Major design considerations for the SOLIDARITY PARTNERS core trial protocol

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R&DBlueprint
Powering research to prevent epidemics

Building research readiness for future filovirus outbreaks
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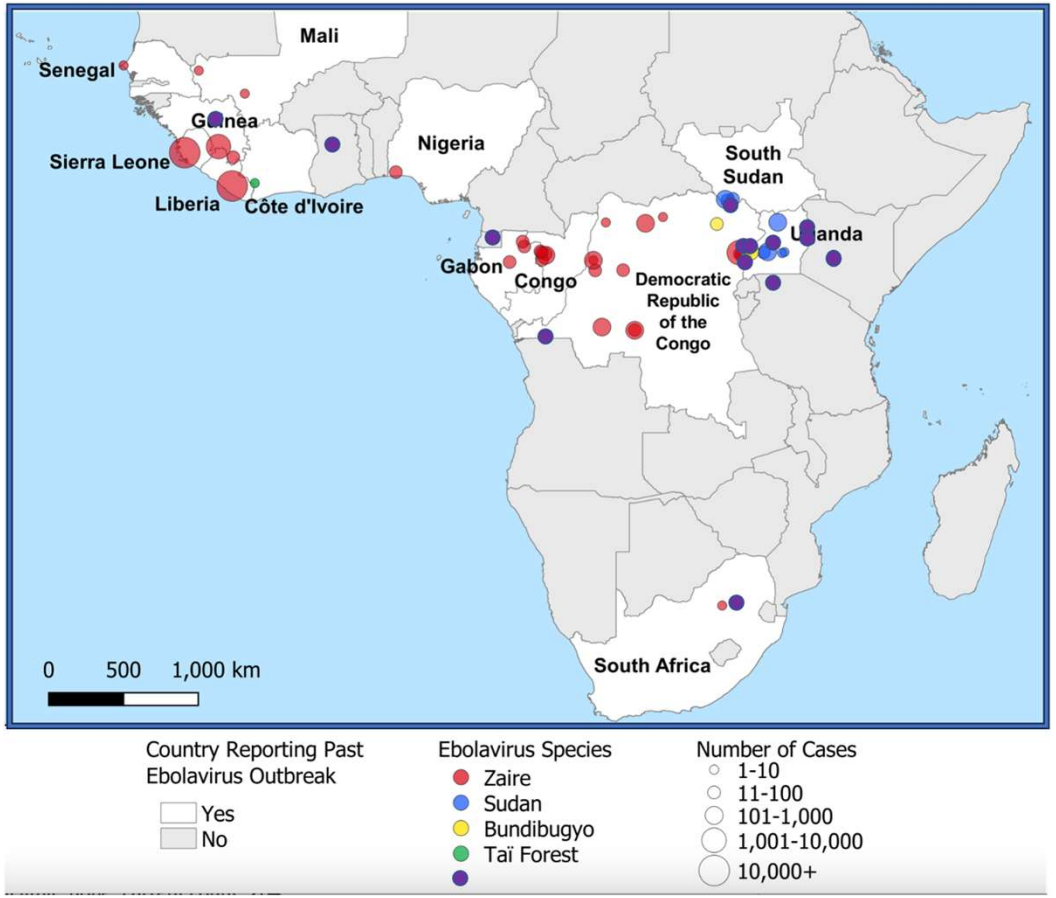
Current status

- > 40 filovirus outbreaks
- 1 completed treatment trial
- Many unsuccessful trials
- Treatment identified for Ebola Zaire
- No treatments for other filoviruses
- Death rate remains very high
- Considerable scope for improving survival (18% vs 40-70%)



Contextual challenges & design solutions

Most outbreaks are short lived & challenging

Designing a trial once outbreak starts = too late

Operationalising a trial once outbreak starts = too late

➢ **Design solution = pre-position a streamlined trial in at-risk countries**

Most outbreaks are relatively small

A separate trial for each outbreak = high risk of failure

➢ **Design solution = core 'pan-filovirus' protocol conserved across outbreaks**

There are several candidate therapeutics

A separate trial for each specific treatment = inefficient & no data on combo.

