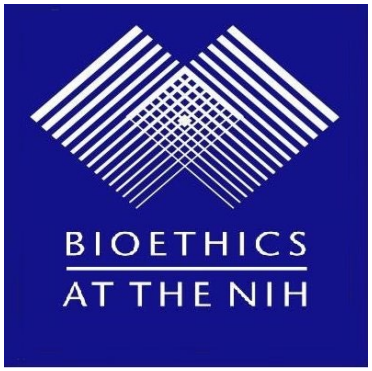


"Mock IRB": Ebola treatment trial

Annette Rid, Department of Bioethics, NIH Clinical Center

With thanks to H. Clifford Lane & team, NIAID

The views expressed are my own and do not represent the views of the NIH, PHS or DHHS

Goals

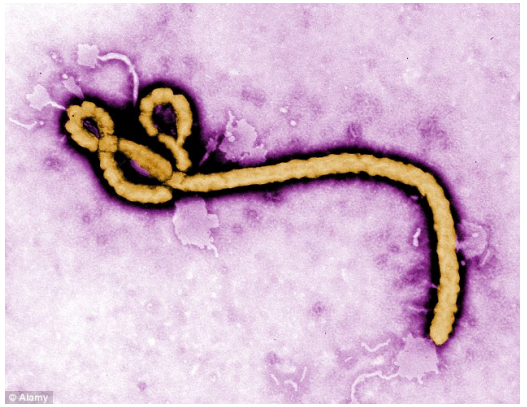
1) Appreciate the challenge of evaluating research protocols
2) Appreciate the challenge of coming to agreement in a diverse group with limited time and information

Ebola virus disease (EVD)

(Feldmann et al 2011)

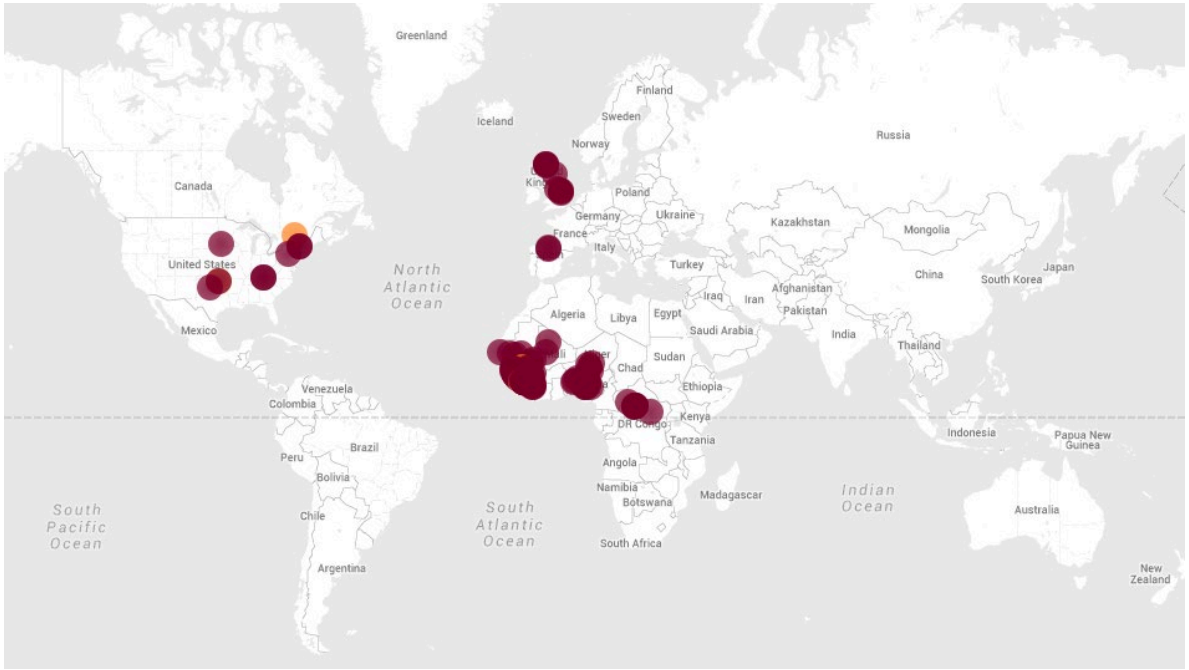
… before 2013:

- Total of ~2,400 infections
- Mortality of up to 90%
- Targeted treatments/vaccines in early development



2013-2016 EVD epidemic

(WHO 2016)



