

Trial, Interrupted

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Ingram Olkin Forum Series

Trial Disruptions

- Trials can be disrupted so that normal procedures are not possible.
- Disruption can motivate design changes
- Changes should respect the basic tenets of clinical trials

Respect Randomization



- *Randomized clinical trials are the greatest medical invention ever*
- Respect randomization
 - Keep the groups pristine
 - Keep the intervention pristine
 - Keep the outcome pristine
- Be creative and responsive
- Unplanned blinded adaptations
 - Be careful
 - Use permutation to be sure

Example #1 mAbs for malaria

- Malaria is parasitic disease spread by mosquitoes
- Young children receive daily prophylactic drugs
 - Inconvenient
 - Non-compliance
- Monoclonal antibodies seasonal protection with 1 administration?
- Plan
 - Establish acceptable dose & efficacy in Bethesda
 - Do a field trial in Mali children

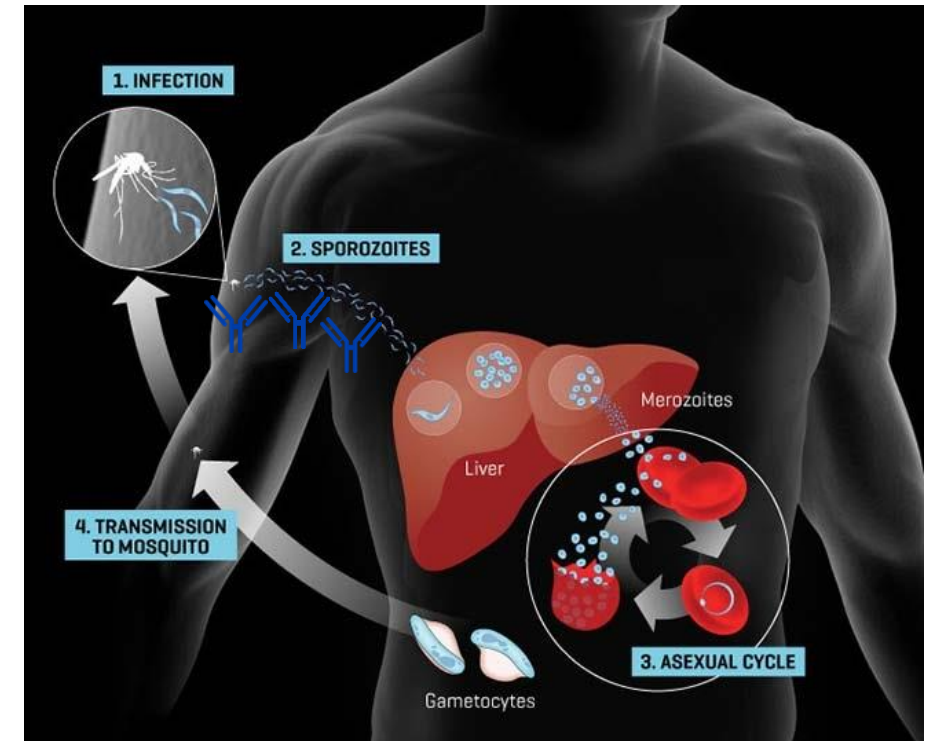
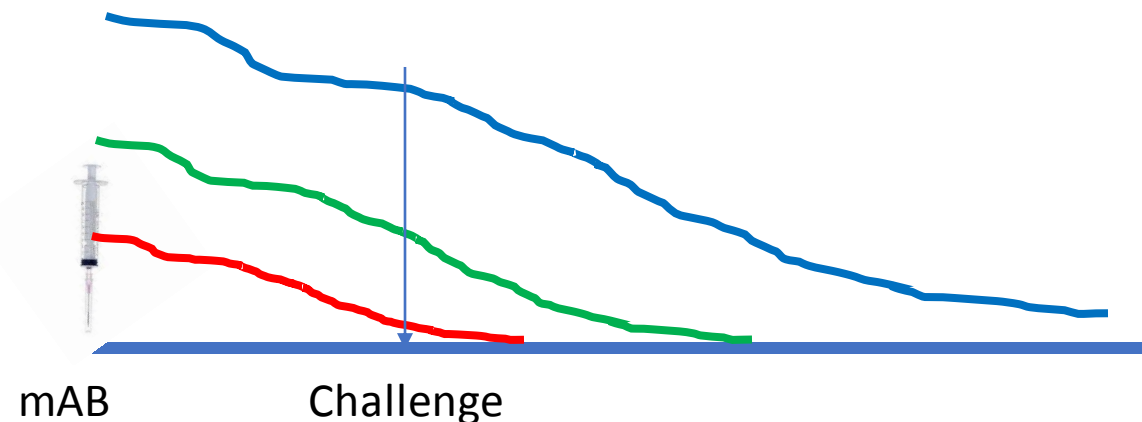
VRC 612: Human challenge trial of malaria mAb

