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

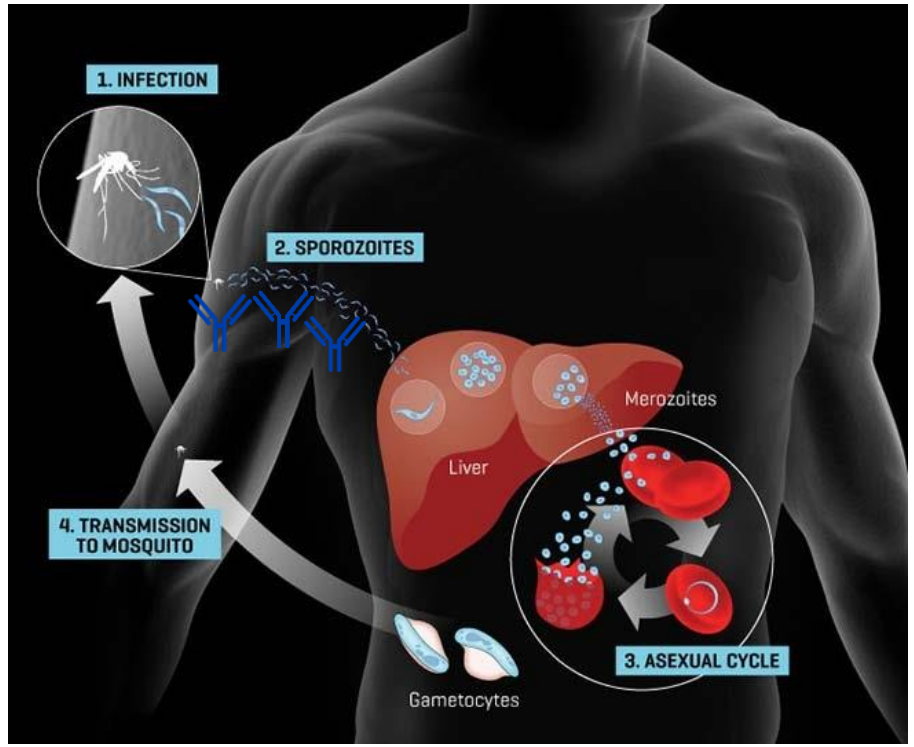
- *Randomized clinical trials are the greatest medical invention ever*
- Respect randomization
  - Keep the groups pristine
  - Keep the intervention pristine
  - Keep the outcome pristine
- Be creative and responsive
- Unplanned blinded adaptations
  - Be careful
  - Use permutation to be sure

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 adminstration?
- Plan
  - Establish acceptable dose & efficacy in Bethesda
  - Do a field trial in Mali children

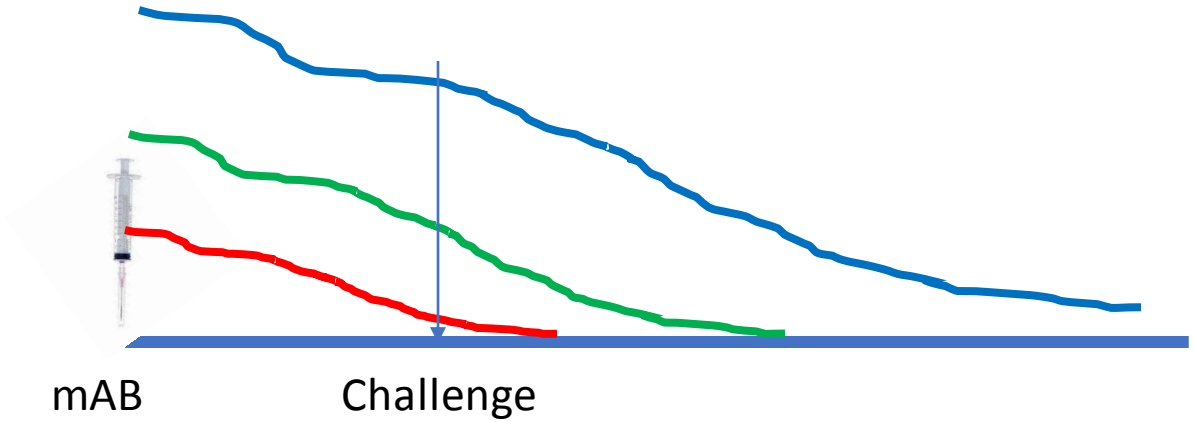
VRC 612: Human challenge trial of malaria mAb

