

# **Conducting research in the context of global health emergencies: identifying key ethical and governance issues**

*Dr Agomoni Ganguli Mitra, Research Associate (Liminal Spaces Project) and Teaching Fellow, Mason Institute, School of Law, University of Edinburgh*

*Dr Nayha Sethi, Research Fellow (Liminal Spaces Project) and Deputy Director, Mason Institute, School of Law, University of Edinburgh*

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**Note**

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**Background paper**

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**Summary**

- 1 This background paper provides an overview of key ethical and governance challenges associated with conducting research and innovation in the context of global health emergencies<sup>1</sup> (GHEs). It considers key existing contributions in this area and identifies gaps where work remains to be done.

**Section one: introduction and background: research during global health emergencies**

- 2 Various facets of global health emergencies (GHEs) give rise to different, context-specific concerns. Infectious diseases (IDs) such as Ebola and Zika necessitate immediate responses to ensure containment, treatment and prevention. Whilst IDs have easily identifiable health implications, non-health emergencies also trigger significant health consequences.<sup>2</sup> For example, conflict or terror related emergencies, extreme weather, situations of mass migration, and other humanitarian emergencies

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<sup>1</sup> While our preferred term for this paper is ‘emergencies’, the reader will find several terms used, apparently interchangeably at times, including ‘disaster’, ‘humanitarian crises’, and ‘outbreaks’. This is largely to reflect the literature and to point to the specific context in which the ethical or governance consideration is being proposed.

<sup>2</sup> WHO (2016) *Migration and health: key issues*, pp1-2: [www.euro.who.int/en/health-topics/health-determinants/migration-and-health/migrant-health-in-the-european-region/migration-and-health-key-issues#292115](http://www.euro.who.int/en/health-topics/health-determinants/migration-and-health/migrant-health-in-the-european-region/migration-and-health-key-issues#292115).

can exacerbate IDs and increase demands for immunisation and nutrition.<sup>3</sup> Environmental disasters such as the 2004 Indian Ocean tsunami have long-lasting impact on health. Haiti is currently dealing with the aftermath of Hurricane Matthew and a resurgence in cholera.<sup>4</sup> In contrast to immediate and current GHEs, the emergence and acceleration of antimicrobial resistance (AMR) has been dubbed a slowly emerging public health disaster, with its own associated health, ethics and governance concerns.<sup>5</sup>

- 3 Research and innovation play increasingly important roles during, after, and in anticipation of future GHEs. Conducting research is linked to “a moral obligation to learn as much as possible, as quickly as possible”.<sup>6</sup> The English Department of Health (DoH) has recently established a UK Public Health Rapid Support Team. Clinicians and researchers will be deployed to tackle disease outbreaks anywhere in the world within 48 hours, and will conduct research on how best to respond to disease outbreaks.<sup>7</sup> Additionally, in partnership with Innovate UK, the DoH will invest up to £35 million towards the development of vaccines against 12 diseases of epidemic potential.<sup>8</sup> At the international level, progress is under way in implementing the WHO Health Emergencies Programme which seeks to reform the ways in which the organisation approaches emergency work,<sup>9</sup> in particular, through its blueprint for research and development.<sup>10</sup> The latter initiative is dedicated to reducing the ‘time lag’ between the declaration of a Public Health Emergency of International Concern (PHEIC) and “the availability of effective medical technologies”.<sup>11</sup>

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<sup>3</sup> Médecins Sans Frontières (1997) Hanquet G (Editor) *Refugee health, an approach to emergency situations* (London: Pan Macmillan Education).

<sup>4</sup> Relief Web (2016) *Haiti: Hurricane Matthew - situation report no. 18*: [reliefweb.int/report/haiti/haiti-hurricane-matthew-situation-report-no-18-31-october-2016](http://reliefweb.int/report/haiti/haiti-hurricane-matthew-situation-report-no-18-31-october-2016).

<sup>5</sup> Viens A and Littmann J (2015) Is antimicrobial resistance a slowly emerging disaster? *Public Health Ethics* **8(3)**: 1-15.

<sup>6</sup> WHO (2016) *Guidance for managing ethical issues in infectious disease outbreaks*, available at: [apps.who.int/iris/bitstream/10665/250580/1/9789241549837-eng.pdf?ua=1](http://apps.who.int/iris/bitstream/10665/250580/1/9789241549837-eng.pdf?ua=1), at page 30.

<sup>7</sup> Gov.UK (1 November 2016) *UK team of health experts to tackle global disease outbreaks*, available at: [www.gov.uk/government/news/uk-team-of-health-experts-to-tackle-global-disease-outbreaks](http://www.gov.uk/government/news/uk-team-of-health-experts-to-tackle-global-disease-outbreaks).

