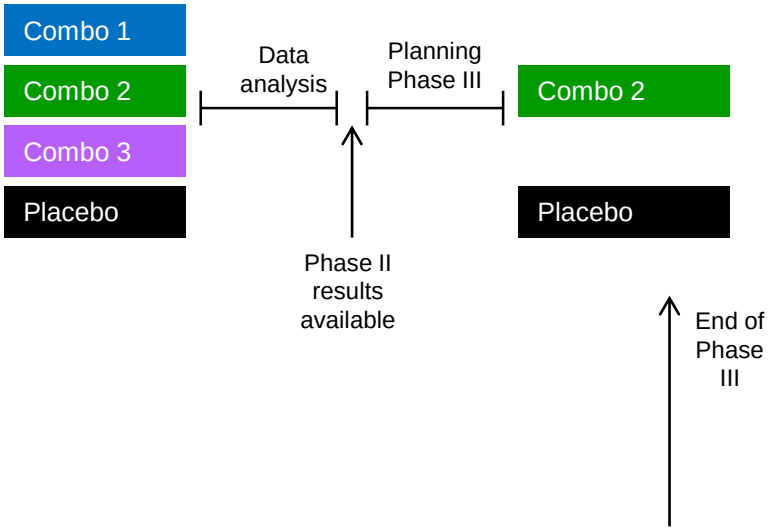
What Could Have Been the Alternative?

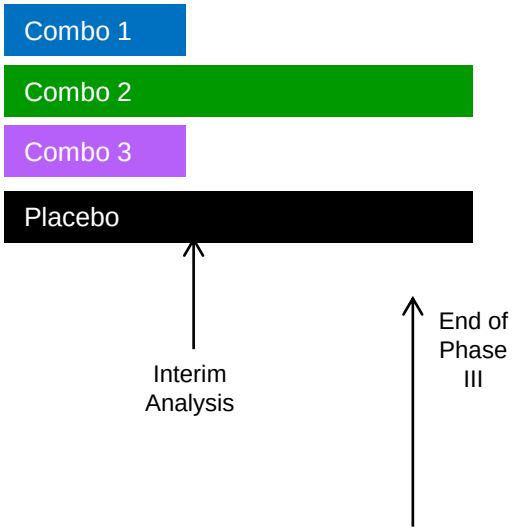


- Nice and simple except if 48 weeks treatment is still the best 60 patients have been wasted.
- The adaptive design only opens up different treatment regimens if there is evidence to do so

IA = interim analysis

Seamless Ph2/Ph3 design





	Seamless Ph2/Ph3	Traditional
Pros	• Eliminates white space between Phase II and III • Increased efficiency with patients from Phase II included in Phase III analysis. • Speeds up Phase III	• Easy to analyse. • Decision to go to Phase III made off Phase II data. • Sponsor sees data from Phase 2 before into Phase 3.
Cons	• Decision to go to Phase III may not be in the hands of the sponsor. • Ph3 design from Seamless design will need upfront agreement from HA at end of Ph1 meetings together with Ph2, unclear experience & acceptance	• Uses more patients as there are two trials. • White space

The Infectious Disease Problem

Traditional Development

Adaptive Platform Trial

Next Steps

Next Steps

- This is a concept accepted at senior management level – details need to be added
- Simulate the designs and refine according to operating characteristics
- Decision criteria are generic at the moment but may need to be refined for different combinations
- Present to regulatory authorities gain their feedback
- Present design at external meetings and conferences
- How do we make this work?

Doing now what patients need next