Reaching out: a meeting to advance clinical research preparedness for infectious disease outbreaks

Brussels
20-21 September 2018

MEETING REPORT

Acknowledgements: This meeting was jointly organised by GloPID-R and PREPARE. The GloPID-R Secretariat is funded through the European Union's Horizon 2020 research and innovation programme under grant agreement number 643434. PREPARE is funded by the European Commission's 7th framework programme under grant agreement No 602525.

GloPID-R and PREARE organising committee: John Amuasi[1], JP Byrne[2], Gail Carson[3], Hugh Davies[4], Nina Gobat[3,5] Herman Goossens[6], Alistair Nichol[2], Sarah Moore[3], Karen Peuteman[6], Angela Watkins[5]
[1]Kumasi Centre for Collaborative Research in Tropical Medicine, [2]University College Dublin, [3]University of Oxford, [4]Oxford A Research Ethics Committee, [5]Cardiff University [6]University of Antwerp

Report dated: 12 November 2018

Suggested citation: *GloPID-R and PREPARE Reaching out: a meeting to advance clinical research preparedness for infectious disease outbreaks – report of proceedings and key outcomes, October 2018*

Disclaimer: This publication reports on the proceedings and discussions of a meeting. The views and opinions expressed represent those of the meeting delegates and the authors and do not necessarily reflect those of the funding bodies.

Report prepared by: Nina Gobat[1,2,] Louise Sigfrid[1], Katherine Maskell[3], Sadie Regmi[4], JP Byrne[5], Alistair Nichol[5] , Sarah Moore[1], Gail Carson[1], Hugh Davies[6], John Amuasi[7] , Angela Watkins[2], Daniele Pazzola[8], Melanie Hoste[8], Herman Goossens[8]
[1]University of Oxford, [2]Cardiff University, [3]Brighton and Sussex Medical School, [4]Imperial College, [5]University College Dublin, [6]Oxford A Research Ethics Committee, [7]Kumasi Centre for Collaborative Research in Tropical Medicine, [8]University of Antwerp

Contacts:

- Daniele Pazzola, PREPARE Knowledge Manager daniele.pazzola@uantwerpen.be
- Melanie Hoste PREPARE Knowledge Manager melanie.hoste@uantwerpen.be
- Sarah Moore GloPID-R sarah.moore@ndm.ox.ac.uk

Table of Contents

Reaching out: a meeting to advance clinical research preparedness for infectious disease outbreaks

INTRODUCTION

> *"In an infectious disease outbreak, the public want, and a have a right to, an effective response. That response can only be effective if we know what to do. Knowing what to do is based on science. Research is central" – Prof. Dame Sally Davies, Chief Medical Officer for England, Chief Medical Advisor to the UK government*

This year marks the centenary of the 1918 Influenza pandemic: a stark reminder of our global vulnerability to infectious disease (ID) outbreaks. Features of modern day life such as urbanisation, changes in land use, climate change, and an increase in global travel and trade, have rendered epidemics and pandemics inevitable, particularly when considered alongside the burgeoning threat of antimicrobial resistance (AMR)[1]. For many emerging infectious diseases, effective diagnostics, medications and vaccines are simply not available. Where these medical counter measures are available, the evidence for their use in specific ID outbreaks is often limited.

Clinical research and development is vital to improve health outcomes and save lives in an infectious disease outbreak by providing evidence-based insights to characterise the disease and populations at risk, inform clinical management and public health responses. Globally, progress is being made to improve preparedness for delivering clinical research as a core component of outbreak response. These efforts are challenging and complex. Experience from previous outbreaks highlights how, time and again, the research response is delayed and the narrow window of opportunity to recruit patients during peak epidemic waves, is missed. To be effective, clinical research must be fast, flexible and integrated with the frontline response. To ensure sufficient patient numbers for conclusive results across demographics, multi-site, multi-country responses are needed. However, research takes time to conceive, plan, conduct and disseminate. Preparation must take place before and in anticipation of outbreaks. Solutions and innovations are needed to address the multiple political, ethical, administrative, regulatory, logistic, economic, and social (PEARLES) factors that influence the viability of conducting research in an outbreak. Fragmentation and competition among stakeholder groups, networks and other research initiatives represents a lost opportunity for groups to share expertise and learning and to strengthen global, national and regional research preparedness.

This meeting sought to "reach out" to the different networks and stakeholders working on ID outbreak preparedness to explore, collaborate, and closely consider the PEARLES factors shaping preparedness research in order to advance our capacity to deliver clinical research as a core part of outbreak response.

MEETING SUMMARY

> *"We have a lot of players in the world trying to do clinical research in the event of a pandemic situation. And there's a lot of fragmentation. We want to bring together those who are struggling with this challenge and to avoid this fragmentation" – Prof. Herman Goossens, PREPARE Co-ordinator*

In coordinating this meeting, we aimed to examine bottlenecks to (rapid) deployment of clinical research in an infectious disease outbreak and to identify what we can do to overcome them. The meeting took place over 2 days (20-21 September 2018) in Brussels and was attended by infectious disease specialists, front-line responders, anthropologists, social scientists, microbiologists, field epidemiologists, public health specialists, regulators, policy makers and funders. Delegates travelled from across Europe, Australia, Canada, Ghana, Republic of the Congo and the United States of America.

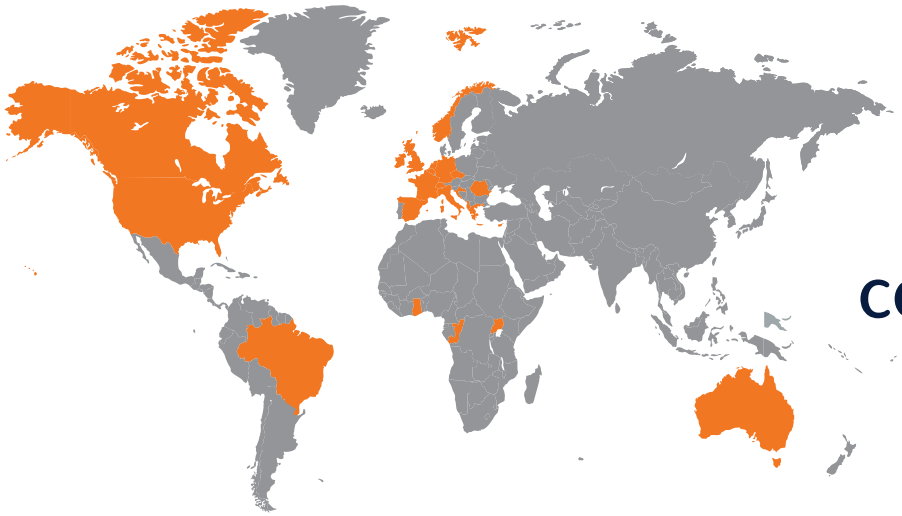
In addition, clinical research networks funded by GloPID-R members (appendix A) came together to discuss challenges and solutions to coordinated cross-country rapid deployment of research in an infectious disease outbreak. These networks have different models of operation adapted to different geographic regions and contexts, but are all funded to build capacity and capability for delivering a clinical research response to new and re-emerging infectious disease outbreaks.