<sup>8</sup> Gov.UK (8 November 2016) *SBRI funding competition: vaccines for global epidemics*, available at: [www.gov.uk/government/publications/sbri-funding-competition-vaccines-for-global-epidemics-clinical](http://www.gov.uk/government/publications/sbri-funding-competition-vaccines-for-global-epidemics-clinical).

<sup>9</sup> The WHO endeavours to improve its activities “through the establishment of one single Programme, with one workforce, one budget, one set of rules and processes and one clear line of authority” and “an independent mechanism of assessment and monitoring of the performance of the Organization, reporting to the governing bodies.” See: WHO (2016) *Health emergencies programme*, available at: [www.who.int/about/who\\_reform/emergency-capacities/emergency-programme/en/](http://www.who.int/about/who_reform/emergency-capacities/emergency-programme/en/).

<sup>10</sup> WHO (2016) *An R&D blueprint for action to prevent epidemics: plan of action*, available at: [www.who.int/csr/research-and-development/r\\_d\\_blueprint\\_plan\\_of\\_action.pdf?ua=1](http://www.who.int/csr/research-and-development/r_d_blueprint_plan_of_action.pdf?ua=1).

<sup>11</sup> WHO (2016) *Progress report on the development of the WHO health emergencies programme*, available at: [http://www.who.int/about/who\\_reform/emergency-capacities/who-health-emergencies-programme-progress-report-march-2016.pdf](http://www.who.int/about/who_reform/emergency-capacities/who-health-emergencies-programme-progress-report-march-2016.pdf), at page 5. Among various initiatives in this area, the European Commission has reiterated its commitment to research efforts and innovation to combat AMR alongside international partners and collaborators. See: European Commission (2015) *Action plan against the rising threats from antimicrobial resistance: road map*, available at: [ec.europa.eu/dgs/health\\_food-safety/docs/road-map-amr\\_en.pdf](http://ec.europa.eu/dgs/health_food-safety/docs/road-map-amr_en.pdf), pp9-19.

4 Conducting research during GHEs raises considerable challenges. The traditional purpose of research, as defined in CIOMS Guidelines<sup>12</sup> is to produce generalisable knowledge. This is generally distinguished from medical treatment / practice which is typically focussed on diagnosis / preventative treatment / therapy i.e. benefit to the patient.<sup>13</sup> However, in reality, the lines between treatment and research can become blurred,<sup>14</sup> and calls have been made to further clarify these distinctions, particularly in the context of GHEs.<sup>15</sup> The draft revised CIOMS Guidelines acknowledge the potential tension between obligations to treat those affected in disaster situations and to conduct health-related research.<sup>16</sup> A fundamental ethical challenge lies in understanding how treatment and conducting research can fit together in an ethically robust and efficient manner. A limited evidence base exists on various health issues relating to GHEs.<sup>17</sup> Further, knowledge gaps remain around the ethics of conducting context-appropriate research during GHEs<sup>18</sup> and on stakeholder attitudes towards research activities during these times.<sup>19</sup> Additional complexities arise when determining how to implement appropriate regulatory frameworks that adequately account for relevant ethical considerations. A recent systematic review of key guidelines has called for further conceptual clarity in this area, concluding that some key terms and concepts “are used in an inconsistent manner and applied in different contexts”.<sup>20</sup> For example, ‘vulnerability’, ‘risk management’, ‘direct / indirect benefit’ appear to be conceptualised / sub-categorised in different ways across varying guidelines.<sup>21</sup>

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<sup>12</sup> See Preamble of Council for International Organizations of Medical Sciences (2002) *International ethical guidelines for biomedical research involving human subjects*, available at: [www.cioms.ch/publications/layout\\_guide2002.pdf](http://www.cioms.ch/publications/layout_guide2002.pdf).

<sup>13</sup> Beauchamp T and Childress J (2013) *Principles of biomedical ethics* (New York: Oxford University Press), at page 332.

<sup>14</sup> Hunt M, Anderson J, and Boulanger R (2012) Ethical implications of diversity in disaster research *American Journal of Disaster Medicine* **7(3)**: 211-21; WHO (2015) *Ethics in epidemics, emergencies and disasters: research, surveillance and patient care: training manual*, available at: <http://www.who.int/ethics/publications/epidemics-emergencies-research/en/>.