- >28,000 infected
- ~11,300 deaths
- West Africa

Conditions for clinical trials

- Ebola virus disease (EVD)
  - Very limited prior knowledge
  - Unprecedented epidemic
- Highly unproven interventions
- Context
  - Fear & distrust
  - Humanitarian emergency
  - Multitude of national & international actors

Key challenges

- Ebola virus disease (EVD)
  - Very limited prior knowledge
  - Unprecedented outbreak
- Highly unproven interventions
- Context
  - Fear & distrust
  - Humanitarian emergency
  - Multitude of national/international actors

Urgency

Uncertainty

Feasibility

Ethical ambiguity & disagreement

EVD treatment trials

(Rojek, Horby & Dunning 2017)

Investigational agent	**Design**	**Results** (as of 11/2016)
ZMapp	iRCT with adaptive design	No statistically conclusive survival benefit
TKM-130803	Single arm (multi-stage)	No overall survival benefit
Favipiravir	Single arm	No overall survival benefit
Brincidofovir	Single arm (multi-stage)	Suspended
Azithromycin, sunitinib, erlonitib, atorvastatin, irbesartan	iRCT with adaptive design	Not yet open
Interferon β	Single arm	Completed
Amiodarone	iRCT	Withdrawn
Convalescent plasma	Single arm	No overall survival benefit

EVD vaccine trials

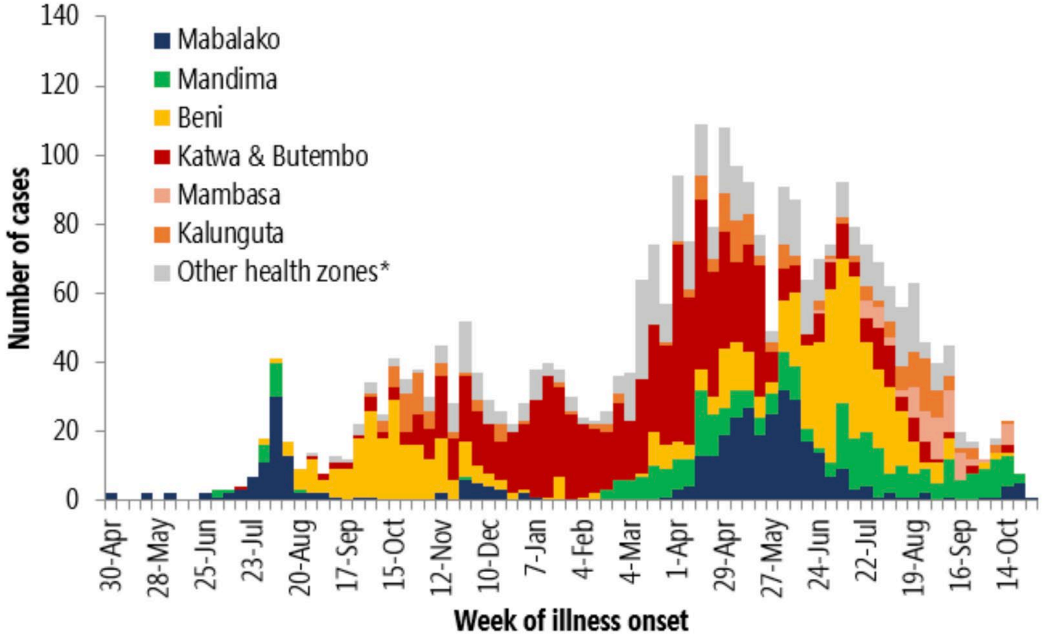
(Rojek, Horby & Dunning 2017)

Investigational agent	**Design**	**Results** (as of 11/2016)
rVSV ZEBOV	cRCT w/ ring vaccination	Substantial protection
	Single arm	Completed
VSV-ZEBOV or Ad26.ZEBOV, MVA-BN-Filo boost	RCT	Not yet open for recruitment
SVG-ZEBOV or ChAd3-EBO Z	RCT	Ongoing/not recruiting
Ad5-EBOV	RCT	Completed
Ad26-ZEBOV, MVA-BN-Filo boost	Single arm > RCT	Recruiting

2018 EVD epidemic

(WHO 2019)

Figure 1: Confirmed and probable Ebola virus disease cases by week of illness onset by health zone. Data as of 29 October 2019*



- >3,000 infected
- >2,100 deaths
- Democratic Republic of Congo (DRC)

Ebola MCM RCT or PALM study

A Multicenter, Multi-Outbreak, Randomized, Controlled Safety and Efficacy Study of Investigational Therapeutics for the Treatment of Patients with EVD