A common goal united delegates and speakers: to make progress in preparedness to deliver clinical research during an infectious disease outbreak in order to improve the evidence base for public health and clinical decision-making in a public health emergency.

Who attended the event?

97 attendees

- Funders
- Public health specialists
- Policy makers
- Clinicians
- Regulators
- Infectious disease specialist
- Field epidemiologists
- Researchers
- Microbiologists
- Social scientists
- Anthropologists



24 countries

Clinical research networks funded by GLOPID-R members represented

REACTing

APPRISE
AUSTRALIAN PARTNERSHIP FOR PREPAREDNESS RESEARCH ON INFECTIOUS DISEASE EMERGENCIES

Platform foR European Preparedness Against (Re-)emerging Epidemics
PREPARE

ISARIC

PANDORA
Pan-African Network For Rapid Research, Response and Preparedness for Infectious Diseases Epidemics

ALERRT
African coaLition for Epidemic Research, Response and Training

KEY MESSAGES

Outbreak relevant clinical research must be **pre-planned, pre-positioned** and **practiced**. Once an ID outbreak has started, it is generally too late to start the planning for clinical research.

Outbreak relevant clinical research must **contribute to and be embedded in the front line response** to be effective and acceptable to the local first line response and clinical teams.

In an acute epidemic or pandemic, both the **generation and the implementation** of evidence are time critical.

Multi-site, multi-country clinical studies are often needed: **coordinated cross-border collaborations** are essential to generate enough data across clinical spectrum, demographics and comorbidities for meaningful statistical results. Data sharing is crucial.

There is a need to build **local preparedness and capacity** for outbreak research.

Unique challenges arise in different global regions. **Solutions need to be tailored to local context and need.** Research response can be pre-planned for a range of different types of scenarios.

The core, scientific process of delivering research is common across multiple scenarios. **Core capabilities can and should be identified**, including those capabilities that are common across outbreak response and for outbreak-related research.

"While each outbreak is unique, all require a core set of capabilities to respond well. If you get the core right, you have the mental agility to focus on what's different" - Nicole Lurie, Harvard and Massachusetts General Hospital

Multi-stakeholder involvement is necessary: Good participatory practice guidelines for emerging pathogens (GPP-EP) offers principles-based guidelines on how to **engage stakeholders in the design and conduct of prevention and treatment trials** for (re-) emerging pathogens.

"Constructive, long-term stakeholder engagement is indispensable for ensuring the ethical and scientific quality of research" – Catherine Hankins, McGill University

Regulators, research ethics committees, legal and contract agreement experts, and funders have important roles in advancing preparedness efforts.

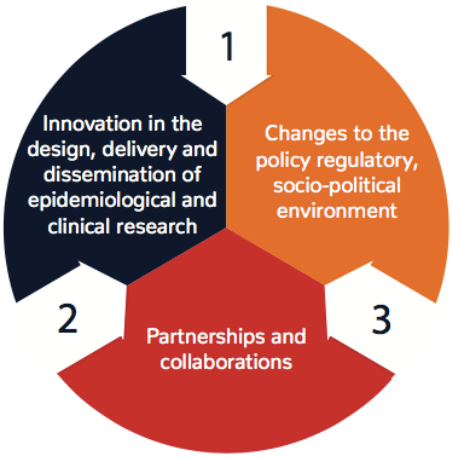
Clinical research preparedness for ID outbreaks requires as much an **understanding of social and socio-political systems** as of biomedical ones. Populism presents a real and present threat to all scientific endeavours. Scientists need to come together with politicians, policy makers and the public to **"stand up for science."**

"Populism devalues competence and brings forward ideas that are based on emotions not facts. Scientists need to be prepared to react in an organised manner and very fast" – Ilaria Capua, University of Florida, former member of the Italian parliament

MAKING PROGRESS: SOLUTIONS TO PEARLES BARRIERS

The two-day "Reaching out" meeting set out multiple challenges, complexities and opportunities to advancing clinical research preparedness for ID outbreaks. Solutions were proposed, however, there were few examples of solutions that had been developed, implemented and also evaluated. This implementation and evaluation feedback loop is critical to advance preparedness and to understand both the anticipated and the unanticipated effects of new solutions and ways of working. To advance the field, progress can and must be made in three interdependent areas. First, in the way that research responses is designed, delivered and disseminated; second, in influences from the policy, regulatory and socio-political environment; and, third, in partnerships and collaborations across stakeholder groups, academic disciplines and geographic regions.

Solutions to PEARLES barriers



1. Innovation in epidemiological and clinical research design and delivery

We need to think differently about research. In an outbreak, there is a narrow window of opportunity for generating new knowledge and insights into how to understand and manage the emerging health threat. Being ready to act in that narrow timeframe requires pre-planning, pre-positioning, and practicing clinical research responses in the same way that public health responses are planned and practiced. The unique questions posed by infectious disease outbreaks require innovation in trial design to provide answers that are pragmatic, workable, and bolster public health responses. Pragmatic and novel trial designs, such as Adaptive Platform Trials, offer promise. Research processes that are embedded, as far as possible, in routine healthcare and response processes are likely to be most acceptable to front line responders, clinical and research staff. Lean research enrolment and informed consent procedures that are proportionate to risk are needed and creative approaches to the information exchange element of the informed consent process can, and have been, employed. Equally, however, informed consent is not the single maker of ethical research and practical guidance on embedded ethics into the whole research process is important to stimulate new thinking about what ethical research in the context of an ID outbreak really involves. Interdisciplinary approaches are key; for

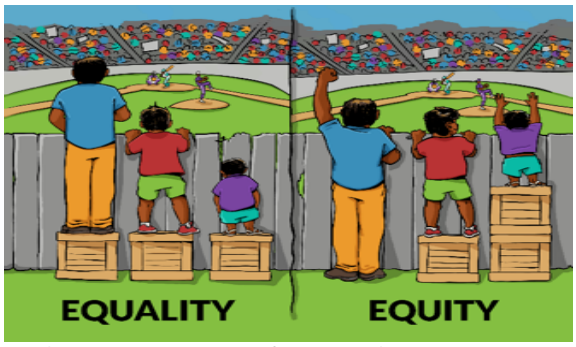
example, integrated social science research can provide insight and innovation for contextually and culturally appropriate research features. Identifying ways to feedback key outcomes of research, as well as considering wider questions about integration of research findings, are also key areas of focus.