- Part A: Dose Evaluation
  - 5 mg/kg
  - 20 mg/kg
  - 40 mg/kg

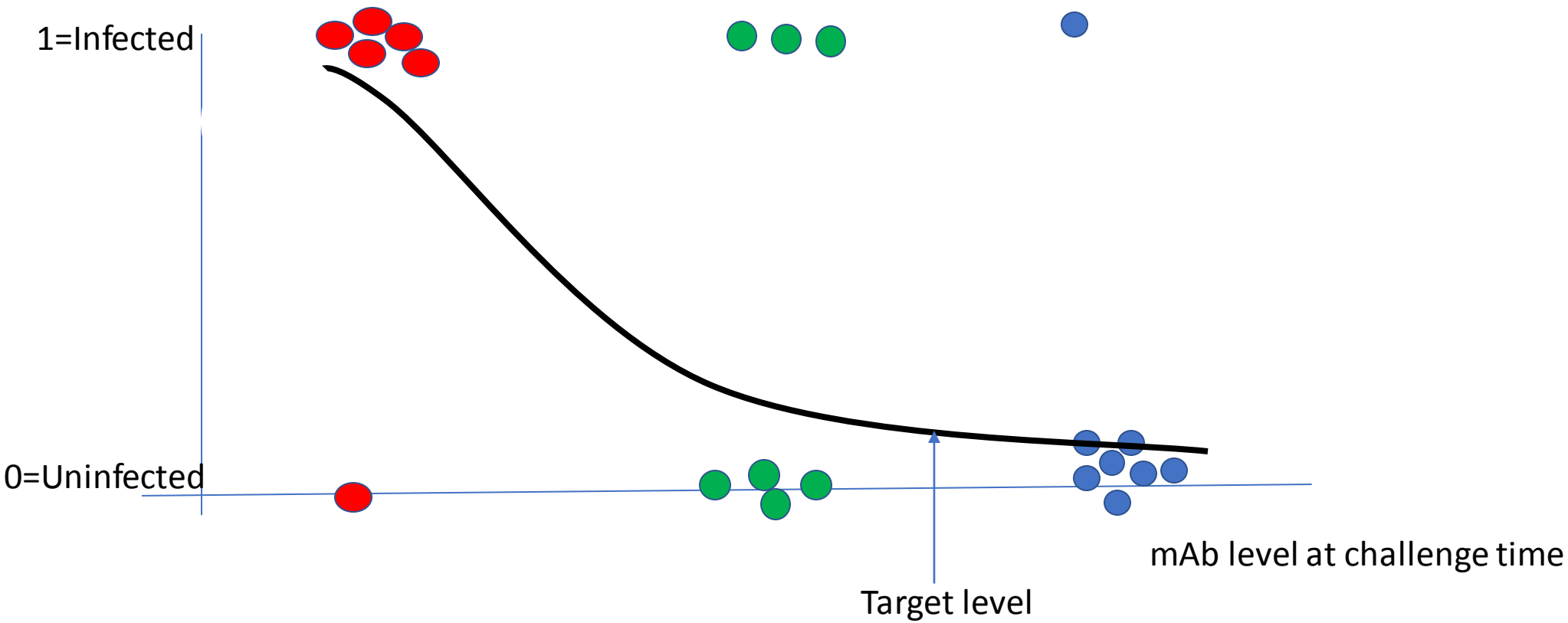


- Part B: Human challenge

  - Give volunteer malaria parasites



Correlate of Risk

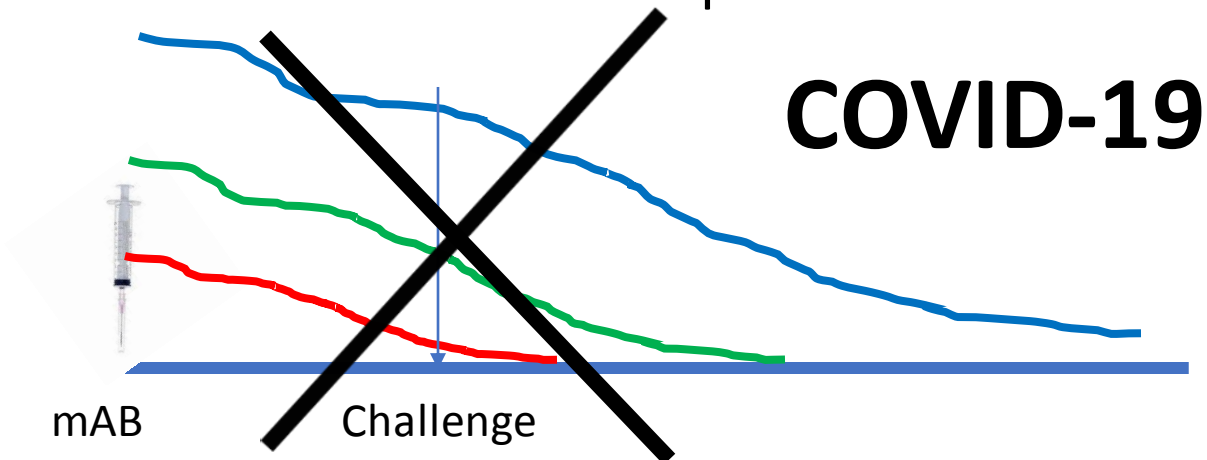


Fit a logistic regression model Y=Infection Indicator
