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Barriers and solutions to clinical research during outbreaks

LEAPing the barriers

Peter Horby

Reaching out, 20-21 September 2018

ISARIC

International Severe Acute Respiratory and emerging Infections Consortium
2011
56 networks
112 countries

Platform foR European Preparedness Against (Re-)emerging Epidemics

PREPARE

ALERRT

African coaLition for Epidemic Research, Response and Training

2017
21 partner organizations
13 countries
9 African and 4 European

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wellcome trust

BILL & MELINDA GATES foundation

FONDATION MÉRIEUX

Inserm
Institut national
de la santé et de la recherche médicale

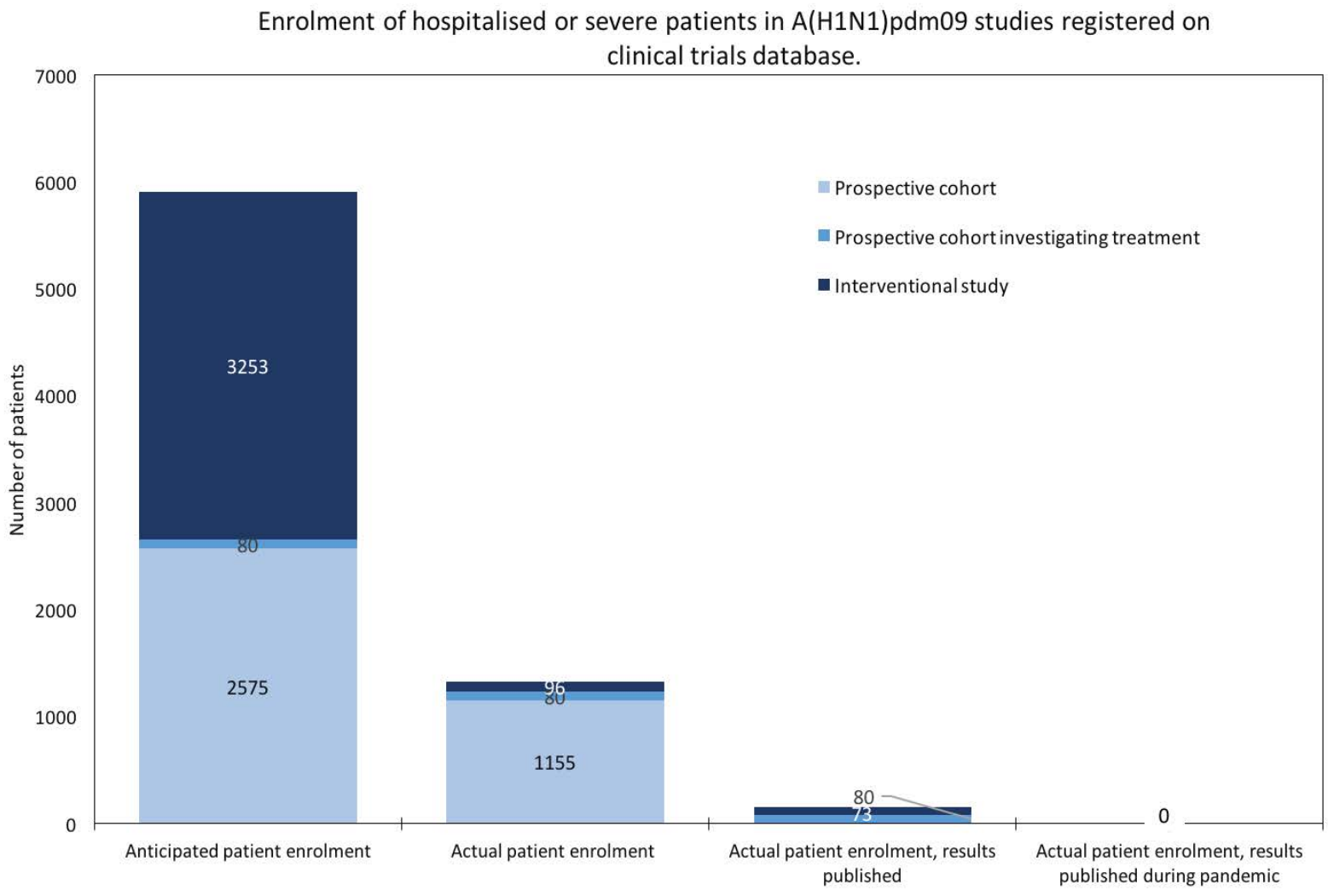
MRC Medical Research Council

LI KA SHING FOUNDATION
Education • Healthcare • Culture • Community

MINISTRY OF HEALTH
SINGAPORE

EDCTP

NHS
National Institute for
Health Research


Enrolment of hospitalised or severe patients in A(H1N1)pdm09 studies registered on clinical trials database.
Number of patients
7000
6000
5000
4000
3000
2000
1000
0
Prospective cohort
Prospective cohort investigating treatment
Interventional study
3253
80
2575
96
80
1155
80
73
0
Anticipated patient enrolment
Actual patient enrolment
Actual patient enrolment, results published
Actual patient enrolment, results published during pandemic

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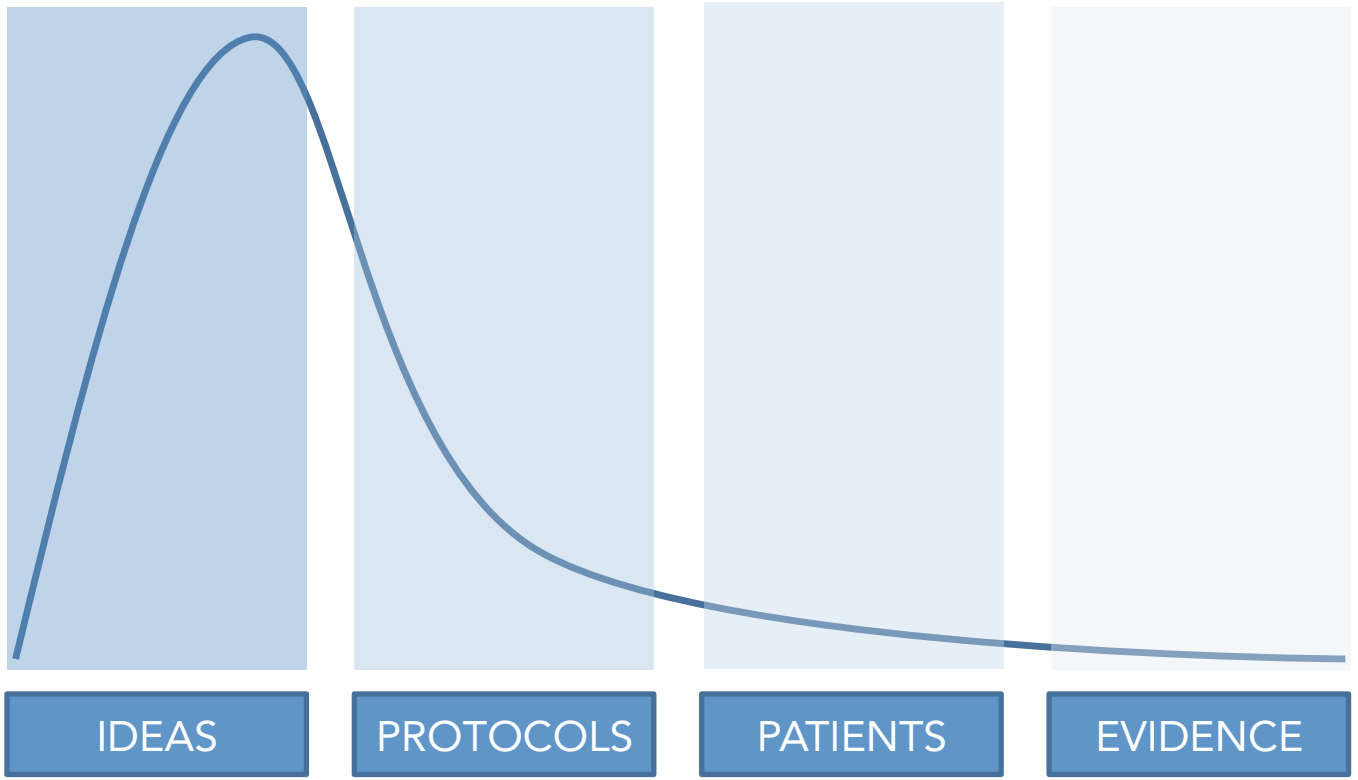
The epidemic curve…..of ambition