2. An enabling regulatory, policy and socio-political environment

Clinical research operates in a wider policy, regulatory and socio-political context. Key features of that context can operate as a barrier or an enabler to the delivery of clinical research during an ID outbreak. Preparedness to participate in clinical research needs a strong policy context and needs to occur across sectors, across professional disciplines and across population groups. Processes and mechanisms for rapid response are needed among regulatory bodies, ethical review boards and funding communities. Progress has been made and speakers at the meeting shared examples of good practice. However, preparedness initiatives need to move faster and further if they are to be ready to effectively support clinical research initiatives. For example, a survey of Research Ethics Committees and National Competent Authorities across European Member states that was conducted in preparation for the meeting, found that the majority of respondents did not know of or did not have expedited review processes, and those that knew of such processes, were not aware of the standard operating procedure to follow if required to expedite review. Clinical research contracts and agreements create the greatest time delay and pragmatic, sensible legal and administrative solutions are required. Socio-political trends signifying a rise of populism and anti-science movements need to be actively countered to build an engaged, informed and receptive public to participate and benefit from ID relevant clinical research. New models of funding that allow for rapid shifting of funds and also for sustainability of ID research initiatives are needed to meet the challenge of ID clinical research preparedness. Equally, new models of research governance that promote and foster co-operation and collaboration are essential.

3. Partnerships and collaborations.

ID outbreak research preparedness requires strong interdisciplinary and inter-sectoral collaborations as well as international, cross-border partnerships that are built on trust and commitment to a common purpose. A shared value base must ensure equity or fairness of benefits, costs and outcomes[2].



Credit: Interaction Institute for Social Change (interactioninstitute.org), Angus Maguire madewithangus.co

PRESENTATIONS AND DISCUSSIONS

The meeting format involved a series of plenary panel sessions with presentations by expert speakers. A full agenda is available at appendix b.

All presentations are available to download at the PREPARE Virtual Learning Centre (prepare.ersnet.org/home.aspx) and on the GloPID-R website (glopid-r.org/resources/).

DAY 1, 20 SEPTEMBER 2018

Presentations at the **opening panel** highlighted **challenges** of conducting clinical research during an ID outbreak and identified **solutions** that have been proposed in different global regions. *Prof. Herman Goossens, University of Antwerp*, presented the value of active clinical research networks as key to ensuring capacity for delivering a research response to ID outbreaks. The EU-funded PREPARE consortium runs active clinical studies in community, hospital and intensive care settings across Europe to forward research into treatments and clinical management of patients. This network can be triggered at any time to consider a graded clinical research response to an emerging ID outbreak of clinical significance and threat to Europe[3]. Prof. Goossens also presented the vision and plans for a European organisation that brings together clinical research on antimicrobial resistance and ID outbreaks.

Prof. Peter Horby, University of Oxford, followed, offering a perspective of challenges of delivering ID outbreak clinical research in Low and Middle Income Countries (LMICs). Contextual features of these settings, for example, in regards to the frequency of ID outbreaks, variable access to healthcare and pragmatic logistical constraints, offer different challenges compared to Europe. However, there are also opportunities to be innovative and creative solutions are often found at the urgent point of need. For example, during a clinical trial conducted during the West Africa Ebola epidemic in 2015 [4], Prof. Horby's research team photographed a signed consent form as verification that patient consent had been obtained and then burned the original – a necessary measure for compliance with infection control procedures.

Prof. Horby also highlighted the epidemiological challenges of conducting research in an ID outbreak, drawing parallels

with research for rare diseases, for example, where low case numbers can be anticipated, there is poor understanding of disease course and progression and little is known about standard of care.

"Clinical trials provide good evidence that a drug is both safe and effective so we can use it with confidence. There is no reason why people suffering epidemics in LMICs should not benefit from that same science. We need to do that clinical research wherever the outbreak is" – Prof. Peter Horby, University of Oxford.

Prof. Alistair Nichol, University College Dublin, shared work from his team of researchers working alongside the PREPARE clinical studies (see also appendix c), highlighting the need to work closely with ethical committees and other regulatory bodies in considering acceptable solutions for rapid enrolment of patients to low risk, publically funded clinical studies [5,6]. Procedural hurdles relevant to the set up of clinical studies, particularly regarding contracting, remain a significant barrier to rapid deployment of research. *Prof. Catherine Hankins, McGill University* closed this session with a presentation of the Good Participatory Guidelines for Emerging Pathogens (GPP-EP)[7]. Multi-stakeholder engagement is key for ensuring ethical and scientific quality, as well as relevance and acceptability of clinical research during an outbreak. GPP-EP provides principles based guidance on the relationships between key stakeholder groups – including community representatives, potential research participants, national and regional response authorities, and regulators.

The **second panel on day 1** considered **technical solutions and design features of outbreak-relevant clinical research**. *Prof. Marion Koopmans, Erasmus MC,* highlighted the priority questions that public health officials have at the start of any ID outbreak and the value of observational research in answering these questions, particularly regarding illness severity and populations at risk of more severe disease. Data from clinical research conducted in different settings needs to be linked and there is a need for better interoperability of ID outbreak research initiatives and plans across public health, pre-clinical and clinical research settings. *Prof. Steve Webb, University of Western Australia,* focused on a pandemic scenario and the urgent need for clinical research to be pre-planned, pre-positioned and practiced[8]. Prof. Webb addressed issues around traditional randomized control trials, which may not be feasible or ethical during a severe ID outbreak with high mortality or where cases are dispersed. In contrast, adaptive platform trials offer real opportunities for being able to run clinical trials that answer real world questions to inform clinical management of patients. *Prof. Webb* illustrated how these principles have been used in the design of Randomised, Embedded, Multifactorial, Adaptive, Platform trial for Community Acquired Pneumonia (REMAP-CAP). REMAP- CAP investigates which treatment options are best for critically ill patients with CAP.