- Part A: Dose Evaluation

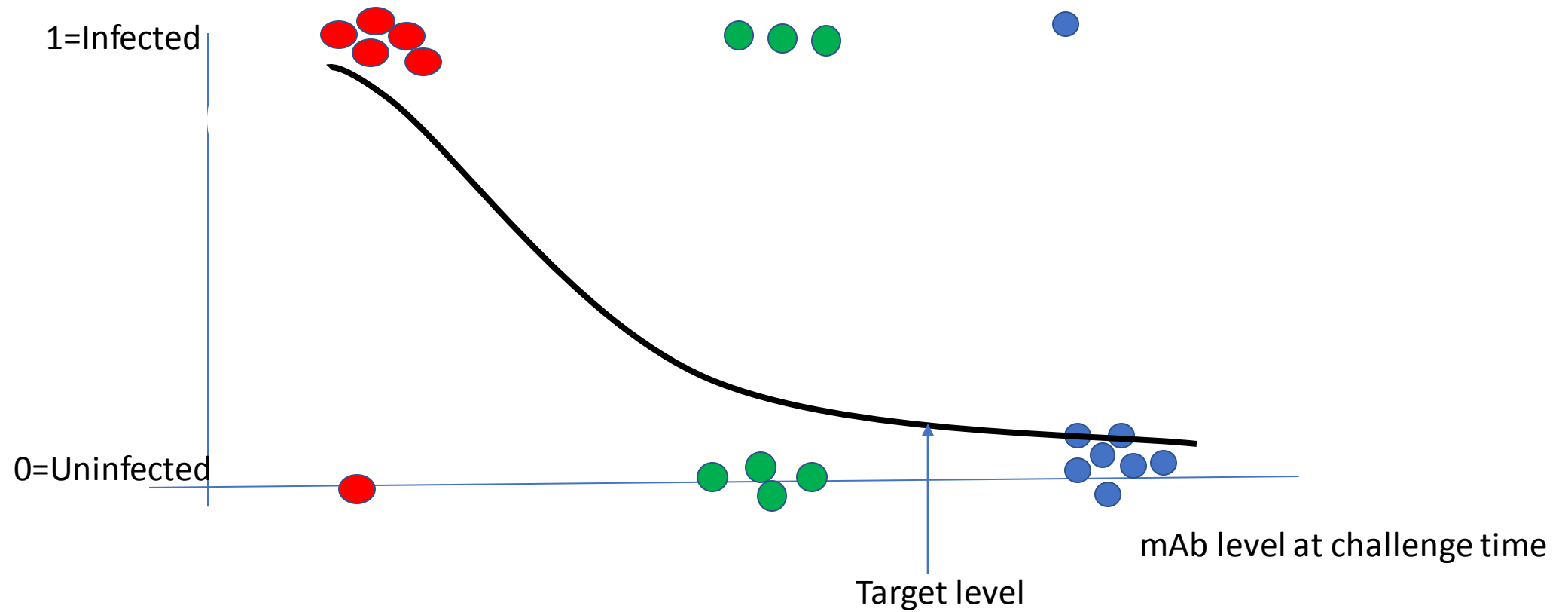
- 5 mg/kg
- 20 mg/kg
- 40 mg/kg

- Part B: Human challenge

- Give volunteer malaria parasites



Correlate of Risk



Fit a logistic regression model $Y = \text{Infection Indicator}$
Identify a mAb level where hardly anyone is infected