Primary objective

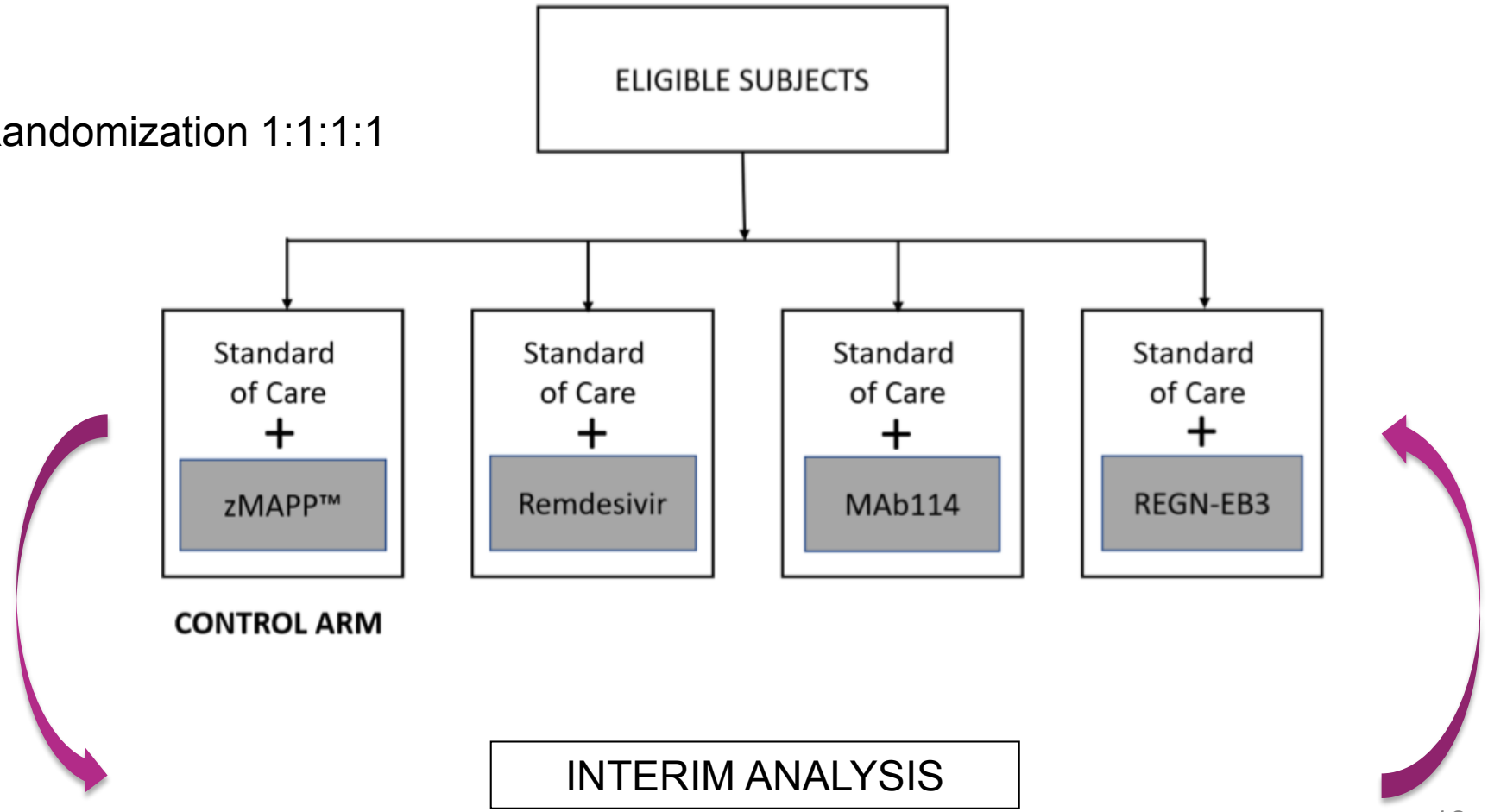
- To compare the mortality at 28 days in patients with EVD who receive different investigational therapeutics relative to the control arm

Inclusion criteria

- Males and females of any age with acute Ebola Virus infection within 3 days prior to enrollment and symptoms of any duration
- Agree to use contraception as needed
- Agree not to enroll in other study
- Provide informed consent or able to obtain surrogate consent