Prof. Chris Butler, University of Oxford followed with a presentation of the ALIC^{4}E trial that evaluated the clinical- and cost-effectiveness of Osteltamivir for patients presenting with Influenza-like Illness in primary care[9,10]. This pragmatic PREPARE study has recruited over 3000 patients from 22 primary care networks in 18 EU countries over the last three years and analysis of the results is currently underway. Trial results will provide much needed evidence on the effectiveness of this antiviral medication, which is now accepted as standard of care in many parts of the world despite no available evidence on the effectiveness for patients with severe Influenza. *Dr. Nicole Lurie, Harvard and Massachusetts General Hospital*, closed the session by presenting key steps needed to strengthen research responses to ID outbreaks. *Dr Lurie* highlighted the need to "pre-position everything", including protocols, approvals, research tools, analysis plans, research information, consent material and trained, deployable staff. during inter-epidemic periods. Preparedness also involves identifying a core set of capabilities necessary for outbreak response, including building research response capacity, and acting on prior lessons and missed opportunities[11].

Three **parallel interactive workshops** were held during the meeting to focus on key areas where progress can be made to strengthen preparedness: How to involve patients and the public (box 1), data sharing practices for microbial and viral genetic sequence and metadata sharing on a global scale[12] (box 2), and an ID specific framework to guide rapid, ethics committee decisions (box 3).

Prof. Dame Sally Davies, Chief Medical Officer, UK closed the day with a keynote presentation, highlighting key initiatives relevant to outbreak preparedness. Solutions presented included a sleeping pandemic portfolio of pre-positioned studies, publicly funded, research active clinical networks across the United Kingdom and full integration of social scientists in emergency response preparedness[13].

"A good response to an outbreak: contains it and treats the patients effectively, with few or no deaths. Without science how on earth can you do that effectively?" – Prof. Dame Sally Davis, Chief Medical Officer, UK

Box 1: Workshop 1 – Patients and the public as partners

Facilitators: Prof. Catherine Hankins (McGill University), Dr. Luisa Enria (University of Bath), and Adama Thorlie (SocialNet, rapporteur).

Aims:

To consider the challenges and opportunities for engaging participants and public throughout the clinical research process.

Description

The workshop was interactive and involved discussion of the views and experiences of workshop participants regarding how clinical trials influence stakeholder relationships, with an emphasis on patients as partners. Discussions centred around issues that often emerge in the engagement of patients as partners during epidemics and around clinical trials in an epidemic context.

Key conclusions

Recommendations were identified across six thematic areas (appendix D). The **language** that is used regarding research participation and community responses to ID outbreak response interventions deserves attention and review. There is a need to devise and share **communication strategies and tools** to reach across all stakeholder groups, but particularly with communities directly contributing to clinical research to build research literacy. Implementing Good Participatory Practice for Emerging and Re-emerging Pathogens (GPP-EP) guidelines[7] and key actions[14] requires **planning and proper funding**. Design of clinical research should consider **socio-cultural context**, for example, related to cultural beliefs and practices in data collection processes. Taking blood samples, for example, may have context-specific sensitivities that arise from the socio-cultural significance of blood and this has the potential to fuel distress between clinicians, researchers, and patients and requires tailored and sustained dialogue. Social science research implemented alongside the clinical trial can help identify salient contextual factors; identify perceptions, anxieties and opportunities for dialogue; and inform **strategies for engaging** participants/ patients as partners.

Box 2: Workshop 2 – Data sharing in a public health emergency

Facilitators: George Haringhuizen (COMPARE), Carolina dos Santos Ribeiro (COMPARE); Sharon Abramowitz (rapporteur)

Aim

The COMPARE consortium designed and delivered an immersive training workshop to facilitate group deliberation about the political, ethical, economic, administrative, regulatory and legal (PEARL) barriers to the sharing of microbial and genetic pathogen data through examination of six case studies.

Description

During the workshop, participants were invited to join an interactive discussion and were given a chance to express 'on the spot' their individual opinions and/or preferred actions through an electronic voting device.

Key conclusions

Considerations around **sharing data regarding source tracing** were linked with the threat of further infection posed by the source, considerations about first-response containment efforts, patients' and families' rights-to-know, and the need for confidentiality. Participants observed that researchers, clinicians, government officials, and policy makers are all bound by existing established norms, contracts, and agreements regarding privacy, confidentiality, data ownership, and the responsibility to report. However, **prevention and treatment needs to be prioritized** above non-epidemic related interests. While there was general support for data sharing, unrestricted open access data sharing was recognized as being a highly risky proposition. There was agreement among participants around the idea of **controlled access to sensitive data**. Most respondents supported **collaborations with low capacity countries** and capacity building to improve the ability to use, analyse, and respond to epidemics.

Participants had considerable expertise, and many pre-existing relationships in different stakeholder roles. They tended to use informal approaches to resolve conflicts posed in the case studies and were reluctant to settle on binding rules. This observation highlights challenges that continue to confront researchers in addressing data sharing across trusted professional networks; and the difficulty in reconciling the concerns of informal data sharing networks with formal data sharing and benefits sharing agreements.

Box 3: Developing a framework of questions and considerations to reach out to all, promote and facilitate proper conduct of pandemic research

Facilitators: Hugh Davies (Oxford A National Health Service Research Ethics Committee, former research ethics advisor, UK HRA), Julian Sheather (Nuffield Bioethics, BMA), Heather Sampson (University of Toronto); Sarah Edwards (University College London, rapporteur)

Aims

To take current ethical guidelines and propose a freely accessible, simple, practical ethical framework to guide regulators reviewing outbreak-related clinical studies and researchers designing them.

Description

Workshop participants critiqued an adapted version of Médecins Sans Frontières Research Ethics Framework[15]– Guidance Document (see appendix E). Participants of the workshop were asked to split into two groups to discuss and comment on concepts behind the prepared Principles and Questions and Considerations (which were adapted from Médecins Sans Frontières Research Ethics Framework – Guidance Document). In addition, they were asked to produce examples of 'good' answers to the questions.

Key Conclusions

As an empirical question, more work is needed on how research and its ethics review can be **organized most efficiently** in this context, as well as **how best to prepare researchers and ethics committee reviewers** in advance for such a situation.

Assuming a list of ID outbreak specific ethical questions is an efficient operational approach, the questions themselves could reflect the **principles as presented for epidemics** rather than a standard application under non-epidemic conditions. Questions missing include how well the research question responds to the needs of the immediate outbreak response, and whether its design risks interfering with that response. The need to engage the public in clinical research responses and raise public awareness was also discussed. Conducting a clinical research response exercise involving healthcare workers, researches, ethics and contracts departments and the public was discussed as an idea to take forward.