➢ **Design solution = platform trial with factorial randomisation**

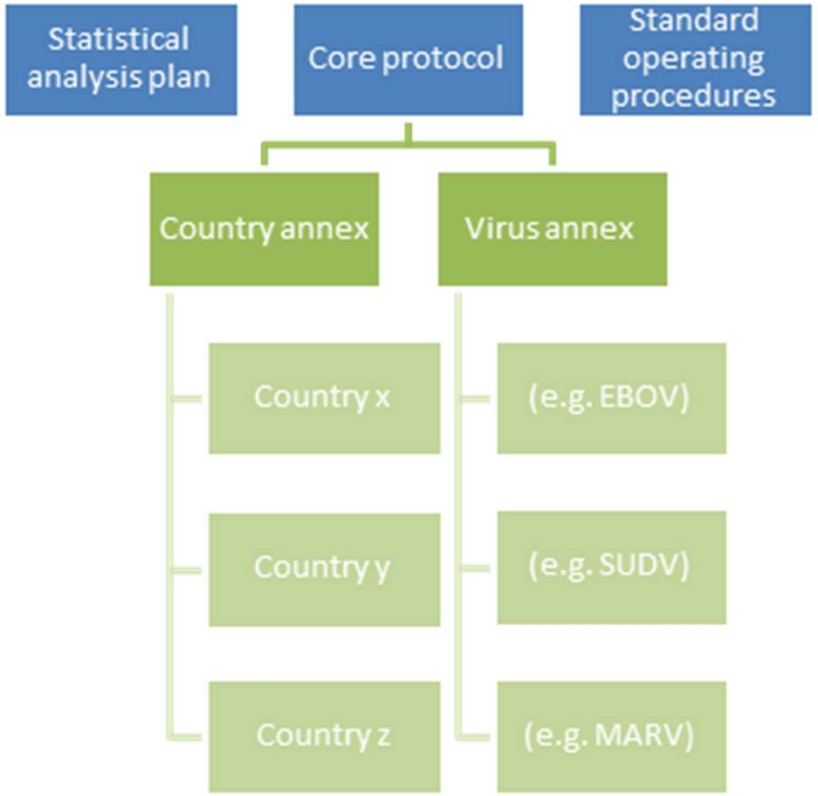
Key design features of proposed trial

1. **Pre-positioned**: to enable inclusion of early cases in an outbreak
2. **Streamlined core protocol**
   a) **Conserved across outbreaks**: data from one outbreak contributes to findings in the next
   b) **Conserved across viruses**: since certain interventions (e.g. broad spectrum antiviral and host-directed therapies) might be applicable to more than one virus subtype
3. **Adaptive platform design**: test multiple interventions simultaneously to identify the best treatment for a disease – focus on 'disease' not one particular drug
4. **Factorial design:** by therapeutic domain for efficient evaluation of >1 drug and to assess combination therapies

Design feature: Core protocol

Single trial that operates across:

1. Multiple at-risk countries: new countries can join the trial within their own regulatory requirements
2. Multiple outbreaks: statistically designed to allow data to accrue across outbreaks *
3. Multiple filoviruses: designed to enrol patients infected with any filovirus, even novel ones



* N Engl J Med. 2020 Apr 2;382(14):1366-1369.
Creating a Framework for Conducting Randomized Clinical Trials during Disease Outbreaks

Design feature: Streamlined “point-of-care”

- Randomized clinical trial that answers critical questions in a clinical care setting rather than in specialised research environments.
- Notable for being “streamlined,” meaning that participant consent forms, data collection instruments, and research procedures are simplified.
- ***‘Streamlining and quality are not opposed***; *rather, by applying quality-by-design principles, reliable evidence can be developed with planned, measurable quality when researchers focus on ensuring both the quality of data that address important research questions and trial conduct that protects patient safety*.’ *