Identify a mAb level where hardly anyone is infected

VRC 612: Human challenge trial of malaria mAb

- Part A: Dose Evaluation
  - 5 mg/kg
  - 20 mg/kg
  - 40 mg/kg

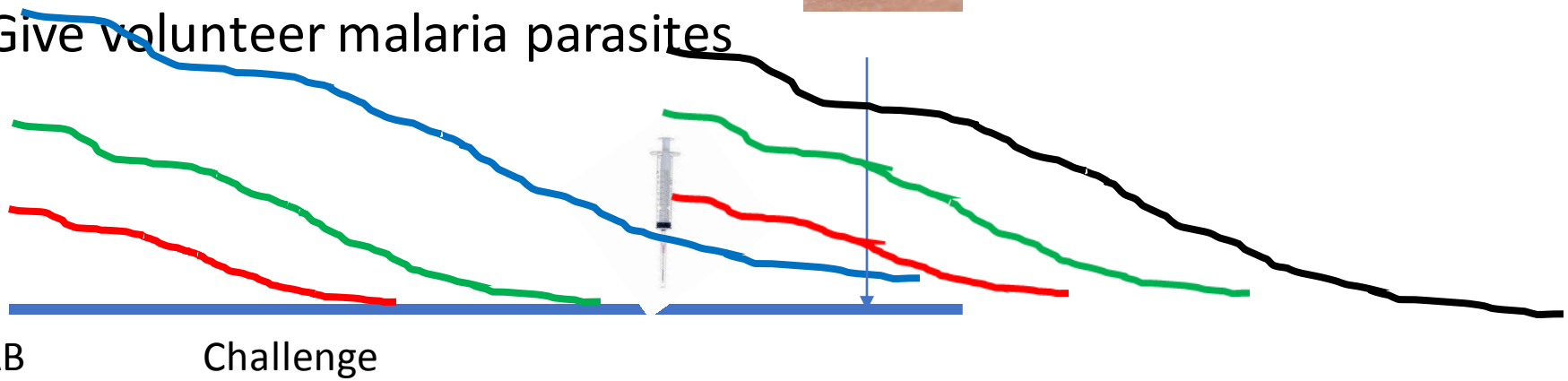
- Part B: Human challenge 
  - Give volunteer malaria parasites