DAY 2, 21 SEPTEMBER 2018

At the **opening panel of day 2**, delegates heard from external stakeholders covering the perspective from policy, the regulators and funders. *Prof. Ilaria Capua, University of Florida*, challenged delegates to "stand up for science" in the face of global trends in populism and "anti-science" movements. These movements threaten scientific and institutional credibility, offering simple emotive explanations for complex scientific ideas.

"Populism is a very big danger for science. Populism provides very easy answers to complex questions: and answers to these complex questions are never easy"– Prof, Ilaria Capua, One Health Center, University of Florida, former member of the Italian parliament.

Clinical research preparedness for ID outbreaks requires as much an understanding of social and socio-political systems as of biomedical ones.

Dr Marco Cavaleri, European Medicines Agency (EMA), followed with a perspective from EMA regarding their plans for responding to health threats. Dr Cavaleri stressed that critical factor for regulatory actions during ID outbreaks for trialing new empirical treatments relate to the status of development of the medicinal product and the availability of data at the time of submission.

"It is very important that we do as much work as possible during the inter-epidemic period, to advance medicinal products - drugs or vaccines. In this way, when the epidemic strikes, we can be prepared and are able to bring up these counter-measures as rapidly as possible to save lives and to decrease the burden of disease" – Marco Cavaleri, European Medicines Agency

Catherine Blewitt, Health Research Authority UK, shared examples of good practice from regulators in the UK, highlighting the advance preparations that have been made for rapid review of clinical research protocols and key initiatives underway to combine and coordinate review and approvals from different regulatory groups. The EU Clinical Trial Regulation, new legislation governing the clinical trials of medicinal products, supports, in principle, expedited review in a public health emergency. However, how this might be operationalized – particularly for cross-European studies – remains unclear. *Prof. Yazdan Yazdanpanah, INSERM,* set out the funder's perspective at the close of the session, highlighting the role of GloPID-R, an international network of major research funding organisations that aims to facilitate a coordinated and rapid response to infectious disease outbreaks and to strengthen global preparedness between crises.

The **second panel** of **day 2**, focused on Ebola Virus Disease. Delegates heard from Prof. Francine Ntoumi, coordinator of PANDORA-

ID Net, and from Prof. Peter Horby and Dr. John Amuasi of ALERRT.

"The major aim is to prepare teams to respond quickly to any emerging infectious diseases arising in Africa or coming from outside Africa" – Francine Ntoumi, PANDORA-ID Net

Both of these newly-funded EDCTP clinical research networks are active in Sub-Saharan Africa and were tasked, almost immediately, to respond to an outbreak of Ebola in the Equateur region in the Democratic Republic of the Congo. Dr. Amuasi stressed the value of partnerships and challenged delegates to consider the nature of partnerships and the values that underpin them. *Dr. Luisa Enria, University of Bath*, followed with an example of embedded social science research conducted as part of a vaccine trial during the Ebola outbreak in Sierra Leone in 2015[16,17]. Through this work, the research team sought to engage with, understand and position clinical research participants within their social, political and historical context. Working in this way allowed the team to generate new insights into the setup and conduct of the vaccine trial. *Dr. Eileen Farnon, Institute Pasteur,* closed the panel by presenting the process and outcome of a meeting coordinated by the ALERRT consortium and the WHO Global Ethics Team with regulators from 29 countries in Africa. This meeting aimed to identify practical processes for ethical review of clinical research protocols in an effort to support national and international outbreak preparedness and response. A full report of the meeting and its recommendations is available[18].

The **final session** of the meeting involved an informal panel discussion among representatives of the clinical research networks. Discussions considered ways in which the networks could work together and share materials, tools and information. A key outcome from this panel was agreement to hold a meeting with network coordinators in early 2019 to identify effective mechanisms for working together to strengthen clinical research outbreak response globally.

OUTCOMES AND ACTIONS

1. Re-endorsement of the **urgency for clinical research preparedness** relevant to ID outbreaks: substantive progress still needs to be made.

2. Strengthening of **partnerships across clinical research networks**: joint scientific symposium Dakar March 2019

3. Strengthening of **partnerships across disciplines**: proposal for a cross network PEARLES advisory group across different global regions

4. Commitment to **sharing resources and tools**: repository of resources for GPP-EP

5. Plans for coordinators of clinical research networks funded by GloPID-R members to meet and identify **mechanisms for sharing** of resources and strengthening partnerships.

6. Commitment to raising **preparedness among regulatory authorities**, particularly in Europe.

7. Increased priority for integration of **social sciences in clinical research** preparedness.

APPENDIX A: CLINICAL RESEARCH NETWORKS FUNDED BY GLOPID-R MEMBERS

ALERRT https://www.alerrt.global/: The African CoaLition for Epidemic Research, Response and Training (ALERRT) is a multi-disciplinary consortium building a patient-centered clinical research network to respond to epidemics across sub-Saharan Africa

APPRISE https://www.apprise.org.au/: The Australian Partnership for Preparedness Research on Infectious Disease Emergencies (APPRISE) brings together Australia's leading experts in clinical, laboratory and public health research to address the key components required for a rapid and effective emergency response to IDs.

ISARIC https://isaric.tghn.org/: The International Severe Acute Respiratory and Emerging Infection Consortium's (ISARIC) mission is to generate and disseminate clinical research evidence whenever and wherever infectious disease outbreaks occur or are a threat.

PANDORA-ID https://www.pandora-id.net/: The Pan-African Network for Rapid Research, Response, Relief and Preparedness for Infectious Diseases Epidemics (PANDORA-ID-NET) aims to strengthen, regional and pan-African clinical research capacities and systems for enabling rapid and effective response to infectious diseases with epidemic potential, arising from within Africa.

PREPARE http://www.prepare-europe.eu/: The Platform foR European Preparedness Against Re-(emerging) Epidemics (PREPARE) is an EU funded network for harmonised large-scale clinical research studies on infectious diseases which aims to be at the basis of establishing a paradigm shift in clinical research in response to severe ID outbreaks.

REACTing https://www.glopid-r.org/clinical-trial-network/reacting-research-and-action-targeting-emerging-infectious-disease/: Research and Action Targeting Emerging Infectious Disease aims to improve research preparedness during peacetime and to optimize research capacity for a prompt response during a crisis.

REDe Research Capacity Network https://rede.tghn.org/: The Preparedness Research Capacity Network for the EU Zika Consortia (REDe) aims to build research capacity and strong partnerships between all sites running Zika studies in Latin America and the Caribbean.