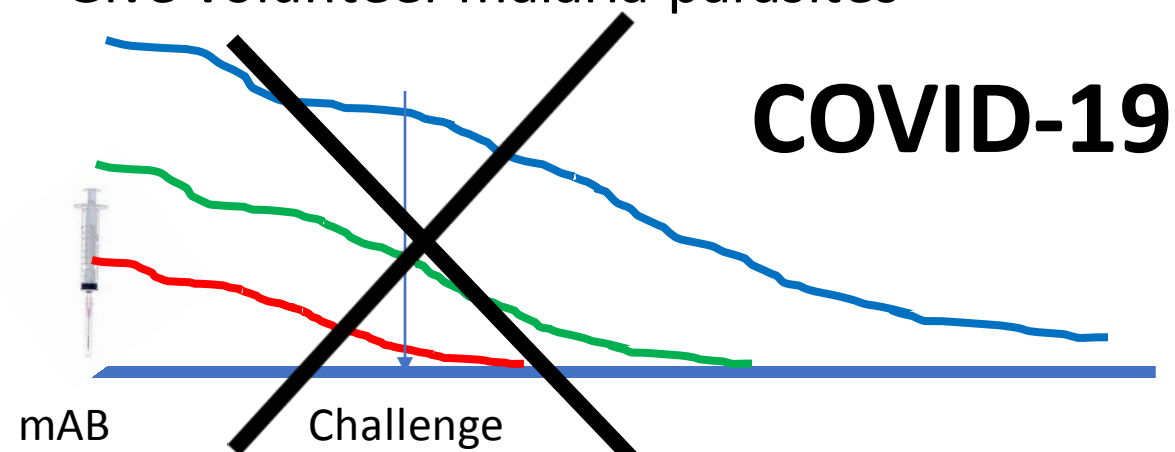
VRC 612: Human challenge trial of malaria mAb