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



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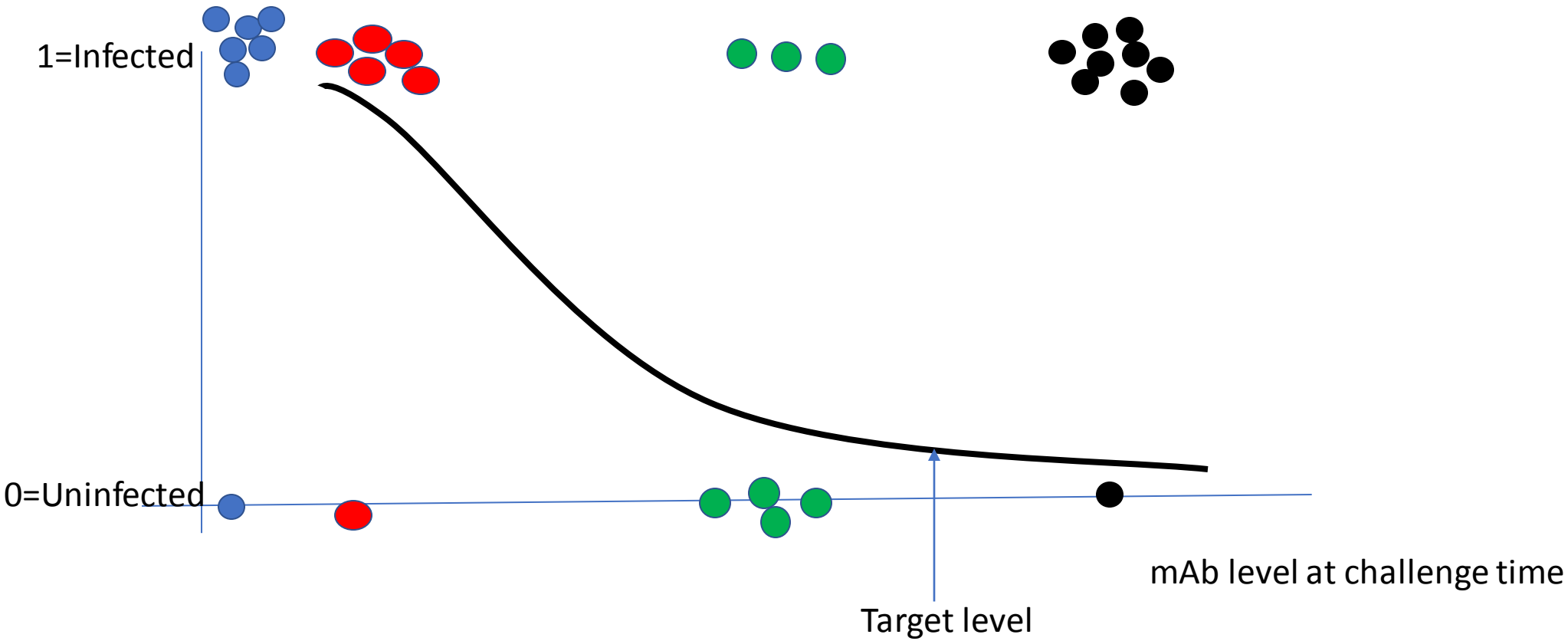
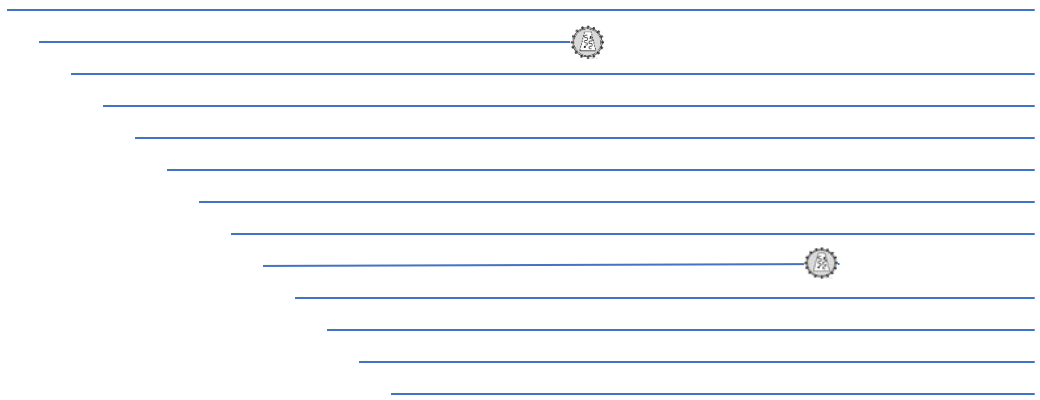


Fit a logistic regression model Y=Infection Indicator
Identify a mAb level where hardly anyone is infected