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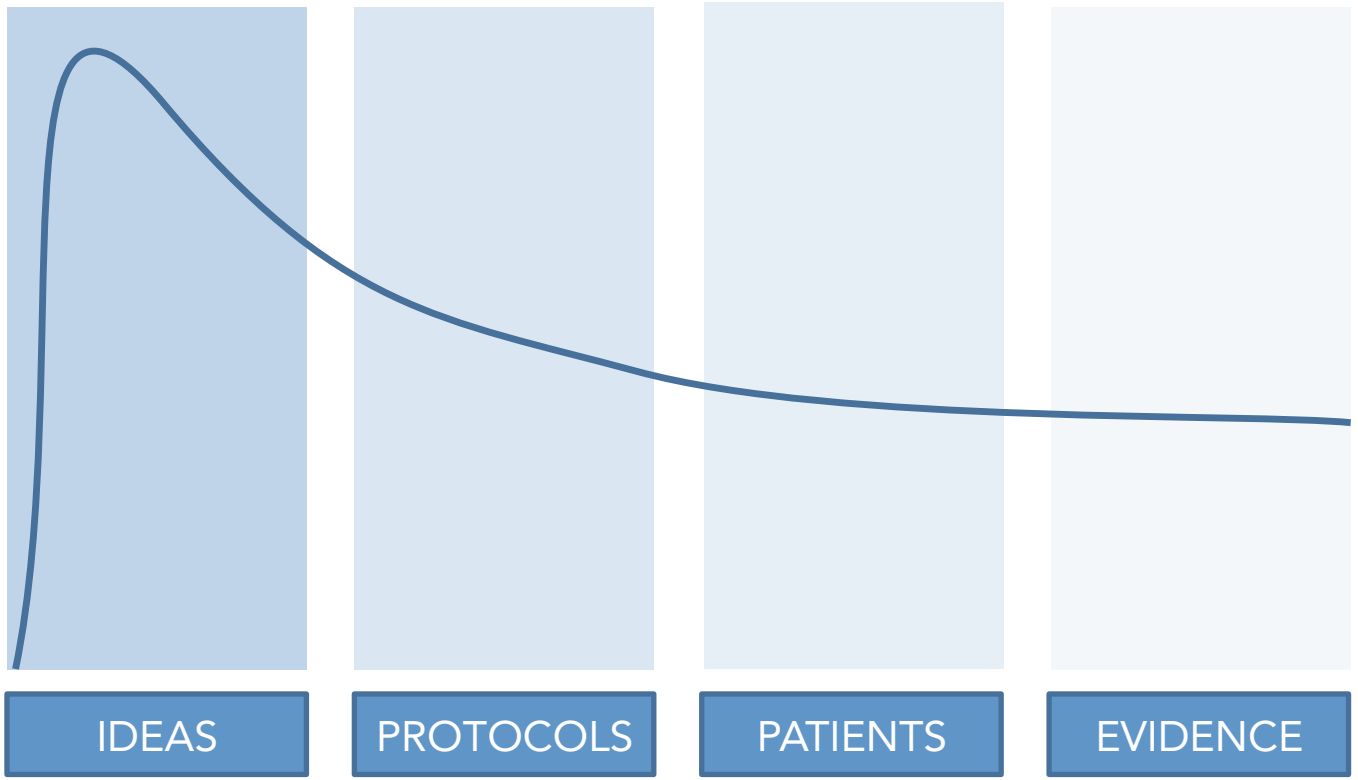
The epidemic curve…..of ambition




Barriers to research
POLITICAL
ETHICAL
ADMIN
REGULATORY
LOGISTICAL
SOCIETAL
EPIDEMIOLOGICAL

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Leaping the barriers

L = Logistical

E = Ethical

A = Administrative

P = ePidemiological

L - Logistics

Yambuku 1976

West Africa 2014

+ +

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ISARIC

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ISARIC

Experimental Treatment of Ebola Virus Disease with TKM-130803: A Single-Arm Phase 2 Clinical Trial.
PLoS Med. 2016 Apr 19;13(4):e1001997. doi: 10.1371/journal.pmed.1001997. eCollection 2016 Apr.

Evaluation of Convalescent Plasma for Ebola Virus Disease in Guinea.
N Engl J Med. 2016 Jan 7;374(1):33-42. doi: 10.1056/NEJMoa1511812.

Experimental Treatment of Ebola Virus Disease with Brincidofovir.
PLoS One. 2016 Sep 9;11(9):e0162199. doi: 10.1371/journal.pone.0162199. eCollection 2016.

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E = Ethical

Oxford Tropical Research Ethics Committee

OXTREC
University of Oxford
Room 8, Ground Floor, Manor House
The John Radcliffe, Headington, Oxford OX3 9DZ
tel. +44 (0) 1865 743005, fax +44 (0) 1865 743 002
e-mail: Fiona.Maclean@admin.ox.ac.uk

11th February 2009

Dr P Horby
OUCRU
NIITD, 78 Giai Phong Street
Hanoi
Vietnam

Dear Dr Horby Peter,

Full Title of Study: Acute post-infectious measles encephalitis in Vietnam

OXTREC Reference Number: 06 09

The OXTREC executive team reviewed the above application at the meeting held on Wednesday 11th February 2009 and thought this to be a very important study for which approval is given on the basis described in the application form.

This approval will be fully implemented upon final approval of the full committee at the meeting on Thursday 26th March 2009.

We look forward to receiving your annual report of this interesting study.

Yours sincerely,

Dick.

Dr Richard Mayon-White
OXTREC Chair

Centre for Tropical Medicine and Global Health

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ALERRT-WHO Ethics workshop

Ethics preparedness: facilitating ethics review during outbreaks.