- Part A: Dose Evaluation

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- Part B: Human challenge

- Give volunteer malaria parasites



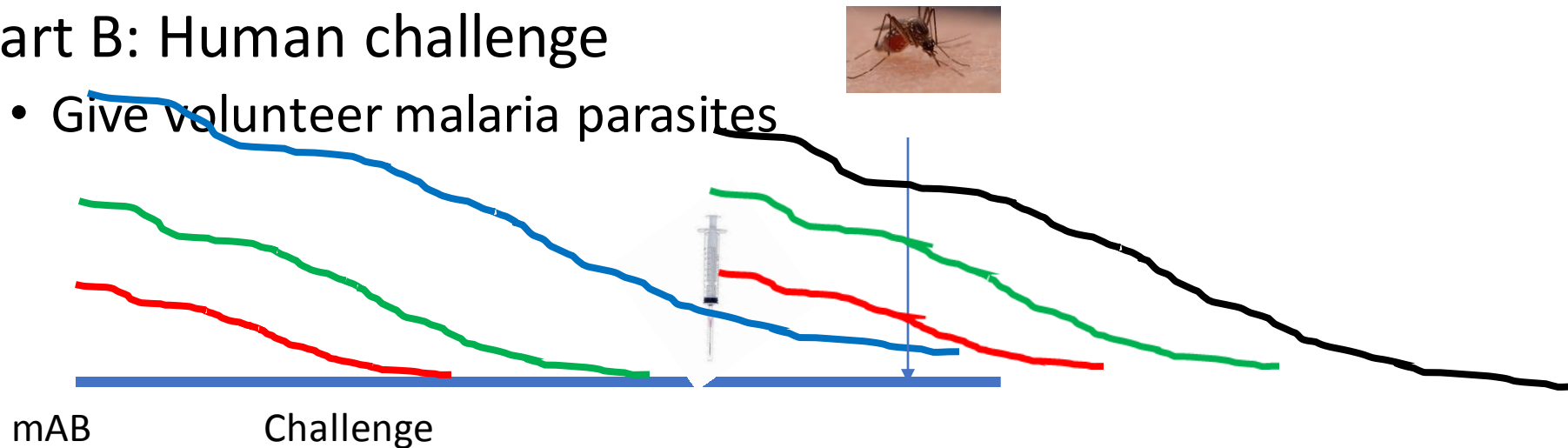
VRC 612: Adaptation

- Part B: Dose Evaluation

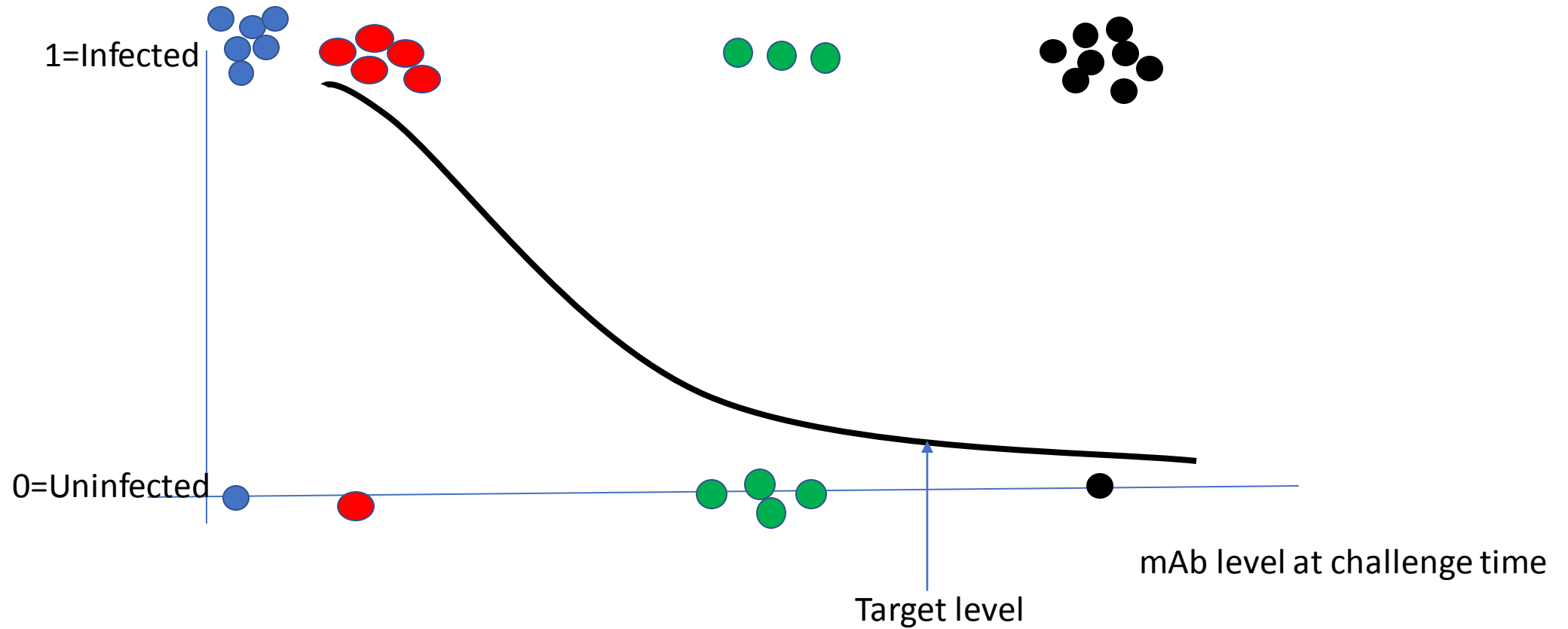
- 5 mg/kg
- 20 mg/kg
- 40 mg/kg
- 40 mg/kg 6 months ago

- Part B: Human challenge

- Give volunteer malaria parasites



Correlate of Risk




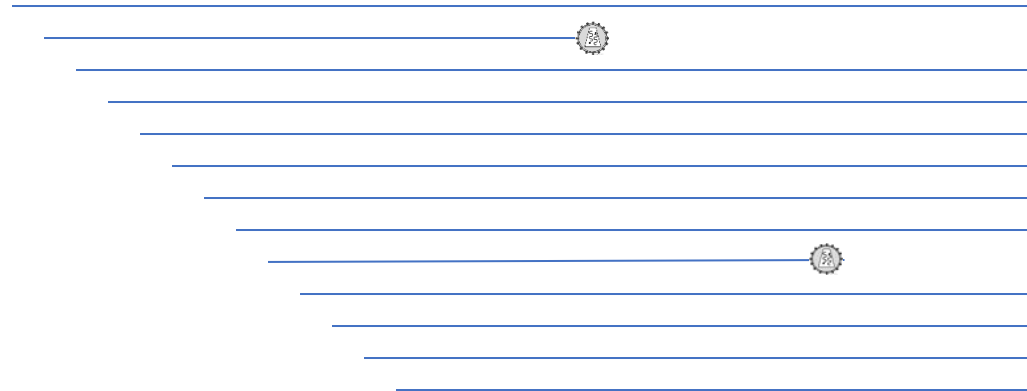
Fit a logistic regression model $Y = \text{Infection Indicator}$
Identify a mAb level where hardly anyone is infected

