A Randomized Adaptive Platform Trial Comparing Multiple Treatments for Ebola Virus Disease: Trial EVD-003

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Outline

- The Ebola problem
- Ebola adaptive platform trial (EVD-003)
- Challenges
- Lessons learned
- Preparing for future outbreaks

The Problem: An Ebola Treatment Trial

- Highly infectious virus with a high rate of mortality
- Resource poor setting
- Unknown route of transmission
- Lack of defined standard of care
- Clinical research naïve setting
- No known treatment
- **Our GOAL:** To determine the most effective treatment for Ebola
  - Not a trial to determine if a single drug X works


Guinea
Sierra Leone
Liberia
Côte d'Ivoire
Levels of Transmission
New Active Area
Active
Not Active
Ebola Treatment Units
Laboratory
Transit Center
Hospital
Ebola Treatment Unit (ETU)
United States
Source: WHO: Ebola Response Roadmap
26 September 2014

Ebola Clinical Research Consortium (ECRC)
EVD 003 Team

- Clinical Research Management (ClinicalRM)
- Duke University:
  - Duke Global Health Institute
  - Duke Dept. of Infectious Diseases
  - Duke Clinical Research Institute
- Berry Consultants, Inc.
- Sierra Leone College of Medicine and Health Sciences (COMAHS)
- Collaborations with:
  - USAMRIID
  - The Bill & Melinda Gates Foundation
  - WHO
  - Pharmaceutical industry partners
  - Drug experts
  - Sierra Leone Pharmacy Board

Funding: Bill & Melinda Gates Foundation

Study: EVD 003
Our Requirements

- Wide source of possible treatments:
  - Ongoing preclinical research (USAMRIID and others), so potential therapies will evolve over time
    - Existing antivirals
    - Drug screening of existing drug libraries (repurposed drugs)
    - New compounds (pharma)
    - Blood products (convalescent plasma, IgG etc)
  - Recognition that combinations may play an important role
- Limited inclusion/exclusion criteria to allow a wide study population
- Trial had to be implementable under very difficult conditions
- Ideally, therapies would be easily attainable in a resource limited setting
- Need for a single trial that can incorporate all these options efficiently!