Dakar 20-21 March 2018

ALERRT
African coaLition for Epidemic Research, Response and Training

51 individuals from 33 countries.
National Research Ethics Committees

Centre for Tropical Medicine and Global Health

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EDCTP

World Health Organization

NHS National Institute for Health Research

"Ethics preparedness": Facilitating Ethics Review During Outbreaks
Recommendations arising from a joint ALERRT & WHO workshop

Dakar, Senegal, 20-21 March 2018

"Préparation dans le cadre de l'éthique ": faciliter les revues éthiques dans un contexte d'épidémie
Recommandations issues d'un atelier conjoint ALERRT & OMS

Dakar, Sénégal, 20-21 Mars 2018

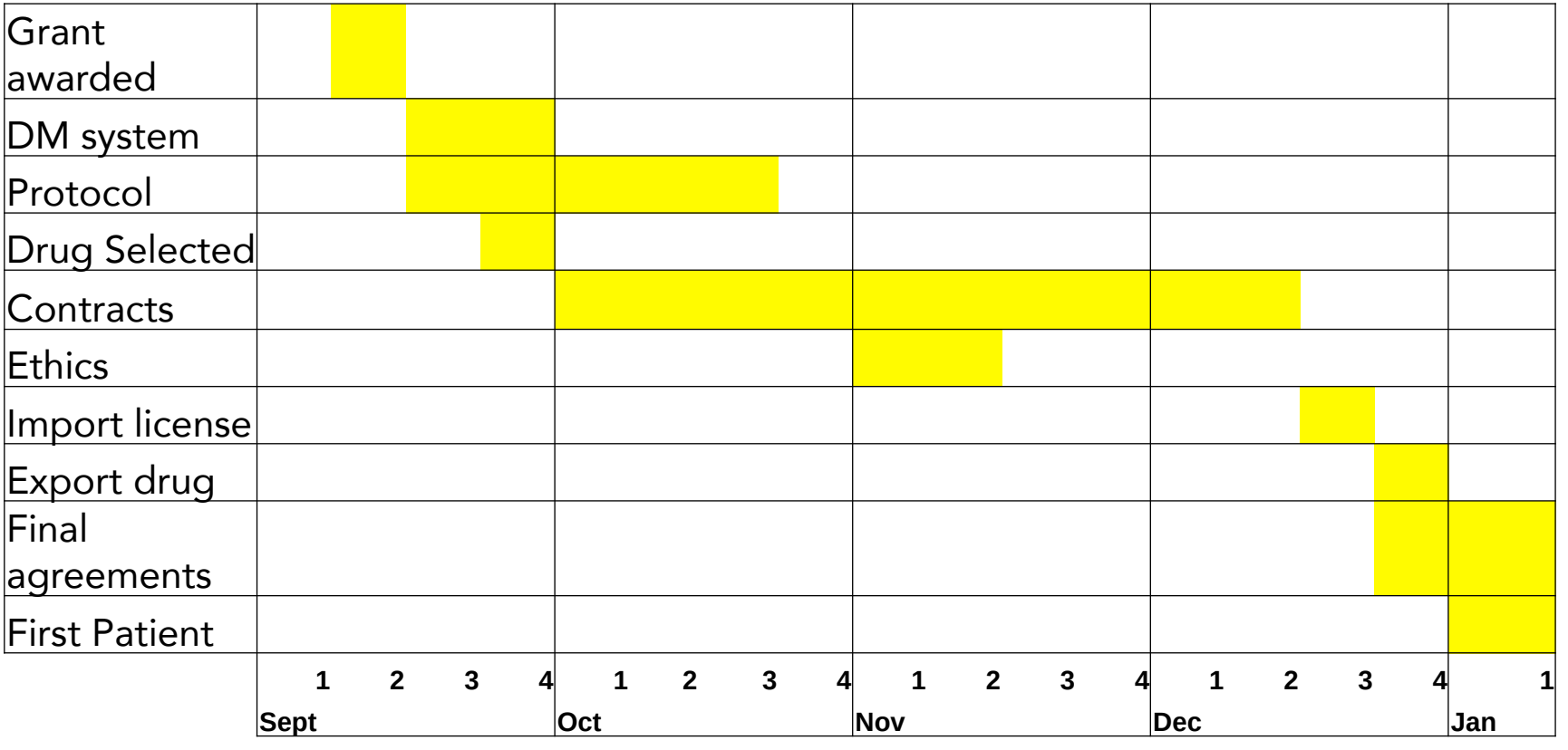
الاستعدادت الأخلاقية ": تسهيل مراجعة الأخلاقيات أثناء الفاشيات
توصيات ناشئة عن ورشة عمل مشتركة بين
منظمة الصحة العالمية و
التعاون الأفريقي للبحوث الوباء والاستجابة والتدريب
(ALERRT & WHO)