Example #2: HIV prevention


- Blinded randomized trial of 3200 women at risk of HIV infection
 - Injectable cabotegravir: every 8 weeks
 - Oral tenofovir: daily
- Accrual 2 years
 - Follow-up 1.6 – 3.6 years
- Analysis
 - Cox model with treatment indicator and stratified by site
 - Intent-to-treat analysis

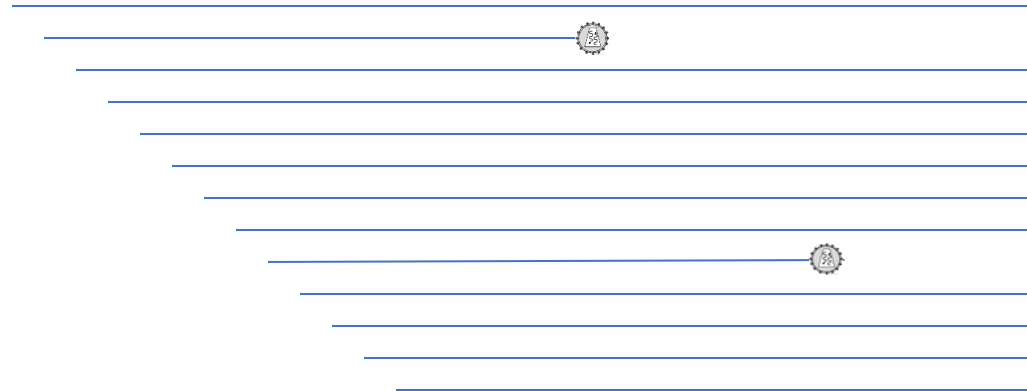
Follow-up

 HIV infection




COVID-19 interruption

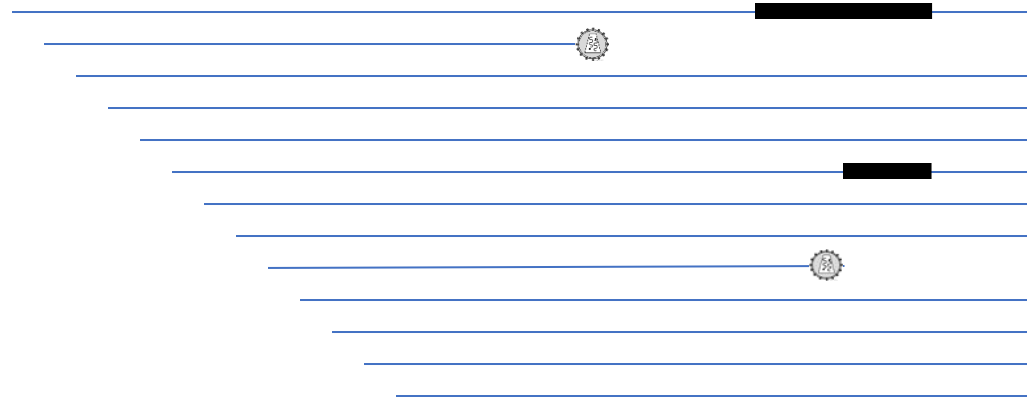
 HIV infection




COVID-19

COVID-19 interruption

 HIV infection



COVID-19

 Periods of site disruption

Adaptation based on COVID-19

- Blackout periods = disruption
 - Study product not available
 - Define periods of potential disruption
- An adjudication committee will define the period(s) of disruption for each site. The adjudication committee will be *blinded* to the number of infection events detected after April 2020.