Example #2: HIV prevention

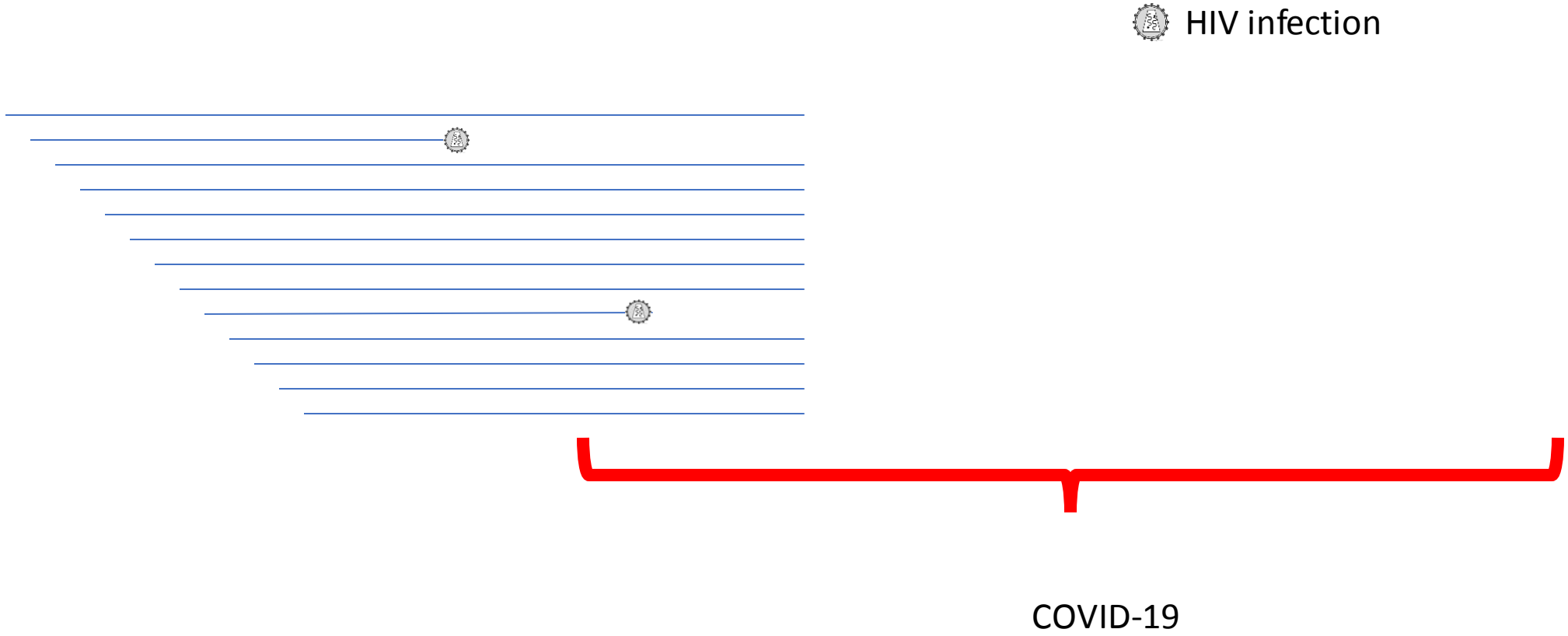
- Blinded randomized trial of 3200 women at risk of HIV infection
  - Injectable cabotegravir: every 8 weeks
  - Oral tenofovir: daily
- Accrual 2 years
  - Follow-up 1.6 – 3.6 years
- Analysis
  - Cox model with treatment indicator and stratified by site
  - Intent-to-treat analysis