ALERRT
African coaLition for Epidemic Research, Response and Training

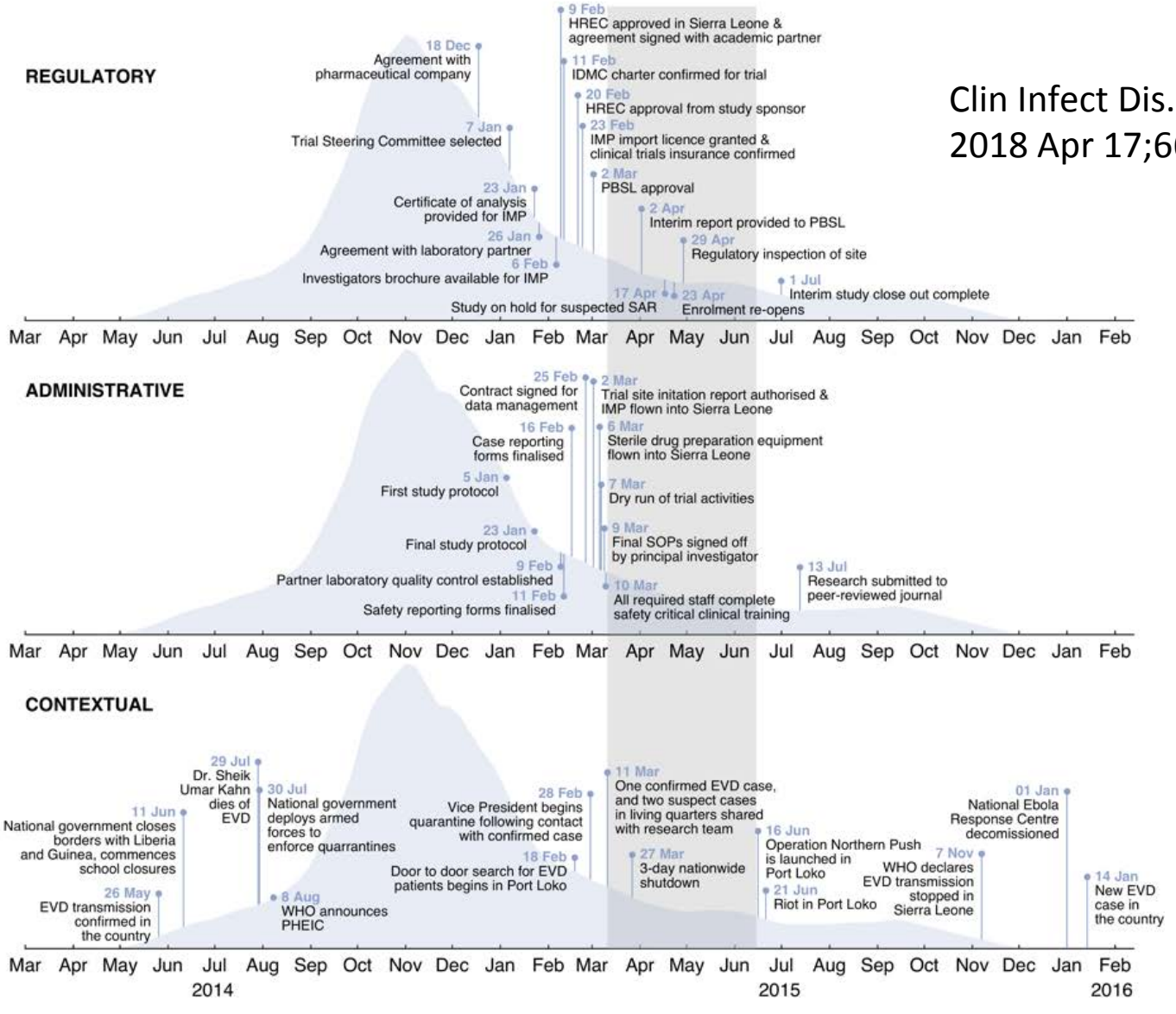
Recommendations

- Preparing RECs for outbreak response
  - Develop national SOPs for emergency response ethical review by NECS or competent authorities
  - Workshops to draft SOPs – Nigeria November 2018
- Pre-review / pre approval of proposals
  - What does this mean, what can be expected? Clarify terminology
  - Publication in preparation
- Multi-country review
  - WHO to consult and develop sub-regional mechanisms
- Data and Benefit sharing
  - What RECs should and should not mandate
- Export of samples
  - REC should engage with relevant authorities – ethically sound template MTAs

A = Administrative



Regulatory or administrative milestone	Time taken			New EVD cases during delay period (n)	
	Start date (dd/mm)	Final date (dd/mm)	Duration (days)	Sierra Leone^	GOAL ETC (Adults)
Research agreements with partners					
Laboratory (Public Health England)	26/01/2015	06/03/2015	39	948-1279	28
Academic (College of Medicine and Allied Health Sciences)	26/01/2015	19/02/2015	24	585-961	23
Site (GOAL Global)	26/01/2015	06/03/2015	39	948-1279	28
Pharmaceutical (Tekmira Pharmaceuticals)		18/12/2014	N/A	N/A	
Human Research Ethics Committee (HREC) Approvals					
Prepare submission (Sierra Leone HREC)	23/01/2015	27/01/2015	4	<178	3
Review process (Sierra Leone HREC)	27/01/2015	10/02/2015	14	222-594	19
Prepare submission (trial sponsor HREC)	23/01/2015	29/01/2015	6	<400	6
Review process (trial sponsor HREC)	29/01/2015	20/02/2015	22	363-783	23
Prepare submission (WHO for opinion)		20/02/2015	N/A	N/A	
Protocol development					
Drafting	05/01/2015	23/01/2015	18	560-1072	28
IMP management					
Drug release	19/02/2015	09/03/2015	18	165-516	5
Import license	16/02/2015	23/02/2015	7	<367	5
Shipment of IMP	27/02/2015	02/03/2015	3	<165	3
Data Management					
Database design, set-up and testing	23/02/2015	16/03/2015	21	318-648	10
Case reporting form development	05/02/2015	10/03/2015	33	532-879	14
Other Required Documents					
Study insurance	03/02/2015	23/02/2015	20	363-783	12
European Medicines Agency opinion	06/02/2015	10/02/2015	4	<194	13



Clin Infect Dis.
2018 Apr 17;66(9):1454-1457.

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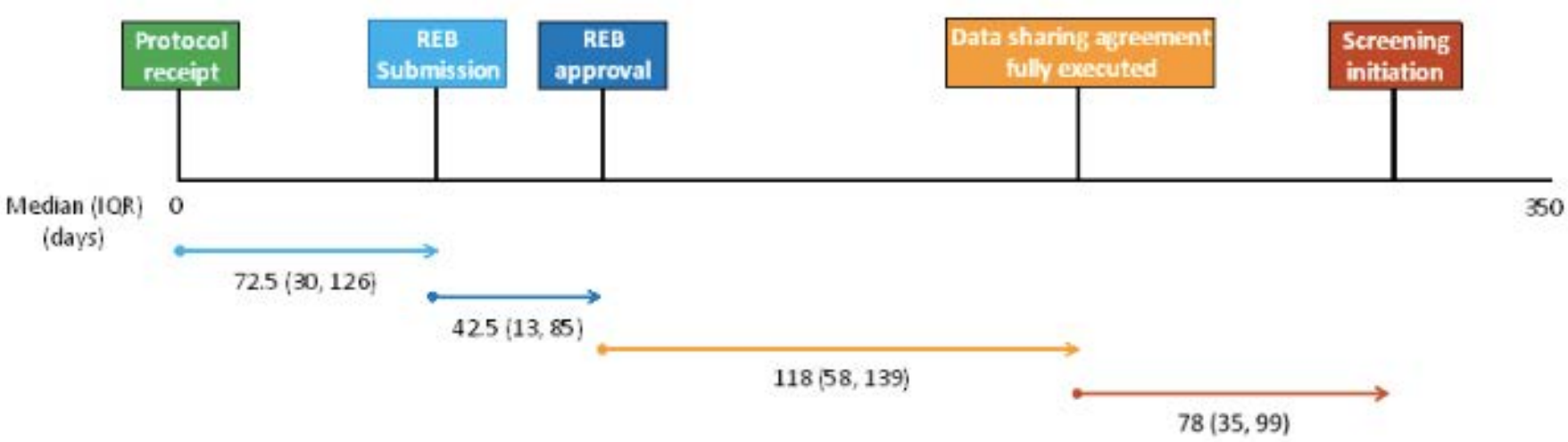
Clinical study agreements

One study in six sites



Time required to initiate outbreak and pandemic observational research.
Journal of Critical Care (2017), doi: 10.1016/j.jcrc.2017.02.009

Solutions?