<sup>15</sup> Calain P, Fiore N, Poncin M *et al.* (2009) Research ethics and international epidemic response: the case of Ebola and Marburg hemorrhagic fevers *Public Health Ethics* **2(1)**: 7-29; Hunt M, Anderson J, and Boulanger R (2012) Ethical implications of diversity in disaster research *American Journal of Disaster Medicine* **7(3)**: 211-21.

<sup>16</sup> Council for International Organizations of Medical Sciences (2015) *Draft CIOMS guidelines*, available at: [www.cioms.ch/final\\_draft\\_CIOMS\\_guidelines-10\\_september\\_2015-WITH\\_WATERMARKS.pdf](http://www.cioms.ch/final_draft_CIOMS_guidelines-10_september_2015-WITH_WATERMARKS.pdf), at page 59.

<sup>17</sup> *Ibid.*

<sup>18</sup> Sumathipala A, Jafarey A, De Castro L, *et al.* (2010) Ethical issues in post-disaster clinical interventions and research: a developing world perspective. Key findings from a drafting and consensus generating meeting of the Working Group on Disaster Research Ethics (WGDRE) 2007 *Asian Bioethics Review* **2(2)**: 124-42.

<sup>19</sup> Bull S, Roberts N, and Parker M (2015) Views of ethical best practices in sharing individual-level data from medical and public health research: a systematic scoping review *Journal of Empirical Research on Human Research Ethics* **10(3)** 225-38.

<sup>20</sup> Mezinska S, Kakuk P, Mijaljica G, Waligóra M, and O’Mathúna D (2016) Research in disaster settings: a systematic qualitative review of ethical guidelines *BMC Medical Ethics* **17(62)**: 1-11, at page 1.

<sup>21</sup> *Ibid.*

- 5 The WHO – a key international actor in the context of GHEs – refers to a global health emergency as a ‘public health emergency of international concern’ (PHEIC).<sup>22</sup> Under the International Health Regulations 2005, a PHEIC is defined as “an extraordinary event which is determined:
- a. to constitute a public health risk to other States through the international spread of disease; and
  - b. to potentially require a coordinated international response”.<sup>23</sup>
- 6 This definition implies a situation that is “serious, unusual or unexpected; carries implications for public health beyond the affected State’s national border; and may require immediate international action”.<sup>24</sup> However, this definition, or any definition of a GHE, raises important questions for research and innovation. For example, what is it that makes a public health issue an emergency, and a public health emergency a global health emergency? Who decides what counts as a public health emergency? What might the implications be for emergencies that do not trigger the WHO PHEIC with regards to seeking interventions and global attention for innovation and research? For example, antimicrobial resistance is an increasingly concerning threat<sup>25</sup> on the verge of becoming a global health emergency.<sup>26</sup>
- 7 Research and innovation during GHEs engage numerous actors. The Director-General (DG) of the WHO is responsible for declaring a state of PHEIC. Under the International Health Regulations (IHR) 2005, member states have an obligation to report any suspected PHEICs. In determining whether an event triggers a PHEIC, the DG must convene with the IHR Emergency Committee (EC). Recommendations can include measures to be taken by the affected member state and by other member states in order to “prevent or reduce the international spread of disease and avoid unnecessary interference with international traffic”.<sup>27</sup> The effectiveness of the WHO in responding to PHEICs has been called into question, most recently in relation to Ebola.<sup>28</sup> Concerns relate to the WHO’s limited implementation capacity and the fact that it is under-resourced to meet the leadership demands placed on it by the international community.<sup>29</sup> A further challenge is that global health law falls under the

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<sup>22</sup> Note that, for the purposes of this discussion, PHEICs (Public Health Emergencies of International Concern) refer to those health emergencies designated as such by the WHO. In all other instances, we refer to global health emergencies (GHEs), envisaging PHEICs as a subset of GHEs.

<sup>23</sup> World Health Organization (2015) *International Health Regulations: third edition*, available at: [apps.who.int/iris/bitstream/10665/246107/1/9789241580496-eng.pdf?ua=1](https://apps.who.int/iris/bitstream/10665/246107/1/9789241580496-eng.pdf?ua=1).

<sup>24</sup> WHO (2016) *Alert, response, and capacity building under the International Health Regulations (IHR)*, available at: [www.who.int/ihr/procedures/pheic/en/](http://www.who.int/ihr/procedures/pheic/en/).

<sup>25</sup> WHO (2016) *Antimicrobial resistance*, available at: [www.who.int/mediacentre/factsheets/fs194/en/](http://www.who.int/mediacentre/factsheets/fs194/en/).

<sup>26</sup> Viens A and Littmann J (2015) Is antimicrobial resistance a slowly emerging disaster? *Public Health Ethics* **8(3)**: 1-15.