Cox Model -> Anderson Gill

- Simpler version

- Estimated treatment effect = $1 - \frac{R_I}{R_D} R_Z = \frac{\text{Number of Events on Arm Z}}{\text{Total Followup on Arm Z}}$

- Anderson Gill

- Remove volunteers from the risk set during periods of disruption
 - Re-enter HIV-negative volunteers into the risk set after period of disruption

Patient	Start	Stop	HIV
1	0	4.3	0
2	0	3.6	1
3	0	2.4	0

Cox

Patient	Start	Stop	HIV
1	0.0	3.8	0
1	4.0	4.3	0
2	0.0	3.1	0
2	3.3	3.6	1
3	0.0	2.2	0

Anderson-Gill

FDA Guidance on Adaptation

Adaptive Designs for Clinical Trials of Drugs and Biologics Guidance for Industry

- *In general, adequately **pre-specified** adaptations based on non-comparative data have no effect or a limited effect on the Type I error probability.*
- <https://www.fda.gov/media/78495/download>

Received 30 September 2011, Accepted 4 February 2012 Published online 27 June 2012 in Wiley Online Library

(wileyonlinelibrary.com) DOI: 10.1002/sim.5361

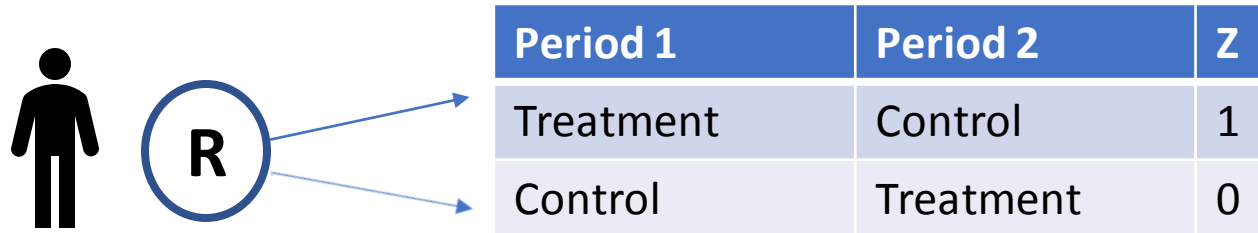
Unplanned adaptations before breaking the blind

Martin Posch^{a*†‡} and Michael A. Proschan^b

Occasionally, things go so wrong in a clinical trial that a change must be made. For example, the originally planned primary outcome may be measured completely unreliably. Is there any recourse? One may still be able to salvage the trial using a permutation test if a change is made before breaking the treatment blind. The solution is not a panacea; we discuss the limitations and legitimate grounds for criticism. Still, when it is needed, the procedure is preferable to rigid adherence to a design that makes no sense. Published 2012. This article is a US Government work and is in the public domain in the USA.