Follow-up

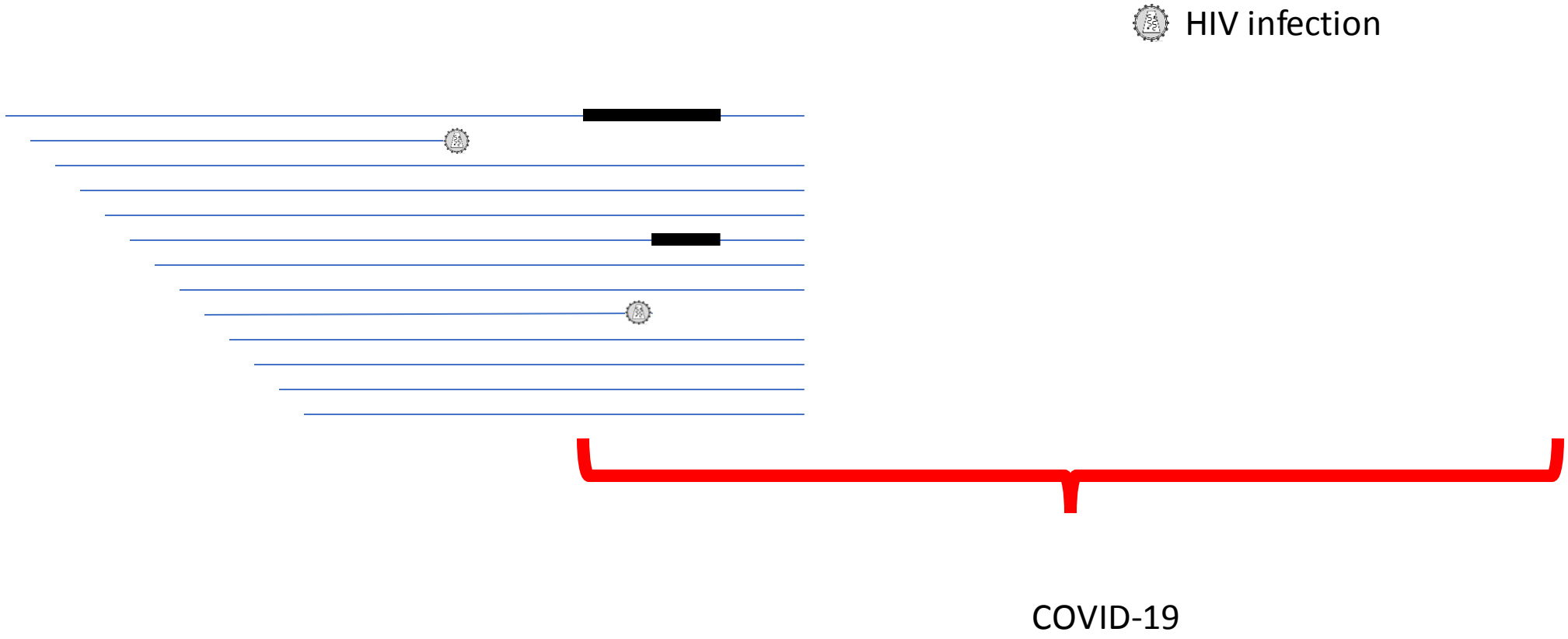


HIV infection

COVID-19 interruption



COVID-19 interruption



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 = $1 - \frac{R_I}{R_D}$ $R_z = \frac{Number\ of\ Events\ on\ Arm\ Z}{Total\ Followup\ on\ Arm\ Z}$
- 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

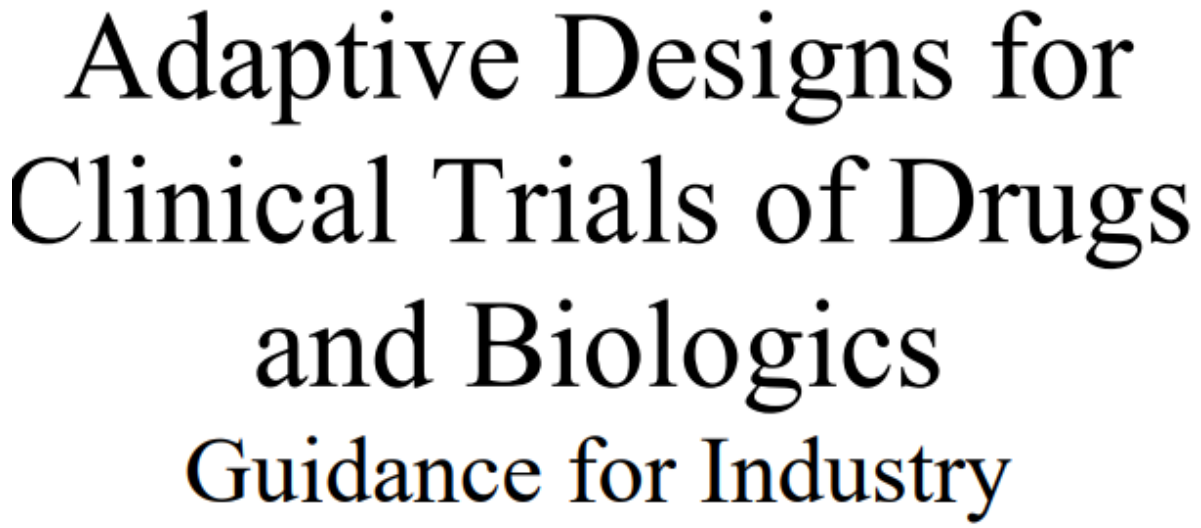
Patient	Start	Stop	HIV
1	0	4.3	0
2	0	3.6	1
3	0	2.4	0