ZIKAlliance https://zikalliance.tghn.org is a multinational, multi-disciplinary research consortium focused on the impact of ZIKV infection during pregnancy and the natural history of ZIKV in humans and their environment. The consortium is also developing a preparedness platform in Latin America and the Caribbean.

ZikaPLAN https://zikaplan.tghn.org aims to address knowledge gaps relevant to the recent ZIKV outbreak and to build a sustainable Latin-American platform for EID preparedness and response.

ZIKAction http://zikaction.org aims to develop a multidisciplinary multinational network capable of rapidly addressing any maternal and paediatric health research need arising from the Zika virus (ZIKV) outbreak and to conduct an interdisciplinary programme of research studies within this network with emphasis on maternal and child health.

APPENDIX B: MEETING AGENDA

Thursday 20 September

9h00 **Welcome and Opening remarks**
Herman Goossens, PREPARE Coordinator and Yazdan Yazdanpanah, GloPID-R chair

9h15 **PLENARY SESSION 1: BARRIERS AND SOLUTIONS TO CLINICAL RESEARCH DURING AN INFECTIOUS DISEASE OUTBREAK**

What is the benefit of integrating clinical research into an outbreak response? What are the challenges and solutions? What progress has been made? Panelists will present their experience and involvement in initiatives to deliver patient-centered clinical research in an infectious disease outbreak, highlighting key bottlenecks and ways to overcome them.

Chairs: Hugh Davies (Oxford National Health Service Research Ethics Committee) and Nina Gobat (PREPARE)

- Herman Goossens (PREPARE): Clinical research response: Preparing Europe for the next infectious diseases outbreak
- Peter Horby (PREPARE, ISARIC, ALERRT): Leaping the Barriers
- Alistair Nichol (PREPARE): Bottlenecks and solutions in pandemic research: lessons learned from PREPARE
- Catherine Hankins (McGill University Faculty of Medicine): Good Participatory Practice: meaningful engagement that strengthens the science

10h45 **Coffee**

11h15 **PLENARY SESSION 2: INTEGRATING RESEARCH AND RESPONSE**

Chair: John Marshall (CAPTIC, ISARIC) and Lennie Derde (PREPARE)

- Marion Koopmans (PREPARE, COMPARE): Bridging the gap between clinical research and public health in infectious disease outbreaks
- Steve Webb (PREPARE, APPRISE): Optimising trial design to evaluate therapeutic interventions during a pandemic
- Chris Butler (PREPARE): Answering patient-centered questions efficiently in primary care through response-adaptive platform trials: the ALIC4E study.
- Nicole Lurie (Harvard and Massachusetts General Hospital): Strengthening Research Response to Outbreaks: What Do We Need To Do Next?

13h00 **Lunch**

14h00 **BREAKOUT SESSION: WORKSHOPS 1-2-3 - REMOVING BOTTLENECKS TO CLINICAL RESEARCH**

Parallel session workshops that focus on key areas of research that can address common bottlenecks to delivering patient-centered clinical research in an infectious disease outbreak.

Workshop 1: Patients and the public as partners
Facilitated by Catherine Hankins, Adama Thorlie and Luisa Enria
This workshop will demonstrate how to involve patients and communities in the design and delivery of clinical research. Experience from different global regions will be shared to illustrate how meaningful patient involvement in clinical research can shift perception of sociocultural "barriers" to research participation. *Rapporteur: JP Byrne (PREPARE)*

Workshop 2: Data sharing in a public health emergency
Facilitated by George Haringhuizen (COMPARE), Carolina dos Santos Ribeiro (COMPARE)
This interactive workshop underscores the vital role of data and materials sharing in a public health emergency and how good data sharing practice can contribute to an efficient and effective response. Barriers and solutions to good practice in data sharing will be highlighted. Making use of actual incidents and cases, participants are challenged to give their opinion on regulatory and ethical dilemmas, discuss desired and feasible options, and vote for the best 'guiding statements' towards solutions. *Rapporteur: Sharon Abramowitz*

Workshop 3: Developing a framework of questions and considerations to reach out to all, promote and facilitate proper conduct of pandemic research
Facilitated by Hugh Davies (Oxford National Health Service Research Ethics Committee), Julian Sheather (Nuffield Bioethics), Heather Sampson (University of Toronto)
This workshop will take ethical guidelines developed by WHO and CIOMS and propose a framework of questions and considerations to guide regulators reviewing outbreak-related clinical studies and researchers designing them. *Rapporteur: Sarah Edwards (PANDORA-ID-Net)*

15h15 **Coffee**

15h45 Feedback from workshops

16h15 **PLENARY SESSION 3: KEYNOTE SPEAKER – DAME SALLY DAVIES**

17h00 **Close**

19h00 **Dinner for all delegates**

Friday 21 September

9h00 **Welcome and summary of day 1**

9h10 **PLENARY SESSION 4: WORKING TOGETHER**

Stakeholders need to work together to make progress. Strong partnerships can help establish an effective environment for outbreak-relevant clinical research. In this session, we hear from stakeholders about how best to work together to remove barriers to clinical research.

Chair: Gail Carson (GloPID-R Secretariat, ISARIC, GOARN)

- Ilaria Capua (One Health Centre, University of Florida, former member of the Italian parliament): Disconnecting competence from science through populism
- Marco Cavaleri (European Medicines Agency): EMA perspective on preparedness for emergent infectious diseases
- Catherine Blewett (Health Research Authority, UK): Combined Ways of Working: How UK Regulators are working together to streamline clinical trial approvals
- Yazdan Yazdanpanah (GloPID-R): The funders' perspective

10h40 **Coffee**

11h10 **PLENARY SESSION 5: EBOLA**

Chair: John Amuasi (ALERRT)

- Francine Ntoumi (PANDORA-ID-Net) – PANDORA-ID-Net: Challenges in building capacities for prompt response to infectious diseases in Central Africa
- Luisa Enria (Bath University): Involving patients and the public in Ebola vaccine and treatment trials: Social Science and community engagement approaches
- Peter Horby and John Amuasi (ALERRT): Clinical research in Ebola
- Eileen Farnon (ALERRT): Facilitating Rapid Ethics Review of Protocols during Outbreaks

12h45 **Lunch**

13h45 **PLENARY SESSION 6: LOOKING AHEAD TO MAKE PROGRESS**

This interactive session will consolidate learning from the meeting: what progress has been made in being ready to deliver clinical research in an ID outbreak? What needs to happen to take this further? How can clinical research preparedness initiatives in different regions learn from each other and work together?