EV-003 Adaptive Platform Design

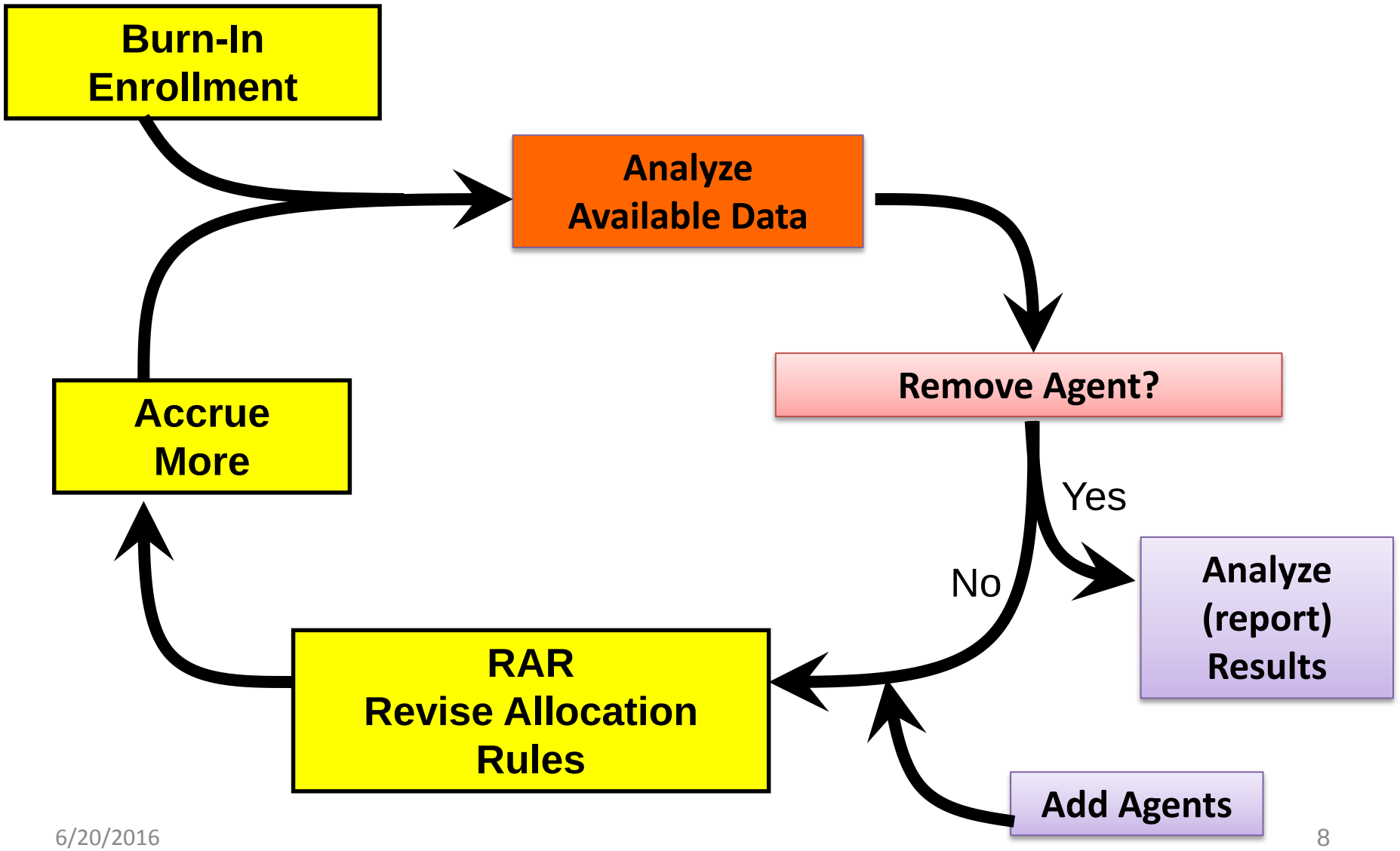
- *Protocol document* dictates trial behavior, with each treatment included as an appendix

- Multiple therapeutic agents:
  - Primary & Secondary agents
  - Single agents and combinations of agents
  - What to do about 'Standard of Care'

- Response Adaptive Randomization (RAR)
  - Run by a single algorithm
  - Assigns treatment regimens that are performing better using collection of primary endpoint data

- Protocol is built so that trial arms evolve as part of the protocol! The trial is <u>perpetual.</u>

Adaptive Platform Design



Primary/Secondary Agents

- All arms receive optimized standard of care (SOC)
- Primary and Secondary agents
  - **Primary:** Expected capability to work as single agent (e.g. anti-viral efficacy)
  - **Secondary:** Expected to work in combination with other agents (not given alone)

Regimens		Treatments					
		P1	P2	P3	P4	S1	S2
Treatments	P1						
	P2						
	P3						
	P4						

Challenges

The only (and most difficult!) time to study Ebola is during an outbreak, which meant:

- No defined standard of care
- Very limited resources (oral rehydration only)
- Lack of infrastructure
- No known treatment, so ethical considerations in excluding vulnerable populations
- Large counterfeit drug market in West Africa
- Community resistance to clinical trials
- How to maintain safety with so many variables?
- Desire for registrational trials by pharma
- Lack of trained research staff
- Regulatory / ethical systems overwhelmed = delays

Overcoming Challenges

- No defined standard of care - define a SOC for the study
- Very limited resources (oral rehydration only) – provision of SOC medications/supplies by the study
- Lack of infrastructure – provision of generators/supplies; creativity!!
- No known treatment, so ethical considerations in excluding vulnerable populations – flexibility to include all vulnerable populations in the study design
- Large counterfeit drug market in West Africa – ship drugs in from trusted sources overseas
- Community resistance to clinical trials. Community involvement and education as early as possible
- How to maintain safety with so many variables? Adaptive design with randomization rules
- Desire for registrational trials – design trial as an IND study
- Lack of trained research staff – deploy teams of experienced research staff to kick start trials and train existing staff
- Regulatory/ethical systems overwhelmed – preparedness….