- Template agreements
  - ALERRT consortium agreement
- Pre-positioned protocols
- Find a sensible lawyer

P is for ePidemiology

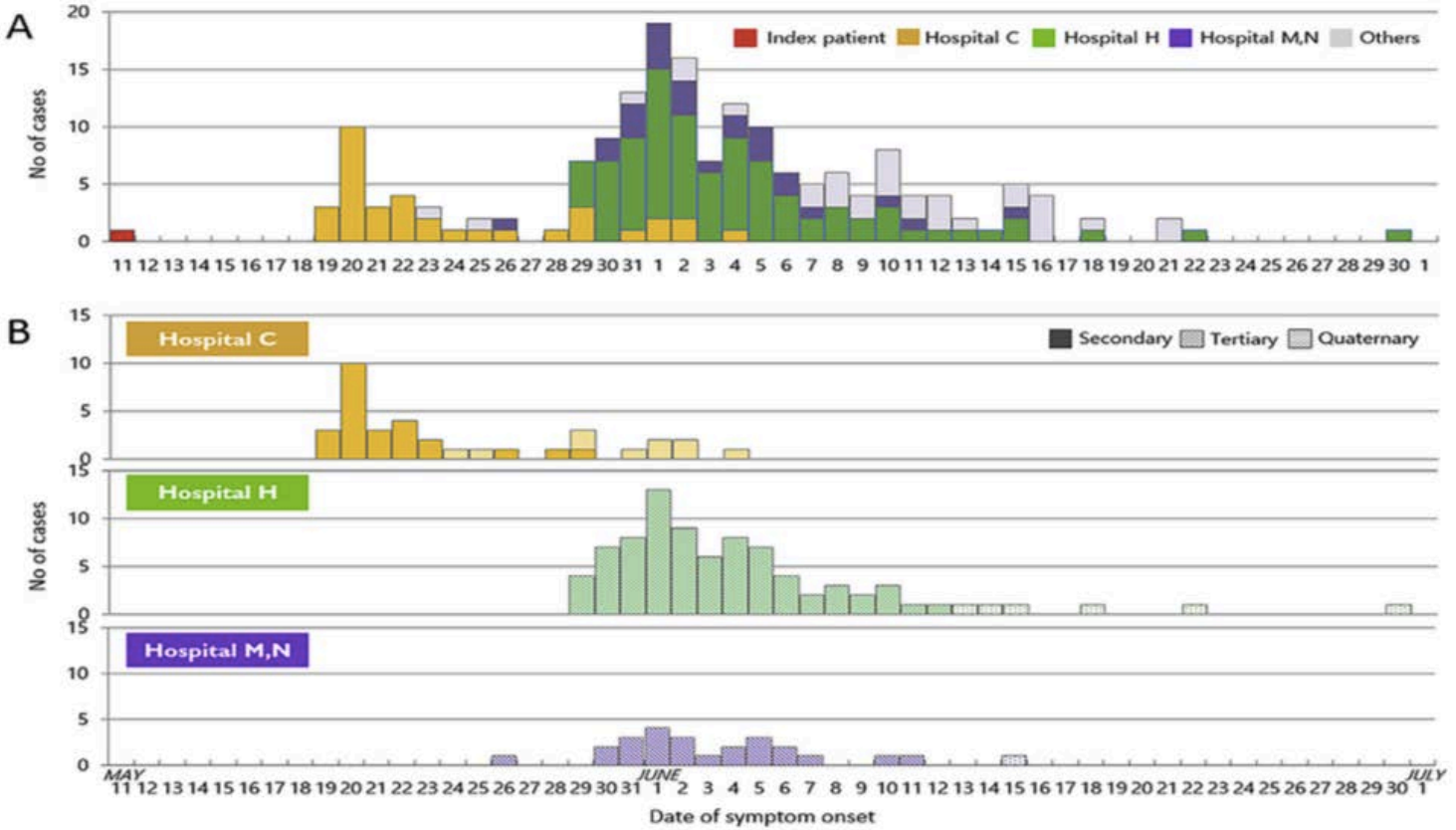
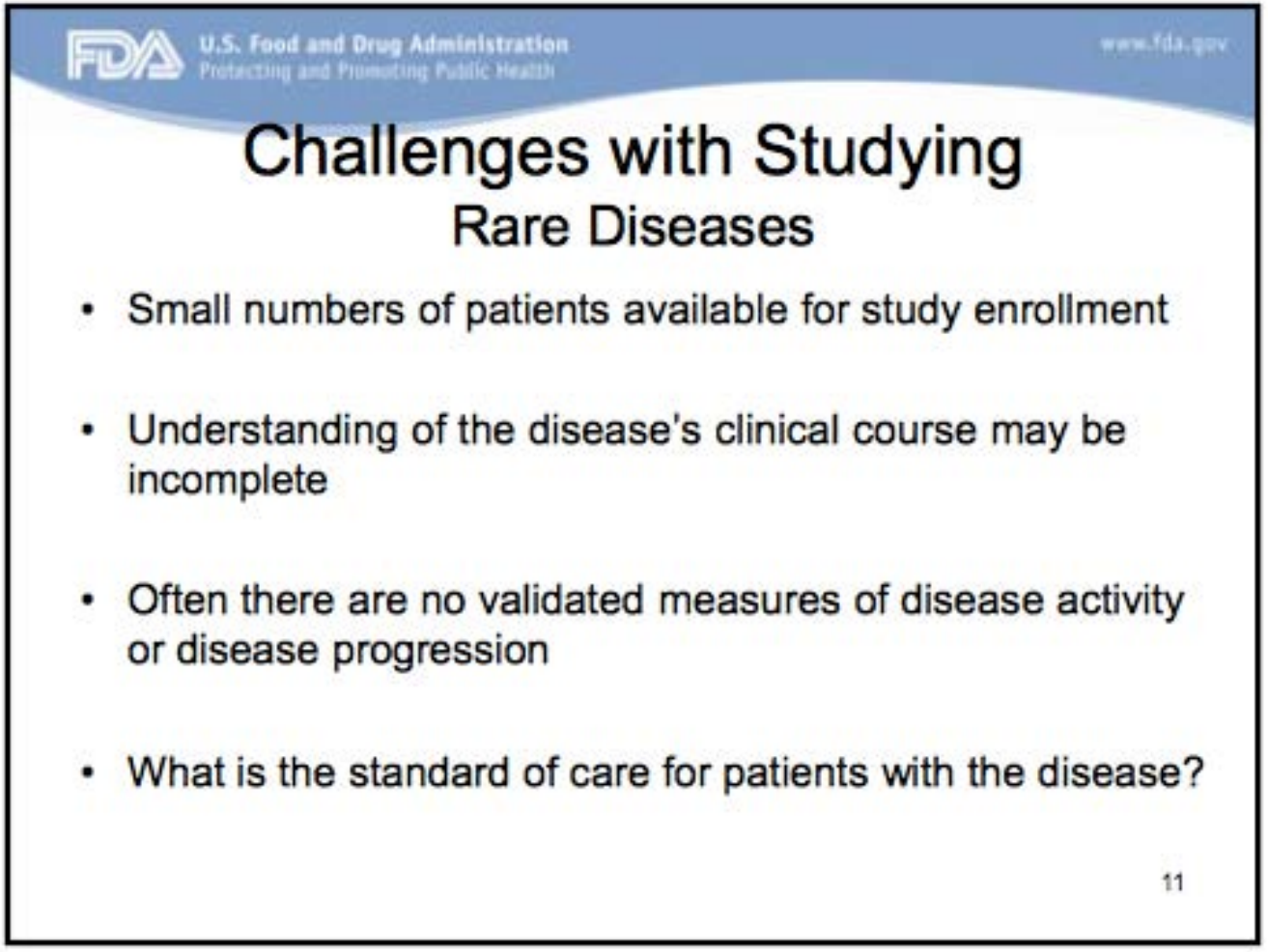


Figure 1. Epidemiologic curve of 178 confirmed cases of Middle East respiratory syndrome coronavirus (MERS-CoV) infection in the Republic of Korea, 2015. Panel A (integrated curve) depicts the overall epidemiologic curve by date of symptom onset. Red

Osong Public Health Res Perspect 2015 6(4), 269e278

EIDs are in part a rare disease problem



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What do we need for an intervention trial?