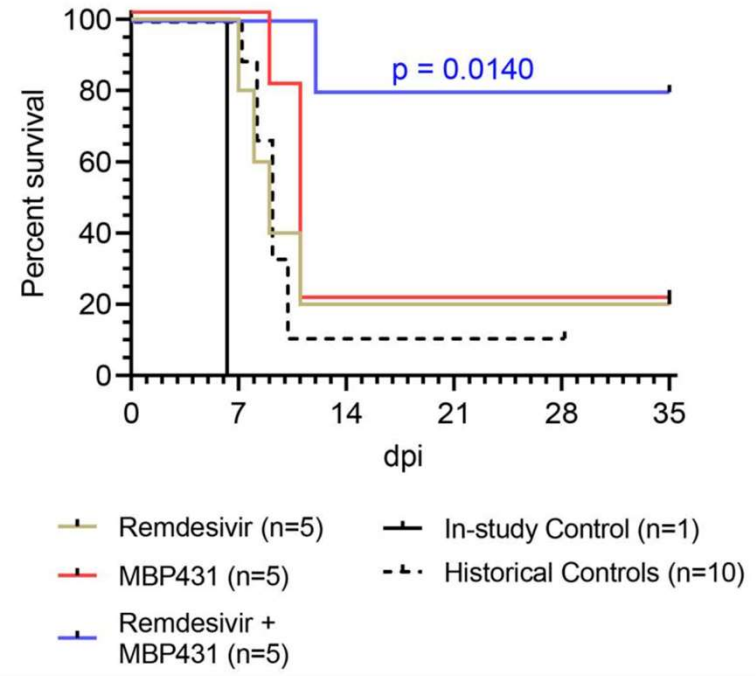
*** Benefits of Streamlined Point-of-Care Trial Designs: Lessons Learned From the UK RECOVERY Study**
Robert M Califf, Patrizia Cavazzoni, Janet Woodcock
JAMA Intern Med. 2022 Dec 1;182(12):1243-1244.

Design feature: Adaptive platform

1. Can study multiple different interventions at the same time
2. Can add new promising interventions as they become available
3. Can remove interventions that no longer require evaluation because they have been shown to be effective or ineffective or unsafe;
4. Can update the ‘standard of care’ if any new treatments are shown to be safe and effective and are adopted into treatment guidelines

Design feature: Factorial randomisation

- Enables efficient evaluation of more than one drug *“Two trials for the price of one”*
- Enables assessment of combination treatments



Cross, Robert W., et al.
"Combination therapy protects macaques against advanced Marburg virus disease."
Nature communications 12.1 (2021): 1891.

Three therapeutic “domains”

Evaluation domain	MARV	SUDV	EBOV
Randomisation 1 Monoclonal	Monoclonal antibody vs no additional treatment (1:1)	Monoclonal antibody vs no additional treatment (1:1)	Receive approved Mab
Randomisation 2 Antiviral	Antiviral vs no additional treatment (1:1)		
Randomisation 3 Host directed treatment	Host directed therapy vs no additional treatment (1:1)		

Where licensed monoclonal antibody treatment exists, patients will receive these as standard of care

Simple for clinical team

RECOVERY
Randomised Evaluation of COVID-19 Therapy

Are the following treatments UNSUITABLE for the patient?
If you answer Yes it means you think this patient should NOT receive this drug.

A14.3 Colchicine	⌄
A14B.1 Convalescent plasma	⌄
A14B.2 Synthetic monoclonal antibodies (REGN10933+REGN10987)	⌄
A14C.1 Aspirin	⌄

Are the following treatments available?

A15.3 Colchicine	⌄
A15B.1 Convalescent plasma	⌄
A15B.2 Synthetic monoclonal antibodies (REGN10933+REGN10987)	⌄
A15C.1 Aspirin	⌄

Possible randomized treatment allocations

antiviral + monoclonal + host directed	antiviral + monoclonal	monoclonal + host directed	monoclonal
antiviral + host directed	antiviral	host directed	No additional

Factorial randomisation: efficient unbiased assessments

RECOVERY Randomised Evaluation of COVID-19 Therapy	Convalescent Plasma (n=5795)	Usual Care (n=5763)
Infusions of convalescent plasma received		
None	494 (9%)	5746 (100%)
One	644 (11%)	2 (<1%)
Two	4657 (80%)	15 (<1%)
Follow-up form received	5647	5617
Other treatments received		
Corticosteroid	4757 (84%)	4693 (84%)
Lopinavir-Ritonavir	5 (<1%)	17 (<1%)
Hydroxychloroquine	13 (<1%)	13 (<1%)
Azithromycin or other macrolides	2026 (36%)	2032 (36%)
Tocilizumab or sarilumab	447 (8%)	589 (10%)
Remdesivir	1803 (32%)	1768 (31%)

Convalescent plasma in patients admitted to hospital with COVID-19 (RECOVERY): a randomised controlled, open-label, platform trial.
Lancet. 2021 May 29;397(10289):2049-2059.