Lessons Learned

- You can never start preparing too early!
- Committees – TEC, Stats
- Need to develop relationships early
- Be creative (e.g. randomization – Plan A, Plan B & Plan C)
- Initially, assume that anything you will need, you will need to bring with you
- Opt for reliable lab equipment with minimal maintenance, that can be run off multiple power sources (e.g. to include car engines!)
- Handheld (POC) devices for laboratory monitoring
- Need to think through how you will get source documents or data out of the hot zone
- Don’t assume getting specimens out of the country will be easy/possible/timely (even if they are for diagnostic testing)

Why we need to be prepared

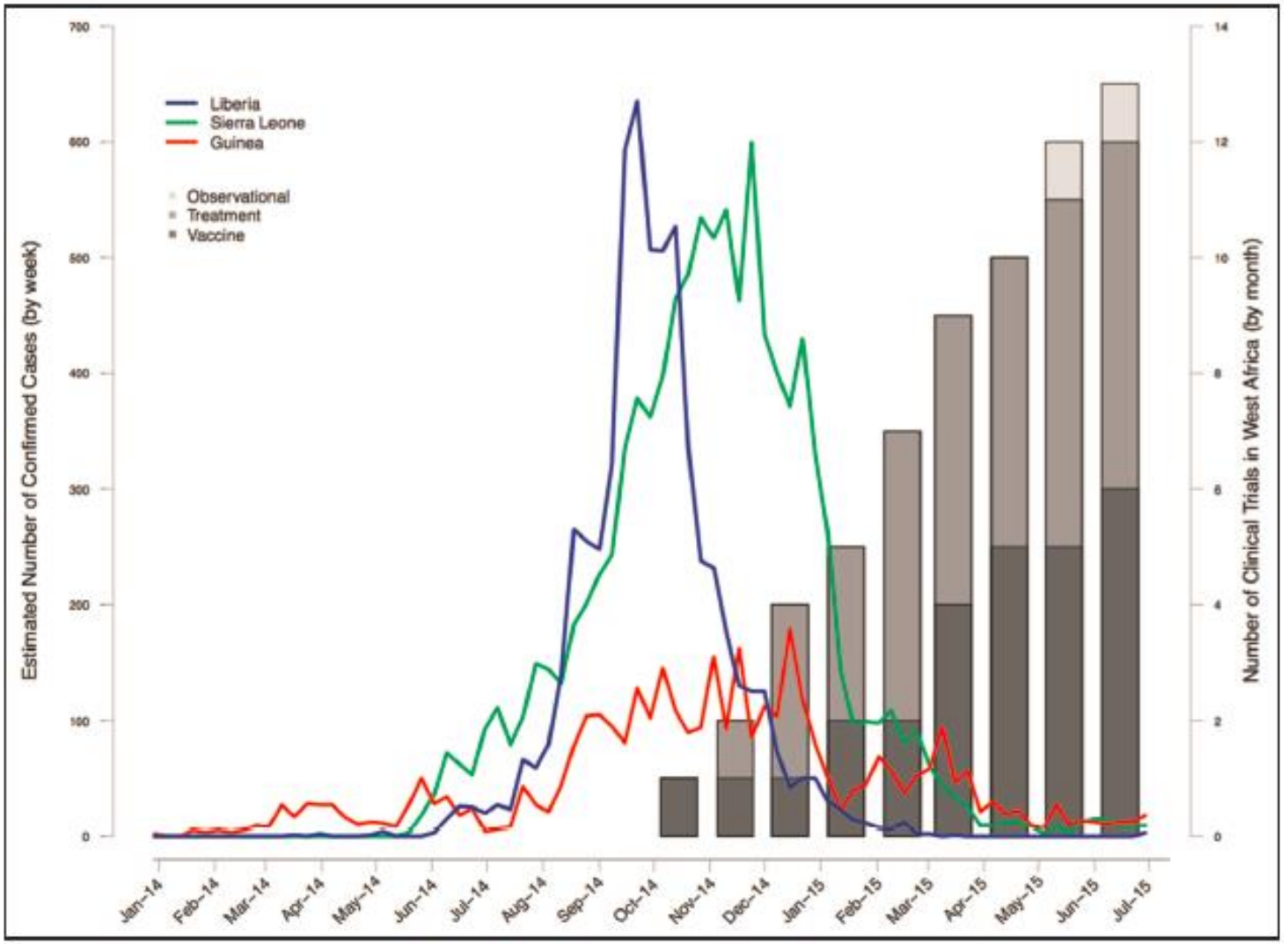


Figure 1. World Health Organization estimates of Ebola cases in West Africa and Ebola clinical trials located in West Africa, as registered at ClinicalTrials.gov.

Future Outbreaks?

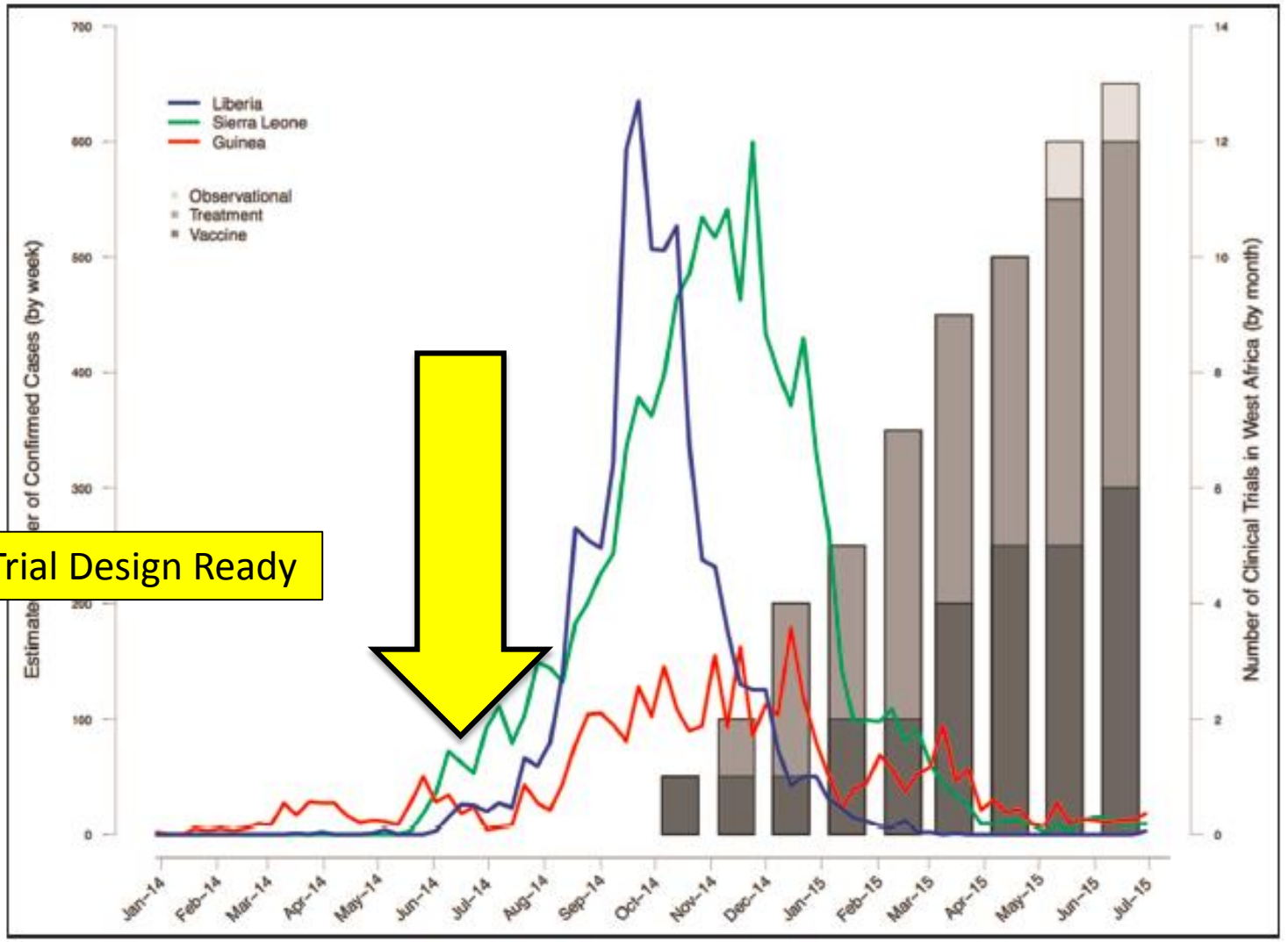
- Lassa fever
- Chikungunya
- Hemorrhagic fever syndrome
- SARS
- West Nile virus
- Influenza
- Dengue fever
- MERS