An hypothesis:

- *Intervention X when given to patients with Y results in improved outcomes compared to treatment Z*
- Patients (n)
- Time (t)

Uncertainties in EIDs and outbreaks

Parameter	Outbreaks
Intervention X	Incomplete R&D pipeline, unpublished data
Patients Y	What if clinical phenotype is uncertain?
Improved	Baseline outcome rate uncertain?
Outcomes	Measured how if natural history uncertain?
Treatment Z	What if no proven comparator?
Patients (n)	Unpredictable
Time (t)	Unpredictable

Preparation & innovation

Parameter	Potential solutions
Intervention X	R&D catalysts – CEPI, Blueprint
Patients Y	Standardised generic severity scores (e.g. NEWS)
Improved	Odds ratios where baseline outcome rate unknown
Outcomes	Standardised ordinal outcomes scales (Ventilated – 0_2 – ward)
Treatment Z	Compare outcomes between arms without a single fixed control
Patients (n)	Efficient – rare diseases approach, seamless phaseII/III, adaptive designs (seq, AR, MSA), meta-analysis
Time (t)	Efficient – simple, early endpoints, sequential analysis, adaptive designs

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RESEARCH ARTICLE

Evaluating Clinical Trial Designs for Investigational Treatments of Ebola Virus Disease

Ben S. Cooper[1,2]*, Maciej F. Boni[2,3], Wirichada Pan-ngum[4], Nicholas P. J. Day[1,2], Peter W. Horby[2], Piero Olliaro[2,5], Trudie Lang[2], Nicholas J. White[1,2], Lisa J. White[1,2], John Whitehead[6]

PLoS Med.
2015 Apr 14;12(4):e1001815.

Design

CLINICAL TRIALS

Trial design for evaluating novel treatments during an outbreak of an infectious disease

John Whitehead[1], Piero Olliaro[2,3], Trudie Lang[2] and Peter Horby[2]

Clinical Trials
2016, Vol. 13(1) 31–38

DOI: 10.1177/1740774515617740
ctj.sagepub.com
SAGE

Clin Trials.
2016 Feb;13(1):31-8.

PLOS | NEGLECTED TROPICAL DISEASES

RESEARCH ARTICLE

GOST: A generic ordinal sequential trial design for a treatment trial in an emerging pandemic

John Whitehead[1]*, Peter Horby[2]

1 Department of Mathematics and Statistics, Lancaster University, Lancaster, United Kingdom, 2 Centre for Tropical Medicine and Global Health, Nuffield Department of Medicine, University of Oxford, Oxford, United Kingdom

PLoS Negl Trop Dis.
2017 Mar 9;11(3):e0005439.

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Performance of different clinical trial designs during an epidemic

Matthias Brueckner[1*], Andrew Titman[1], Thomas Jaki[1], Amanda Rojek[2], Peter Horby[2]

1 Department of Mathematics and Statistics, Lancaster University, Lancaster, United Kingdom
2 Centre for Tropical Medicine and Global Health, University of Oxford, Oxford, United Kingdom

* m.bruckner@lancaster.ac.uk

PLoS One.
2018 Sep 11;13(9):e0203387.