Summary of key proposed design features

1. Single collaborative core protocol for all outbreaks and all filovirus types
2. Streamlined “point-of-care” trial design
3. Pre-positioned in countries at-risk of filovirus outbreaks
4. Adaptive platform design to allow multiple therapeutics to be evaluated
5. Separate “domains” for monoclonals, antibodies, and host-directed therapies
6. Factorial design to permit efficient simultaneous evaluation of multiple drugs and to study effect of drug combinations

Thank you

Single randomisation

Randomisation in grey

Patient allocation in green

Antiviral randomisation	
Antiviral	No additional treatment
Patient receives antiviral	Patient receives no additional treatment

Two treatment domain randomisation

		Antiviral randomisation	
		Antiviral	No additional treatment
Monoclonal randomisation	Monoclonal	antiviral + monoclonal	Monoclonal alone
	No additional treatment	Antiviral alone	No additional treatment

Three treatment domain randomisation

		Antiviral randomisation			
		Antiviral		No additional treatment	
Monoclonal randomisation	Monoclonal antibody	***Host-directed randomisation***		***Host-directed randomisation***	
		HDT	*No additional*	*HDT*	*No additional*
		antiviral + monoclonal + HDT	antiviral + monoclonal	monoclonal + HDT	monoclonal
	No additional treatment	***Host-directed randomisation***		***Host-directed randomisation***	
		HDT	*No additional*	*HDT*	*No additional*
		antiviral + HDT	antiviral	HDT	No additional

Management of factorial design in statistical analysis

Theoretical impact of e.g. corticosteroids effect on other comparisons

Reduce by 40%	Reduce by 20%	No effect	Increase by 20%
• All antiviral arms would be affected similarly so comparisons would not be biased • Antiviral arms might require about 1/5 more patients • Corticosteroids would from this point on become standard of care, any future consideration of antivirals would estimate their effects on a background of corticosteroid use.	• All antiviral arms would be affected similarly so comparisons would not be biased • Antiviral arms might require about 1/10 more patients • again, corticosteroids would from this point on become standard of care	• No impact on the antiviral comparisons	• The event rate in the antiviral arms would be a bit higher (about 1/10 higher) • The heterogeneity of prognosis between those given corticosteroids and those not would be slight in comparison with the substantial heterogeneity of prognosis between sicker and less sick patients.

Host-directed therapy

The WHO therapeutics group recommended the evaluation of low dose steroids for the following reasons:

Ebola clinical experts agree there is plausibility of a clinical benefit.	If safe and effective, are readily scalable and affordable interventions.	Being given in practice. Randomising such practice evaluates efficacy and safety. It also reduces confounding by corticosteroid use in evaluation of other therapeutics

A more detailed rationale for the selection of low-dose corticosteroids is included as an appendix to the protocol.

Safety reporting

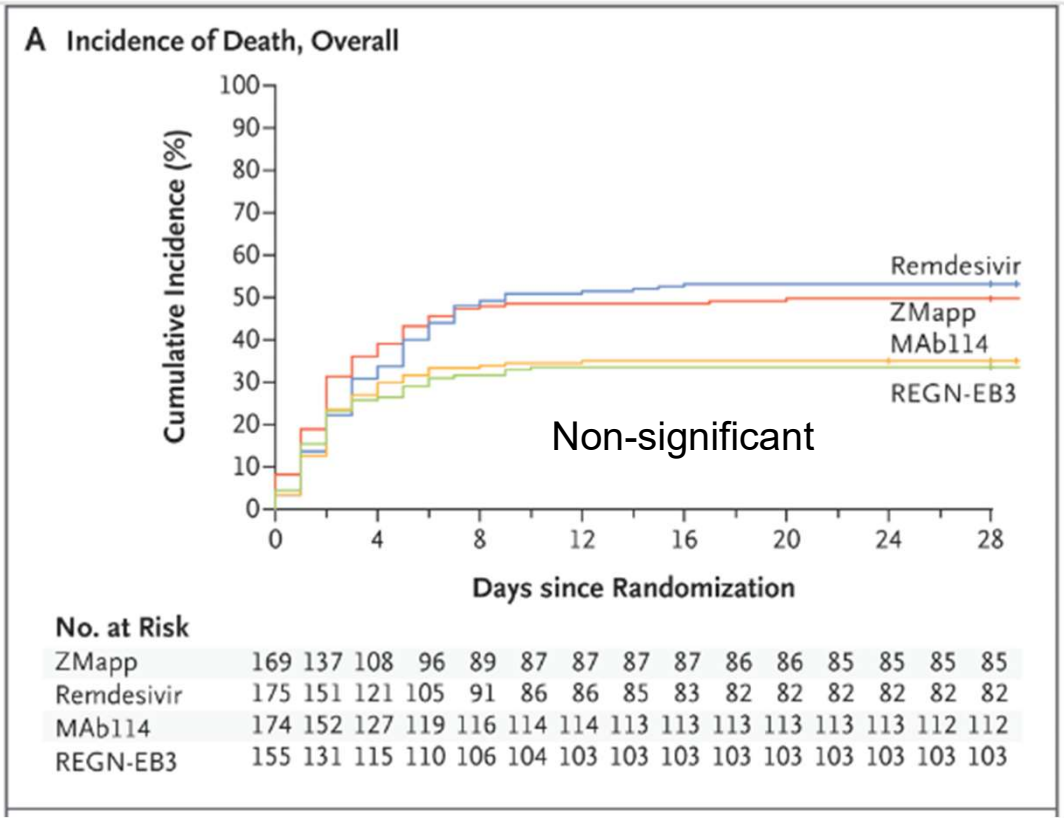
This approach is consistent with the PALM RCT, which did not collect all SAEs regardless of causality.