<sup>27</sup> WHO (2016) *Alert, response, and capacity building under the International Health Regulations (IHR)*: [www.who.int/ihr/procedures/pheic/en/](http://www.who.int/ihr/procedures/pheic/en/).

<sup>28</sup> Kamradt-Scott A (2016) WHO’s to blame? The World Health Organization and the 2014 Ebola outbreak in West Africa *Third World Quarterly* **37(3)**: 401-18; WHO (2015) *Report of the Ebola interim assessment panel*, available at: [who.int/csr/resources/publications/ebola/report-by-panel.pdf](http://who.int/csr/resources/publications/ebola/report-by-panel.pdf).

<sup>29</sup> Brown T, Cueto M, and Fee E (2006) The World Health Organization and the transition from “International” to “Global” public health *American Journal of Public Health* **96(1)**: 62-72; Godlee F (2004) The World Health Organization: WHO in crisis *British Medical Journal* **309(1424)**; Gostin L, Sridhar D,

umbrella of public international law, which traditionally takes a state-centric approach to rights and obligations. Such an approach poses challenges for GHEs due to the difficulty in governing and holding non-state actors accountable and the challenges associated with coordinating response activities. Additional regulatory problems relate to, at times, vague and aspirational standards (often in the form of soft norms), the lack of monitoring and enforceability,<sup>30</sup> and the potential power struggles that can arise between state parties and the WHO.<sup>31</sup>

- 8 In addition to: (i) the IHR 2005 and associated state obligations of prompt notification and (ii) the development of national surveillance and response to PHEICs, numerous other legal and ethical obligations must be fulfilled. For example, the revision of the CIOMS Guidelines (shortly to be finalised) is particularly noteworthy in its introduction of a new specific guideline on conducting researching in disaster situations.<sup>32</sup> Further, given that GHEs “do not respect national borders”, governments have an ethical obligation to “consider the needs of the international community”, not only during, but before and after GHEs.<sup>33</sup> This is particularly so in the case of wealthier nations assisting low-income countries.<sup>34</sup>
- 9 Many additional actors play significant roles in the context of GHEs and research and innovation, including: local communities / potential participants affected by the GHE; local / national researchers and research institutions; governments; NGOs; humanitarian response workers and organisations; charitable foundations; pharmaceutical companies; multilateral organisations; and numerous collaborative networks. Each actor brings with them diverse and, at times, conflicting values, perspectives and priorities, adding yet a further layer of complexity. For example, considerable influence might be exerted by these actors, in different ways, on the selection and prioritisation of specific research and innovation agendas during GHEs.<sup>35</sup> Intellectual property considerations are also engaged and the interactions between organisations such as the WHO, World Trade Organization (WTO), and World Intellectual Property Organization (WIPO)<sup>36</sup> can impact research and innovation. Tensions can arise out of the need to balance high costs associated with research and development of new drugs (particularly costs associated with patent protection) and the concern that these drugs be affordable and accessible to low- and

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and Hougendobler D (2015) The normative authority of the World Health Organization *Public Health* **129(7)**: 854-63.

<sup>30</sup> For example, the WHO refers to enforceability being limited to ‘skilful negotiation’. See: WHO (2016) *PIP Review Group preliminary findings*, available at:

[http://www.who.int/influenza/pip/2016review/pip\\_review\\_group\\_prelim\\_findings.pdf?ua=1](http://www.who.int/influenza/pip/2016review/pip_review_group_prelim_findings.pdf?ua=1), at page 8.

<sup>31</sup> For an overview of different institutions and interactions in global health, see: Gostin L (2014) *Global health law* (Cambridge, Massachusetts: Harvard University Press).

<sup>32</sup> Council for International Organizations of Medical Sciences (2015) *Draft CIOMS guidelines*, available at: [www.cioms.ch/final\\_draft\\_CIOMS\\_guidelines-10\\_september\\_2015-WITH\\_WATERMARKS.pdf](http://www.cioms.ch/final_draft_CIOMS_guidelines-10_september_2015-WITH_WATERMARKS.pdf).

<sup>33</sup> WHO (2016) *Guidance for managing ethical issues in infectious disease outbreaks*, available at: <http://apps.who.int/iris/bitstream/10665/250580/1/9789241549837-eng.pdf?ua=1>, pp13-4.

<sup>34</sup> United Nations Economic and Social Council (2000) General comment no. 14: the right to the highest attainable standard of health (Article 12) International Covenant on Economic, Social and Cultural Rights.

<sup>35</sup> Gostin L (2014) *Global health law* (Cambridge, Massachusetts: Harvard University Press).