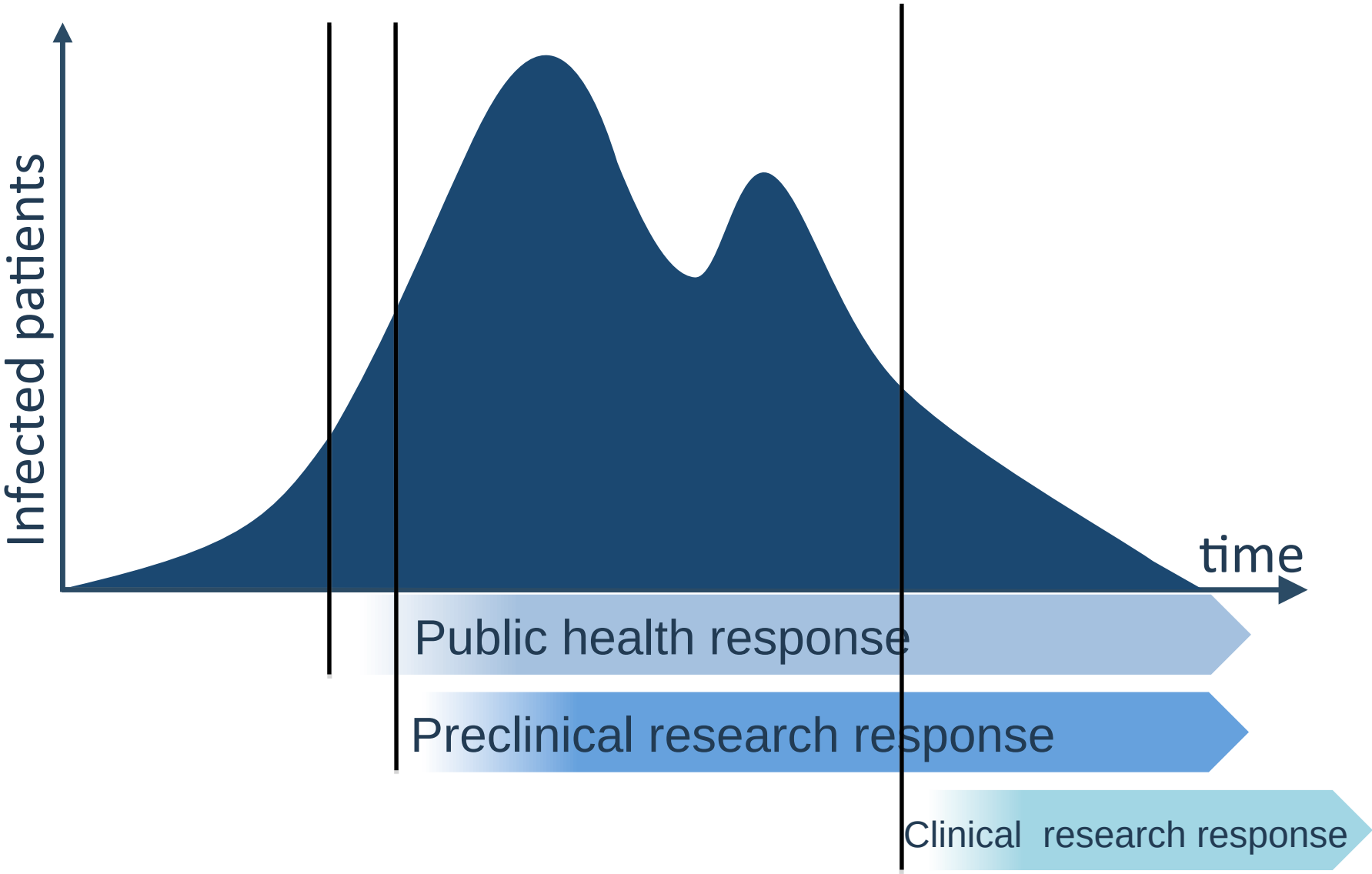
Science Translational Medicine AAAS

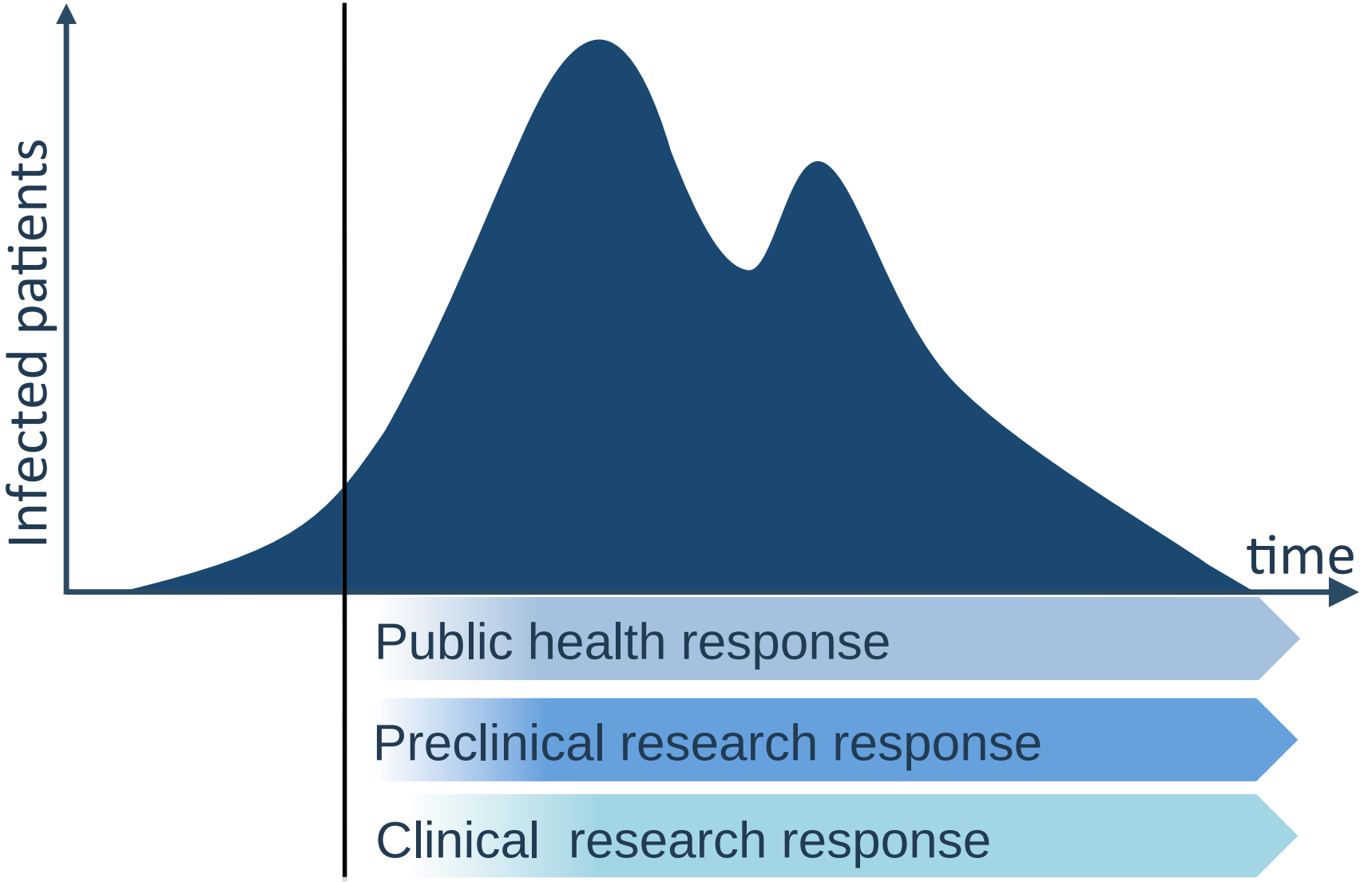
Submitted Manuscript: Confidential template updated: February 28 2012

Title: Combining evidence from randomized clinical trials across outbreaks

Authors: Natalie E. Dean[1]*, Ira M. Longini, Jr[1], Ron Brookmeyer[2], Christl A. Donnelly[3], M. Elizabeth Halloran[4,5], Pierre-Stéphane Gsell[6], Peter W. Horby[7], Martha C. Nason[8], Victor De Gruttola[9]*

1. Master protocol
2. Blinded data combination
3. Prospective meta-analysis


Infected patients
time
Public health response
Preclinical research response
Clinical research response