PALM Protocol states

- "*ONLY [their emphasis] the following SAEs are graded and are required to be individually reported to the Clinical Safety Office:*
  - *New/worsening events considered unlikely/definitely unrelated to underlying Ebola infection, and/or*
  - *New/worsening events considered possibly, probably, or definitely related to study interventions or to a non-Ebola condition, including any baseline comorbidity that has worsened.'*

This approach is also consistent with other trials for patients with severe acute infectious diseases e.g. REMAP- CAP https://www.remapcap.org/protocol-documents.

Randomisation to no additional care



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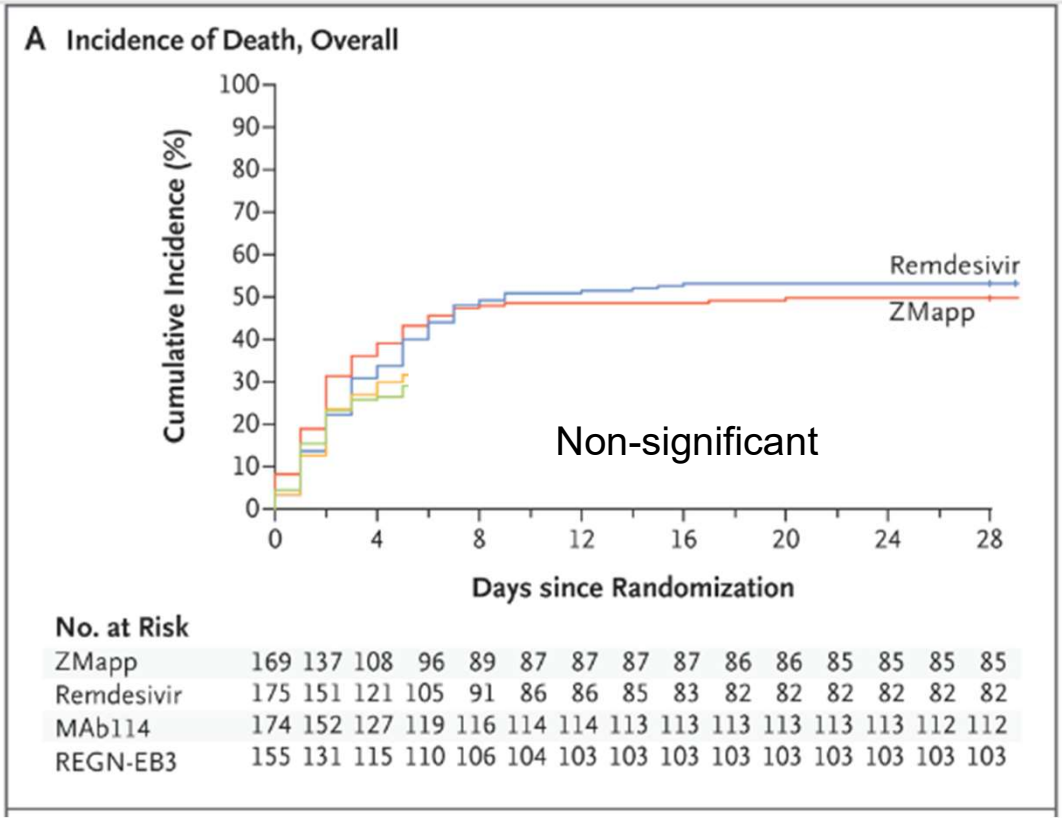

Randomisation to no additional care