Crossover trial



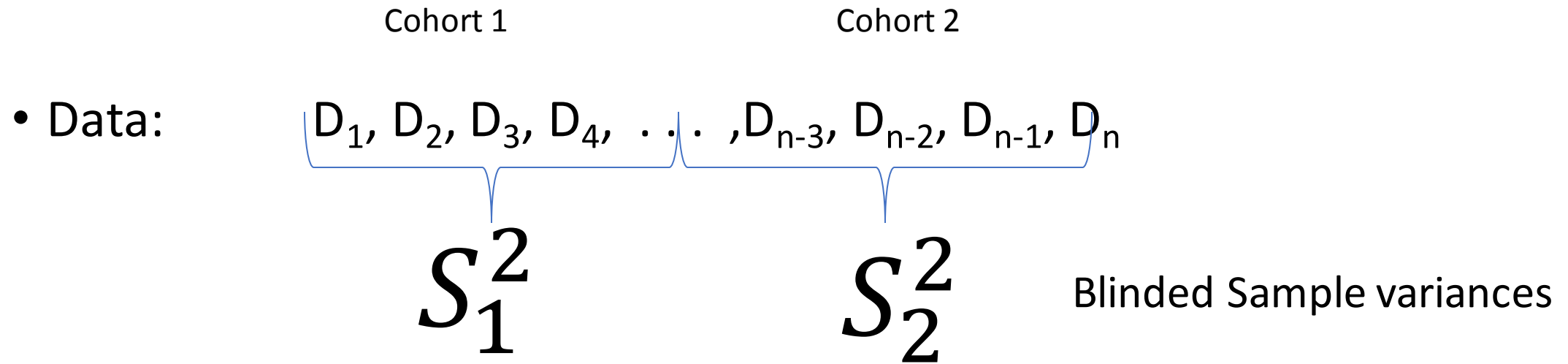
D = Period 1 Outcome –
Period 2 Outcome

Data: $D_1, D_2, D_3, D_4, \dots, D_{n-3}, D_{n-2}, D_{n-1}, D_n$
 $Z_1, Z_2, Z_3, Z_4, \dots, Z_{n-3}, Z_{n-2}, Z_{n-1}, Z_n$

Analysis: one-sample t-test using

$$Y = Z D - (1-Z)D = \text{Treatment} - \text{Control}$$

Blinded adaptation



Blinded Adaptive t-test BAT

Use the smaller variance

$$\frac{\bar{Y}}{\sqrt{S_{(1)}^2 / (n-1)}}$$

The advantage

n	# cohorts	Type I error rate
20	2	.08
160	2	.06
640	2	.05

n	# cohorts	Type I error rate
20	4	.14
160	4	.08
640	4	.06

Real world example: Pick the 'most efficient' Wald test statistic

Numerator unbiased

Pick smallest denominator

Can we save ourselves from well-intentioned adaptations that cheat?

Permutation = Salvation

- Data: $D_1, D_2, D_3, D_4 = (0.4, -0.3, 0.5, -0.1)$
 $Z_1, Z_2, Z_3, Z_4 = (1, 0, 1, 0)$ $\longrightarrow S_{(1)}^2 = 0.13$

- Analysis: Permutation Distribution of BAT

Permutation	Mean Difference $\bar{Y} = ZD - (1-Z)D$	BAT = $\frac{\bar{Y}}{\sqrt{S_{(1)}^2/(n-1)}}$
1100	-0.075	-0.036
1010	0.325	1.56
1001	0.025	0.12
0110	-0.025	-0.12
0101	-0.325	1.56
0011	0.075	0.036

$\longrightarrow p=1/6$

Permutation Punishes Sneakiness

- Use Drug as proxy for treatment indicator



- `Blinded' adaptations:
 - Pick best of 17 different tests
 - Double the sample size if t-test p-value >0.05 .

Outcome	Drug Level	Treatment Indicator
8	1.1	?
3	0.0	?
9	1.2	?
4	0.0	?
7	1.4	?
1	0.0	?

- Permutation Punishment

- Null: Treatment has no effect on outcome, *drug level*



Blinded unplanned adaptations



- COVID-19 interruptions may lead to unplanned adaptations
 - Respect randomization
 - Be creative
- Unplanned blinded adaptations can be fine
 - Can use permutation distribution for inference
 - Read Posch & Proschan 2011