Infected patients
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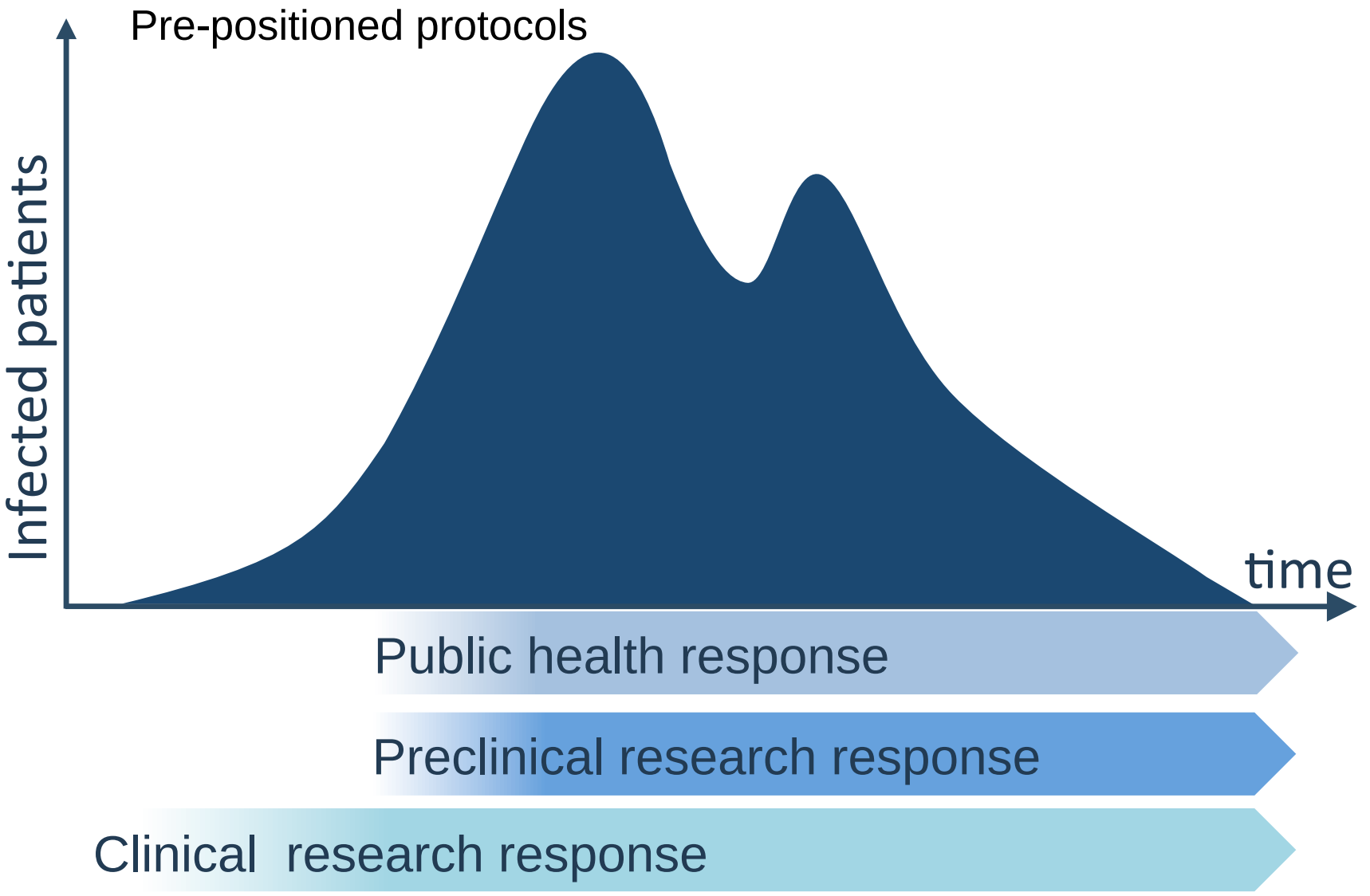
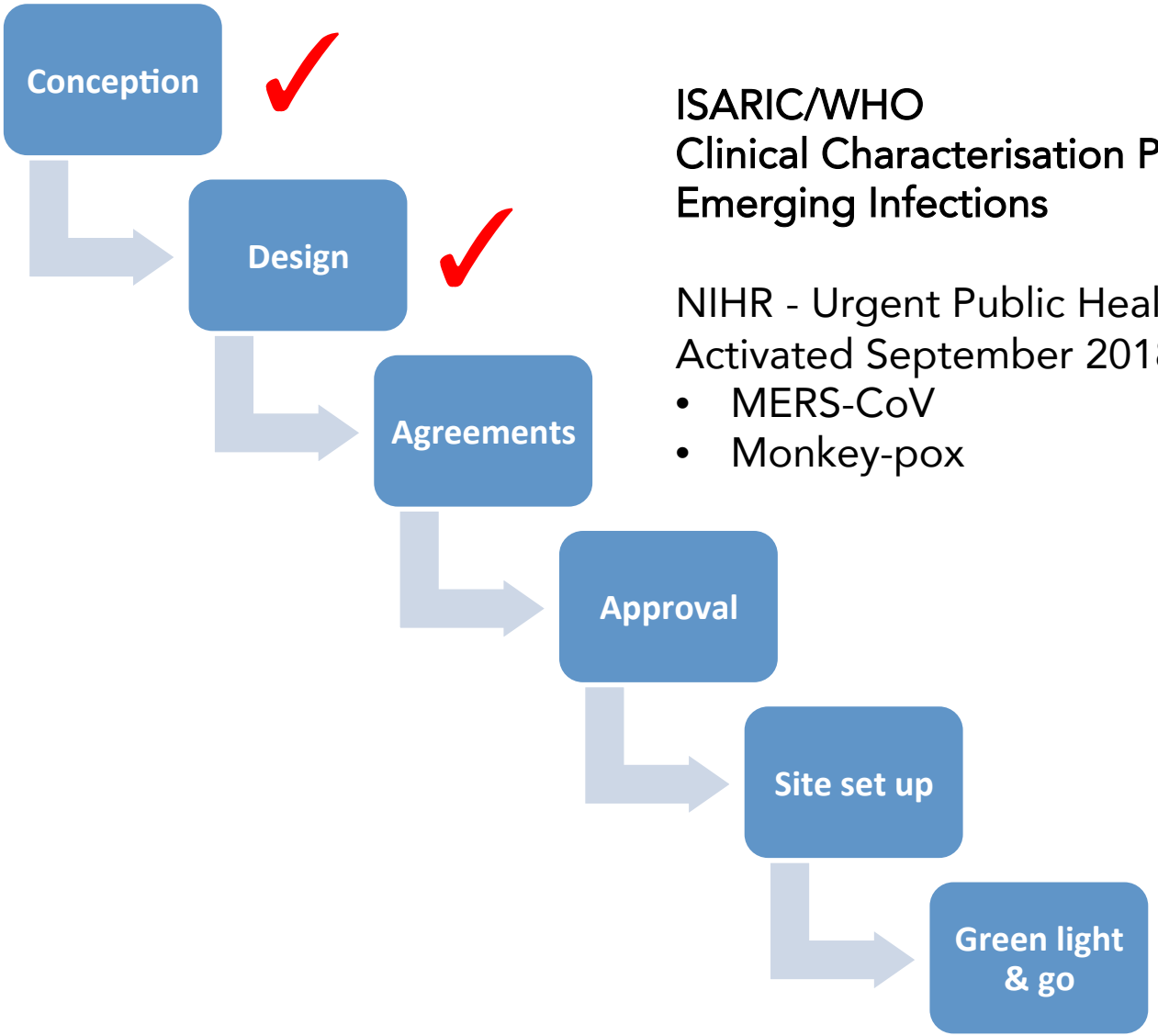

Pre-positioned protocols
Infected patients
time
Public health response
Preclinical research response
Clinical research response



ISARIC/WHO
Clinical Characterisation Protocol for Severe Emerging Infections

NIHR - Urgent Public Health Research Status
Activated September 2018

- MERS-CoV
- Monkey-pox

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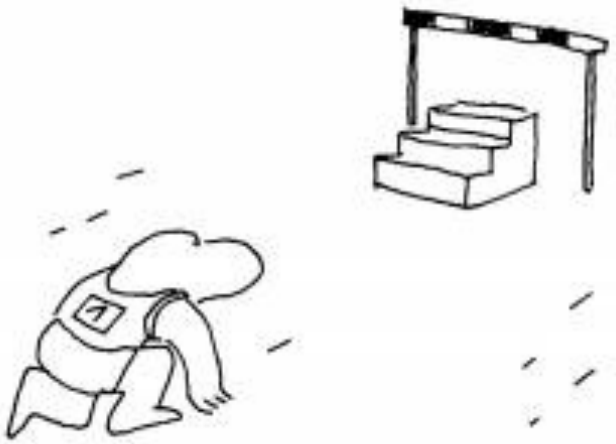
Some remaining challenges



- Finances and contracting
- Academic model
  - competition & impact
- ICH GCP

Thank you for your attention