Facilitators: Nina Gobat (PREPARE), Gail Carson, (ISARIC, GOARN) J-P Byrne (PREPARE) Hugh Davies (Oxford National Health Service Research Ethics Committee)

15h15 **Close of meeting:** Alistair Nichol (PREPARE)

APPENDIX C: PREPARE WP1 SUMMARY

Alistair Nichol[1] (lead), Christopher Butler[2], Nina Gobat[2,3], Micaela Gal[3], Nicholas Francis[3] Angela Watkins[3], Kerry Hood[3], Ronald Moore[1], JP Byrne[1], Prasanth Sukumar[1] and Steve Webb[5].
[1]University College Dublin, [2]University of Oxford, [3]Cardiff University, [5]University of Western Australia.

PREPARE WP1 is examining ethical, administrative, regulatory and logistical (EARL) barriers and solutions for pandemic-relevant clinical research in Europe.

REGULATING PANDEMIC-RELEVANT STUDIES IN EUROPE: ARE WE READY?

National Competent Authorities (NCAs) and Research Ethics Committees (RECs) across Europe are not uniformly ready to expedite review of clinical research in a public health emergency[1,2]. NCAs and RECs support the need for clinical research in an infectious disease outbreak and for swift review. However, there is variability across EU member states regarding the availability of expedited review and lack of clarity regarding the standard operating procedures for such review[1,2]. Guidance needed regarding expedited review under the forthcoming Clinical Trials Regulation.

WHAT DO POTENTIAL RESEARCH PARTICIPANTS THINK ABOUT RESEARCH IN A PANDEMIC?

Potential research participants consider it important that medical research is done during an influenza pandemic[3,4]: 84% of 6804 respondents thought clinical research should be done in an influenza pandemic and 75% thought that "special rules" should apply to make it happen[3]. We also found support for more proportionate research protection procedures for publically funded, low-risk comparative effectiveness research[4,5]. We need to bring people with us in our efforts to integrate research into response. Wider public dialogue is needed, particularly initiatives to build research literacy[3].

ADPATIVE PLATFORM TRIALS: A CLOSER LOOK

Novel trial designs offer promise for delivering clinical research in an ID outbreak. However, little is known about stakeholder experiences of these designs[4,5]. PREPARE WP1 is leading a qualitative study embedded within the REMAP-CAP clinical trial. As part of this study, we will evaluate the effect of a novel audio-visual intervention designed to enrich information exchange about the multifactorial component of the REMAP design and about response adaptive randomisation. This audio-visual intervention will be shared with patients or proxy decision makers during the consent process for this trial.

REFERENCES

1. *Pandemic Research Preparedness Survey of National Competent Authorities and Research Ethics Committees across Europe..*
2. Sukumar, P. 2018. *Epidemics, Ethics and Clinical Trials: A Sociological Investigation into the Ethical Approval of Clinical Trials in Europe in the Context of Severe Infectious Disease Outbreaks.* Submitted for examination, UCD.
3. [*Forthcoming Conference Paper*] Gobat, N., Butler, C.C., Harris, V., et al. "Knowledge, trust and experience make the difference: what members of the public think about taking part in medical research during an Influenza pandemic – an international cross-sectional survey across eight OECD countries". Lancet Public Health Science Conference, November 2018, Belfast
4. Gobat, N. H., M. Gal, C. C. Butler, et al (2018). "Talking to the people that really matter about their participation in pandemic clinical research: A qualitative study in four European countries." Health Expect 21(1): 387-395
5. Gobat, N. H., M. Gal, N. A. Francis, et al (2015). "Key stakeholder perceptions about consent to participate in acute illness research: a rapid, systematic review to inform epi/pandemic research preparedness." Trials 16: 591.

APPENDIX D: RECOMMENDATIONS REGARDING GPP-EP (WORKSHOP 1)

Language:

- Review medical language and terminology. Patients and families often perceive the medical terminology that is used to engage with them in an outbreak as hierarchical, criminalising, and stigmatizing. Examples include 'suspects' and 'cases'.
- Train staff and others about community engagement in an outbreak setting to ensure that both the response and research have a humanitarian face. This includes thinking through conversations ahead of time and showing humanity in all interactions.
- Distinguish between resistance, refusal, and reluctance[19]: These distinctions suggest the need for a graded response to what can be perceived by response teams as community "push back". Resistance implies that a security response may be needed while refusal or reluctance does not need such a heavy-handed approach.
- Use Social Science approaches to promote a change of culture or of behaviours adapted for the context.

Communication

- Engage communities in a positive way to increase understanding of how research can enhance clinical care in outbreak settings
- Actively consider how clinical trials can go beyond the sequelae post-epidemic to empowering affected communities to form a collective through education and mobilisation. E.g. Survivors of Ebola in Guinea are currently supporting the risk communication component of the Ebola outbreak response in DRC.
- Devise appropriate communication strategies regarding research in advance, based on population demographics (age, religion, gender, level of education), pre-test communication messages using key informants and, where possible, focus groups, and use preferred communication media, e.g. local radio in simplified different languages.
- Simplify and provide a forum to feedback findings of research results to all stakeholders, including regular communication with the response coordination team.
- Communicate with clinical care providers about patient engagement so that it becomes an integral component of all healthcare systems and institutionalized as a norm in research design and planning so as to strengthen the research capacity and the conduct of ethical research.

Funds

- Cite Good Participatory Practice for Emerging and Re-emerging Pathogens (GPP-EP) guidelines[7] and key actions[14]. Reference GPP-EP guidelines in protocols and include an adequate budget to make GPP implementable.

Context

- Engaging communities in the epidemic response and research is highly context-specific and will vary according to engagement objectives.
- Recognise that the context of the epidemic is often vivid in people's minds during or just after epidemic onset and these experiences influence people's attitudes to both the response and any proposed research.
- Previous clinical trials in the setting, and the ways in which this research was perceived will influence interest and acceptability.
- Work through the moral obligations of implementing research and be mindful of not pulling resources from an emergency response, especially in settings were human resources are limited. Balance the recruitment and retention of expertise to research during an epidemic, understand that this can pose an ethical challenge

Socio-Cultural Context

- The study design should take into consideration potential difficulties related to cultural beliefs and practices in data collection processes. For example, taking blood samples may have context-specific sensitivities (depending on socio-cultural significance of blood). This has the potential to fuel distress between clinicians, researchers, and patients and requires tailored and sustained dialogue.
- Social science research implemented alongside the clinical trial can help identify salient contextual factors; identify perceptions, anxieties and opportunities for dialogue as they arise; and inform strategies for engaging participants/ patients as partners.
- In settings that are vulnerable to emerging and re-emerging pathogen outbreaks, conduct research literacy programmes to enhance research capacity.
- Introduce patient panels for patients to have their say and advocate for funding

Operations

- Appreciate that anthropological studies can take time but that there are local sources of understanding about community beliefs and practices, such as key community leaders, and community health providers, who can provide information to ensure that mistrust and fears around research and epidemics, are issues that can be solved as quickly and appropriately as possible.
- Devise ways of operationalizing social science inputs into the operational structures of an epidemic response and to keep abreast of emerging issues in order to devise practical solutions in real time.
- Develop systematic practical tools to gather qualitative data /indicators that can be quickly applied in the field during an epidemic outbreak to inform both the epidemic response and research conduct.