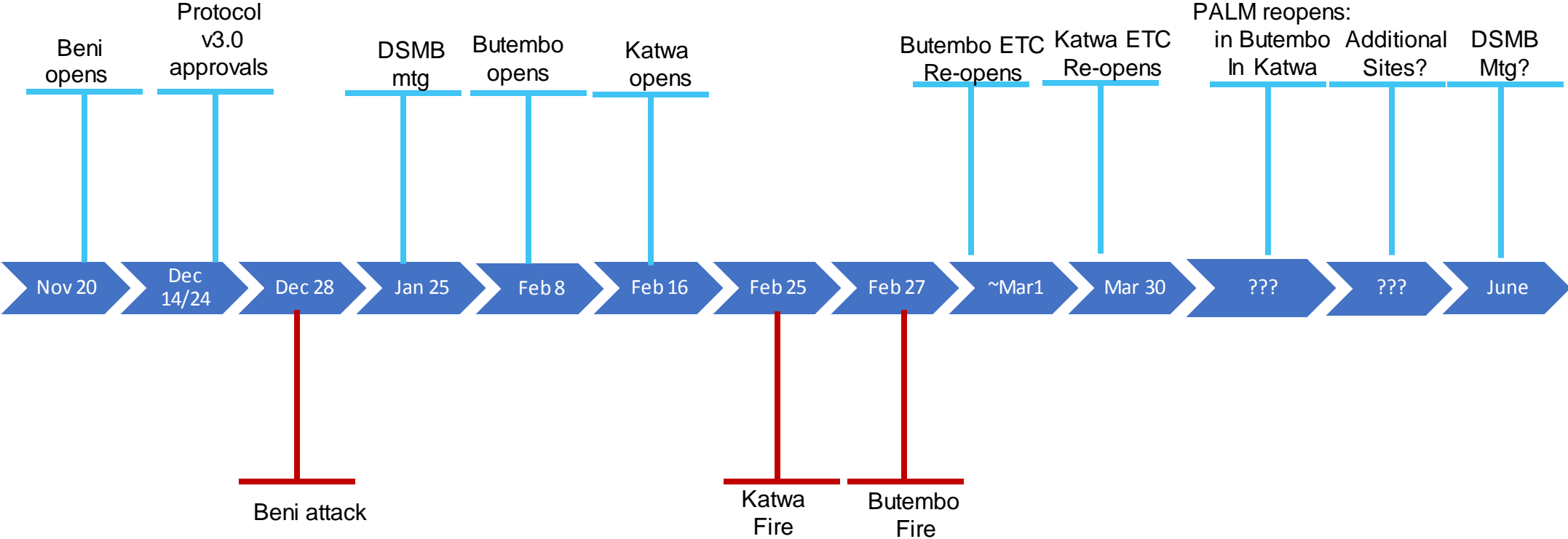


Summary

PALM Fire and Ice

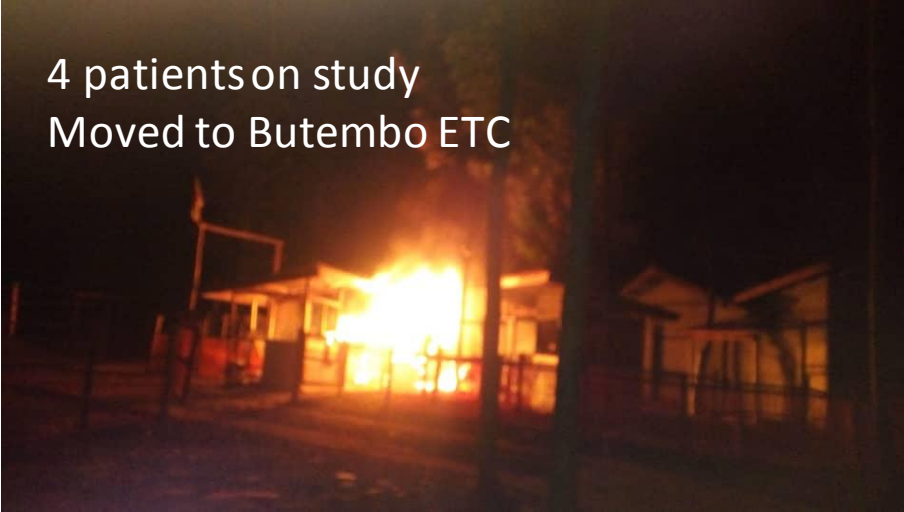
- Compare 28-day mortality in EVD patients who receive investigational therapeutics relative to Zmapp
- 1:1:1:1 randomization to Zmapp, Mab114, Remdesivir, Regeneron
Regeneron added in Protocol v.3.0 on 12Dec2018
- Sample size: 500 EVD patients
85% power to detect a 50% improvement in 28-day mortality from 30% (Control) to 15%
- Multi-outbreak, multi-country

Trial Timeline



Katwa ETC Fire: 25 Feb 2019

Butembo ETC Fire: 27 Feb 2019



4 patients on study
Moved to Butembo ETC



6 patients on study + 4 patients
moved from Katwa



CRF binders were here



PALM
Investigator

Home (Accueil)

Investigator
(Chercheur)

Enrollment

[Enrollment Report](#)

[CRF Entry Tracking Report](#)

SITE/North Kivu,
DRC



INRB Coordinating
Center, Kinshasa, DRC



Data flow in remote, high-conflict region

- CRFs uploads were current up to day of fire.
- Three randomization assignments day of fire.
 - Participant data recovered
- No missing primary outcome data

NIAID/DCR, Bethesda