What can we do to prepare for these?

Emerging Infectious Diseases Preparedness

- Can we construct a master protocol to be “on-the-shelf” for the next pandemic?
- The study design can be mapped out to handle a large class of possible outbreaks
  - Very easily customizable
  - Get software for simulations premade and “on-the-shelf”
- Do the groundwork at WHO / ethics committees / countries on readiness plans?

Ebola Preparedness



Have Trial Design Ready

Figure 1. World Health Organization estimates of Ebola cases in West Africa and Ebola clinical trials located in West Africa, as registered at ClinicalTrials.gov.

Other Platform Trials

- Breast cancer: iSPY-2
- Lung cancer: LUNG-MAP
- Severe CAP: PREPARE-ADSCAP
- Influenza: PREPARE FLU
- Brain cancer: GBM-AGILE
- Inherited Alzheimer's: DIAN
- Others "in the works"….

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Summary

- Adaptive platform designs are an incredibly powerful design for finding effective therapies and combinations in the universe of treatments
- Allows the arms to evolve internally and externally to the changing science
- Improved Embedded Care: Efficiently and quickly identifies best agents, *while treating patients more effectively*
- Preparation is key to an efficient response
- New trial designs are imperative to expedite drug development
- Have design ready—on the shelf for next pandemic
  - A number of parameters can be optimized quickly
  - Protocol ready (add appendices)
  - Models + simulations ready

Design

CLINICAL TRIALS

Clinical Trials
1–9

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A response adaptive randomization platform trial for efficient evaluation of Ebola virus treatments: A model for pandemic response

Scott M Berry[1,2], Elizabeth A Petzold[3], Peter Dull[4], Nathan M Thielman[5], Coleen K Cunningham[6], G Ralph Corey[5], Micah T McClain[6], David L Hoover[7], James Russell[8], J McLeod Griffiss[7] and Christopher W Woods[3,5,6]

Abstract

The outbreak of Ebola virus disease in West Africa is the largest ever recorded. Numerous treatment alternatives for Ebola have been considered, including widely available repurposed drugs, but initiation of enrollment into clinical trials has been limited. The proposed trial is an adaptive platform design. Multiple agents and combinations will be investigated simultaneously. Additionally, new agents may enter the trial as they become available, and failing agents may be removed.

Perspective

CLINICAL TRIALS

Clinical Trials
1–4
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Ebola clinical trials: Five lessons learned and a way forward

Nathan M Thielman[1], Coleen K Cunningham[1], Christopher Woods[1], Elizabeth Petzold[1], Mark Sprenz[2] and James Russell[3]

You learn how to cut down trees by cutting them down.
Bateke proverb

Compounding the tragedies of over 11,000 deaths and the untold economic and societal impact of Ebola in West Africa is the reality that some of the best-designed, most scientifically rigorous clinical research efforts were initiated too late to yield meaningful data. We sought to implement two clinical trials in the midst of the Ebola outbreak in Sierra Leone and Liberia: one such as the US Centers for Disease Control and Prevention (CDC) in September 2014,[2] the research and research funding communities were relatively slow to mobilize and to operationalize clinical trials in West Africa. Figure 1 underscores the point graphically. The primary y axis shows WHO derived estimates of the weekly number of cases of Ebola in Liberia, Sierra Leone, and Guinea, and the secondary y axis shows the number (cumulative, by start date) of clinical trials conducted in West Africa, as registered at ClinicalTrials.gov. The obstacles to conducting emer-