APPENDIX E: ETHICS FRAMEWORK - DRAFT

The workshop material was shaped with reference (and thanks) to the Médecins Sans Frontières Research Ethics Framework[15] – Guidance Document

Particular principles underpinning research in pandemics

1. Research in a pandemic must not compromise the public health response or provision of clinical care.
2. All (public, patients professionals) should be part of a planning partnership before the pandemic.
3. Research must accommodate this devastating context. People, patients and possible participants may have changed risk perspectives in the midst of a pandemic and willing to take risks. They may be frightened, vulnerable and possibly with compromised capacity.
4. The balance between individual and community (other people's) interests changes in a pandemic.
5. The balance between data sharing and individual confidentiality needs additional consideration and may change from "non-pandemic" situations: 'Every researcher who engages in generation of information related to a public health emergency or …with the potential to progress to an emergency has the fundamental moral obligation to share preliminary results once they are adequately quality controlled for release'. (WHO consultation, 2015) (Caldicott 7)

"Questions and considerations"

1. *Research Question and Methodology*

What is the research question and will the proposed method answer it?

2. Respecting and Protecting Research Participants and Communities

- What are the anticipated benefits and harms?
- (How) will consent be obtained?

a. What information ought to be provided?

b. Providing information does not guarantee it has been understood. How can information be provided at an appropriate linguistic level, without jargon or technical terms, and appropriate to the local language and culture?

c. Should information be provided in oral and/or written form?

d. How will the consent process be conducted?

e. Alternative or additional consent procedures may need to be developed where potential participants are minors, minor parents, or suffering from short or long-term incapacities etc. Using a patient advocate?

- How will confidentiality be protected?

3. *Implications and Implementation of the Research Findings*

What will happen when the research is either stopped or is complete?

How will participants be managed as they leave the study?

REFERENCES

1. Osterholm MT, Olshaker M. Deadliest Enemy: our war against killer germs. US: Little, Brown Book Group; 2017.

2. TDR Reserch Fairness Initiative report. Geneva: WHO, 2018.

3. Gobat NH, van Someren Greve F, Sigfid L, et al. Preparedness for clinical research during pandemics: a perspective from the Platform for European Preparedness Against (Re-) emerging Epidemics (PREPARE) Lancet Public Health Conference; 2018; Belfast: Lancet; 2018.

4. Dunning J, Sahr F, Rojek A, et al. Experimental Treatment of Ebola Virus Disease with TKM-130803: A Single-Arm Phase 2 Clinical Trial. *PLOS Medicine* 2016; **13**(4): e1001997.

5. Gobat NH, Gal M, Butler CC, et al. Talking to the people that really matter about their participation in pandemic clinical research: A qualitative study in four European countries. *Health expectations : an international journal of public participation in health care and health policy* 2018; **21**(1): 387-95.

6. Gobat NH, Gal M, Francis NA, et al. Key stakeholder perceptions about consent to participate in acute illness research: a rapid, systematic review to inform epi/pandemic research preparedness. *Trials* 2015; **16**: 591.

7. Hankins C. Good participatory practice guidelines for trials of emerging (and re-emerging) pathogens
that are likely to cause severe outbreaks in the near future and for which few or no medical countermeasures exist (GPP-EP). WHO: WHO, 2016.

8. Webb SA, Nichol AD. Bending the Pandemic Curve: Improving Decision-Making With Clinical Research. *Crit Care Med* 2018; **46**(3): 442-6.

9. Butler CC, Coenen S, Saville BR, et al. A trial like ALIC(4)E: why design a platform, response-adaptive, open, randomised controlled trial of antivirals for influenza-like illness? *ERJ open research* 2018; **4**(2): 00046-2018.

10. Bongard E, van der Velden AW, Cook J, et al. Antivirals for influenza-Like Illness? A randomised Controlled trial of Clinical and Cost effectiveness in primary CarE (ALIC⁴ E): the ALIC⁴ E protocol. *BMJ Open* 2018; **8**(7).

11. Money and microbes: strengthening clincal research capacity to prevent epidemics, 2018.

12. Ribeiro CDS, van Roode MY, Haringhuizen GB, Koopmans MP, Claassen E, van de Burgwal LHM. How ownership rights over microorganisms affect infectious disease control and innovation:

A root-cause analysis of barriers to data sharing as experienced by key stakeholders. *PLoS ONE* 2018; **13**(5): e0195885-e.

13. Boseley S. Sally Davies: CMO, scientist and campaigner. *The Lancet* 2016; **387**(10032): P1987.

14. Key actions: Good participatory practices in trials of emerging and re-emerging pathogens (GPP-EP).

15. Schopper D, Dawson A, Upshur R, et al. Innovations in research ethics governance in humanitarian settings. *BMC Med Ethics* 2015; **16**: 10.

16. Enria L, Lees S, Smout E, et al. Power, fairness and trust: understanding and engaging with vaccine trial participants and communities in the setting up the EBOVAC-Salone vaccine trial in Sierra Leone. *BMC Public Health* 2016; **16**(1): 1140.

17. Mooney T, Smout E, Leigh B, et al. EBOVAC-Salone: Lessons learned from implementing an Ebola vaccine trial in an Ebola-affected country. *Clin* 2018: 1740774518780678.

18. "Ethics preparedness": Facilitating Ethics Review During Outbreaks. Recommendations arising from a joint ALERRT & WHO workshop, 2018.

19. WHO WHO. Risk Communication and Community Engagement Preparedness and Readiness Framework: Ebola Response in the Democratic Republic of Congo in North Kivu. Geneva, WHO: WHO, 2018.

http://www.prepare-europe.eu

https://www.glopid-r.org

Video of the event: https://vimeo.com/297671913