Study design

Randomization 1:1:1:1

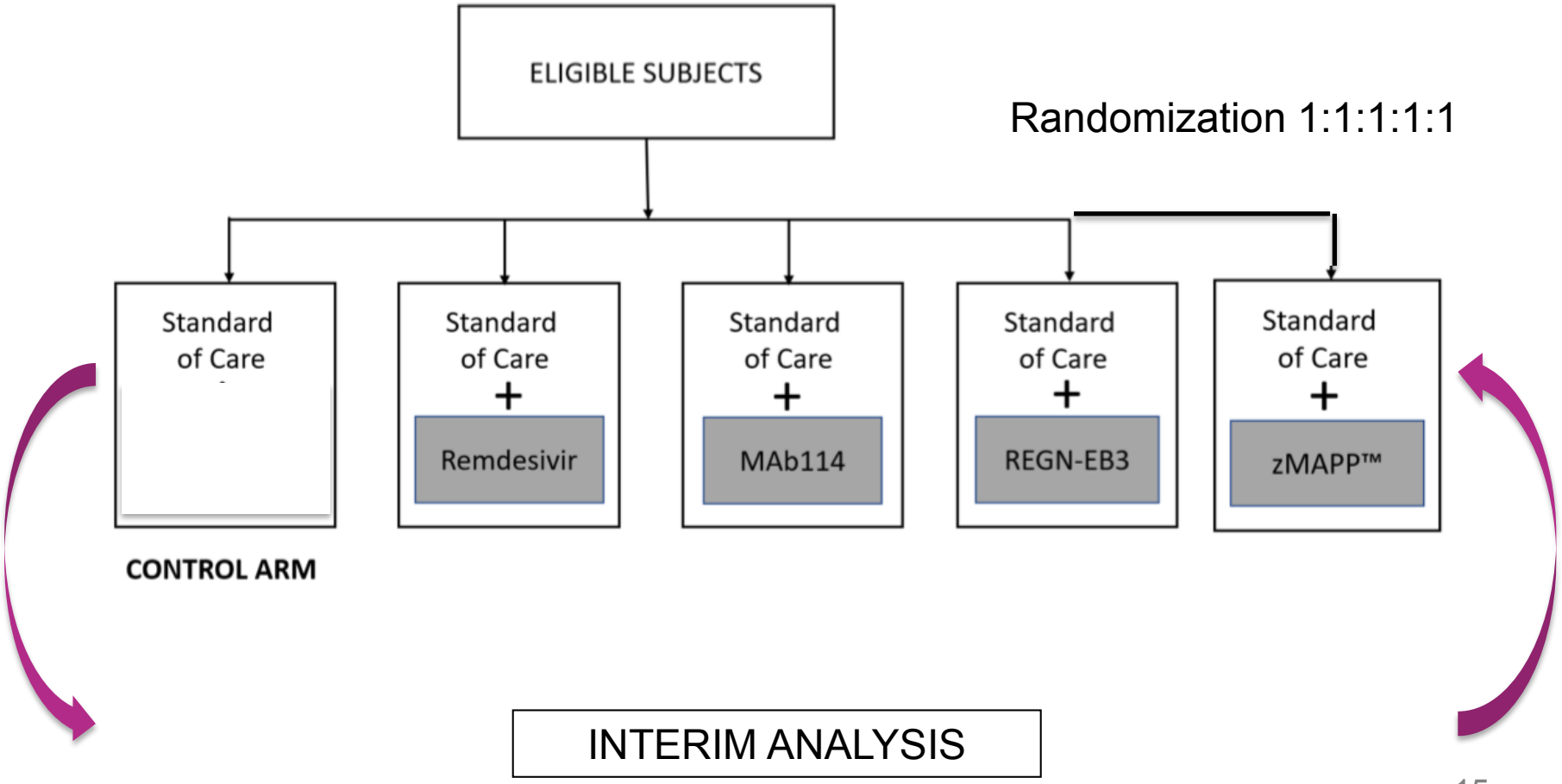


Local preferences

(Ebola MCM RCT protocol 2019)

"It is assumed that this study will continue across more than one outbreak and in several countries. To allow for country specific preferences about what constitutes an ethical and scientifically acceptable control arm, there are two design options … the Democratic Republic of Congo … has chosen Option 1"

Alternative study design



1) Would you approve the study as described?
2) If not… What further information do you need? What changes would you require?

What makes research ethical?

(Emanuel, Wendler & Grady 2000)

- At least (in chronological order):

1) Socially valuable research question
2) Scientific validity
3) Fair subject selection
4) Acceptable risk-benefit ratio
5) Informed consent

And more…

(Emanuel, Wendler & Grady 2000)

- Engage community
- Protect confidentiality
- Share results
- Respect the right to withdraw
- Provide additional clinical care
- …