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



- *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

Statistics
in Medicine

Special Issue Paper

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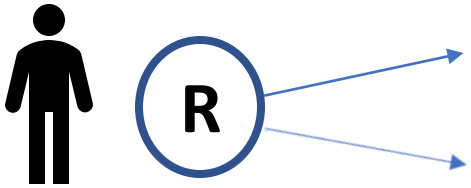
(wileyonlinelibrary.com) DOI: 10.1002/sim.5361

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



Period 1	Period 2	Z
Treatment	Control	1
Control	Treatment	0

D = Period 1 Outcome – Period 2 Outcome

Data: $D_1, D_2, D_3, D_4, \ldots, D_{n-3}, D_{n-2}, D_{n-1}, D_n$

$Z_1, Z_2, Z_3, Z_4, \ldots, Z_{n-3}, Z_{n-2}, Z_{n-1}, Z_n$

Analysis: one-sample t-test using

$Y = Z\,D - (1-Z)D$ = Treatment – Control

Blinded adaptation

Cohort 1 Cohort 2

- Data: $D_1, D_2, D_3, D_4, \ldots, D_{n-3}, D_{n-2}, D_{n-1}, D_n$

S_1^2 S_2^2 Blinded Sample variances

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: $D_1, D_2, D_3, D_4 = (0.4, -0.3, 0.5, -0.1)$

  $Z_1, Z_2, Z_3, Z_4 = (1, 0, 1, 0)$

→ $S^2_{(1)} = 0.13$

- Analysis: Permutation Distribution of BAT

Permutation	Mean Difference $\bar{Y}$ = Z D - (1-Z)D	BAT = $\frac{\bar{Y}}{\sqrt{S^2_{(1)}/(n-1)}}$
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

→ 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

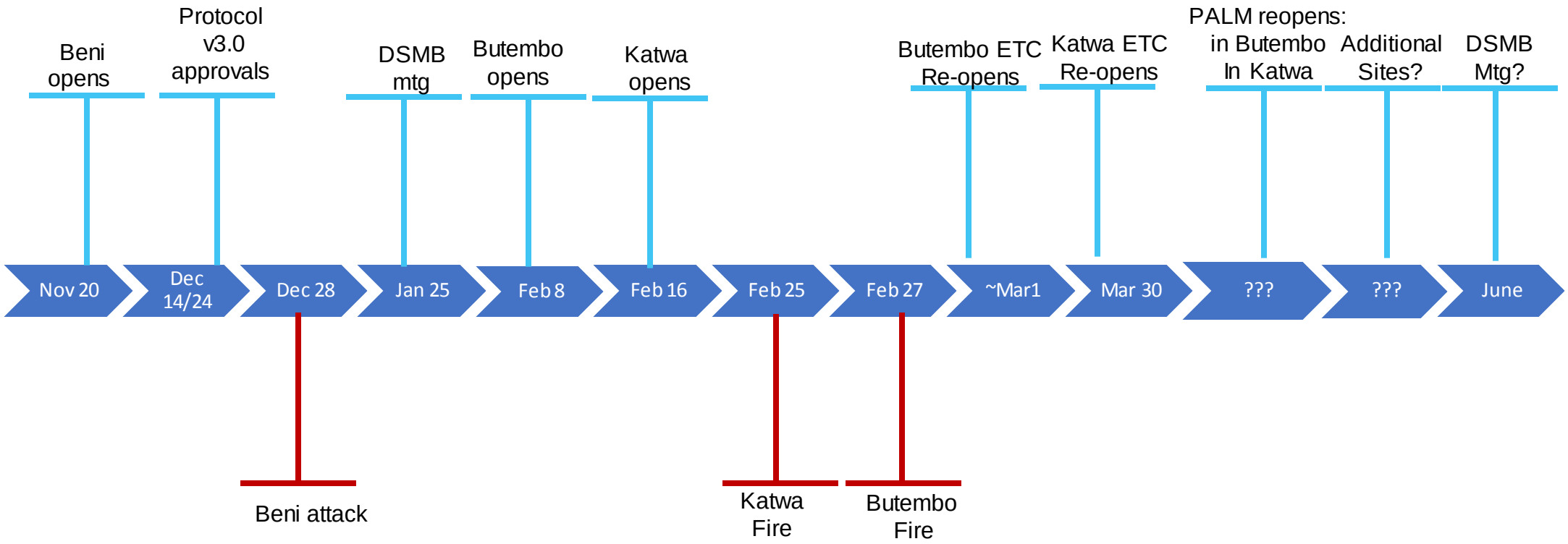
PALM Fire and Ice

- 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

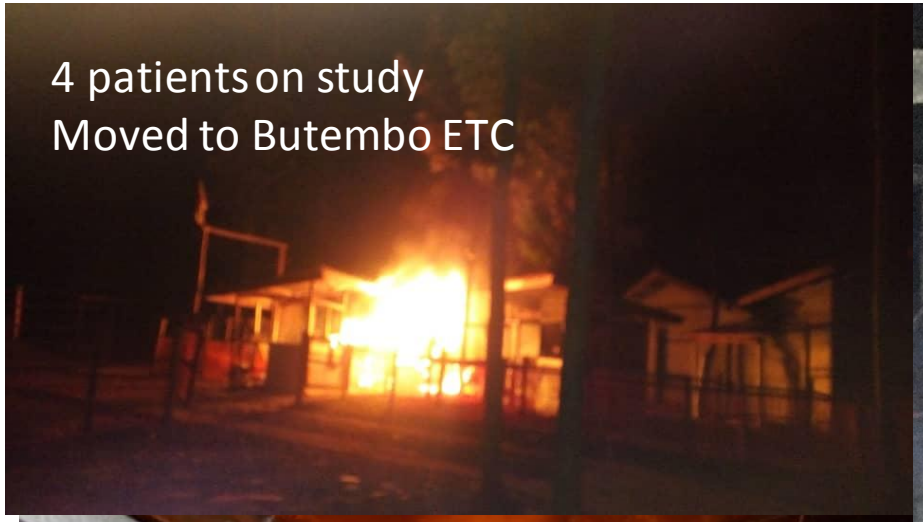
  85% power to detect a 50% improvement in 28-day mortality from 30% (Control) to 15%
- Multi-outbreak, multi-country

Trial Timeline



Katwa ETC Fire: 25 Feb 2019

Butembo ETC Fire: 27 Feb 2019



SCHOOL OF PUBLIC HEALTH
UNIVERSITY OF MINNESOTA

PALM
Investigator

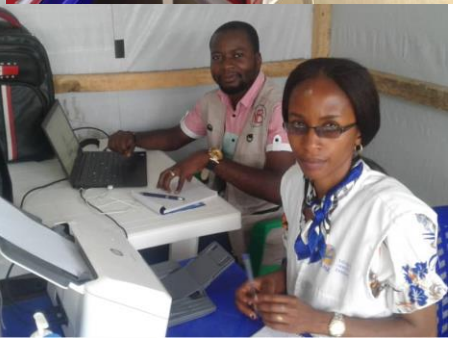
Home (Accueil)
Investigator (Chercheur)

Enrollment
Enrollment Report
CRF Entry Tracking Report

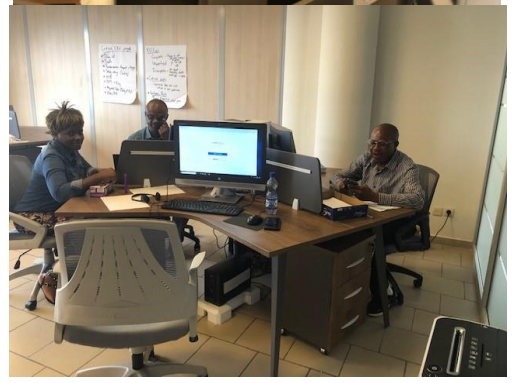
Data flow in remote, high-conflict region

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

SITE/North Kivu, DRC



INRB Coordinating Center, Kinshasa, DRC



NIAID/DCR, Bethesda