<sup>36</sup> WTO, WIPO and WHO (2012) *Promoting access to medical technologies and innovation: Intersections between public health, intellectual property and trade*, available at: [https://www.wto.org/english/res\\_e/publications\\_e/who-wipo-wto\\_2013\\_e.htm](https://www.wto.org/english/res_e/publications_e/who-wipo-wto_2013_e.htm).

middle-income countries.<sup>37</sup> Whilst developments have been made in terms of reconciling these tensions (for example via the Doha Declaration<sup>38</sup> and, in the UK, the DoH competition for developing vaccines for global epidemics,<sup>39</sup>) fundamental challenges to drug development and access for GHEs remain.<sup>40</sup>

10 Various initiatives coordinate research and advise on ethical and governance issues related to conducting research during GHEs.<sup>41</sup> For example:

- the WHO is responsible for coordinating the Global Outbreak Alert Response Network (GOARN) (a network of collaborating institutions and networks),<sup>42</sup> the recent WHO blueprint for research and development recognises that research is “an integral element to the response of any epidemic”;<sup>43</sup>
- the Pandemic Influenza Preparedness (PIP) Framework plays an important role in facilitating sharing of virus samples, and the development of, and access to, vaccines by poorer countries;<sup>44</sup>
- the Global Forum on Bioethics in Research offers a platform for organisations interested in the ethics around conducting research involving (low- and middle-income countries) LMICs;<sup>45</sup> and
- the Global Research Collaboration for Infectious Disease Preparedness (GLOPID-R) brings together funding organisations and facilitates effective rapid response, research and innovation.<sup>46</sup>

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<sup>37</sup> Consider in particular the Agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS) and the implications for access to medicines; Helfer L (2015) *Pharmaceutical patents and the human right to health: the contested evolution of the transnational legal order on access to medicines* in Halliday T and Shaffer G (Eds) *Transnational Legal Orders* (Cambridge: Cambridge University Press).

<sup>38</sup> Declaration on the TRIPS Agreement and Public Health (2001). In particular, the Declaration allows WTO members to issue compulsory licences.

<sup>39</sup> Gov.UK (8 November 2016) *SBRI funding competition: vaccines for global epidemics*, available at: [www.gov.uk/government/publications/sbri-funding-competition-vaccines-for-global-epidemics-clinical](http://www.gov.uk/government/publications/sbri-funding-competition-vaccines-for-global-epidemics-clinical).

<sup>40</sup> Balasegaram M, Bréchet C, Farrar J, Heymann D, Ganguly N, *et al.* (2015) A global biomedical R&D fund and mechanism for innovations of public health importance *PLoS Medicine* **12(5)**: e1001831.

<sup>41</sup> Note in particular the WHO Health Emergencies Programme and, in the context of clinical trials, the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

<sup>42</sup> Global Outbreak and Response Network: [who.int/ihr/alert\\_and\\_response/outbreak-network/en/](http://who.int/ihr/alert_and_response/outbreak-network/en/).

<sup>43</sup> WHO (2016) *An R&D blueprint for action to prevent epidemics: plan of action*, available at: [http://www.who.int/csr/research-and-development/r\\_d\\_blueprint\\_plan\\_of\\_action.pdf?ua=1](http://www.who.int/csr/research-and-development/r_d_blueprint_plan_of_action.pdf?ua=1), at page 5.

<sup>44</sup> Pandemic Influenza Preparedness (PIP) Framework: [who.int/influenza/resources/pip\\_framework/en/](http://who.int/influenza/resources/pip_framework/en/).

<sup>45</sup> Global Forum on Bioethics in Research: [www.gfbr.global/](http://www.gfbr.global/).

<sup>46</sup> Global Research Collaboration for Infectious Disease Preparedness: [ich.org/about/organisational-changes.html](http://ich.org/about/organisational-changes.html).

Despite the increasing number of collaborations and partnerships, systematic coordination of response and research<sup>47</sup> in the context of GHEs remains a key challenge locally and globally.<sup>48</sup>

- 11 From a resource perspective, the “mismatch in surveillance and capacity” remains a primary concern: emerging disease hotspots often occur in poor countries, whereas rich countries benefit from the capacity for research and surveillance.<sup>49</sup> The lack of adequate infrastructure for future preparedness, detection, rapid treatment and containment, let alone conducting research under such circumstances raises important considerations around building sustainable capacity in LMICs and on the roles played by more resource-rich countries and organisations.<sup>50</sup> Additional logistical considerations centre on: ethics approval; design protocols; consent; timeliness; and IP issues around ‘viral sovereignty’<sup>51</sup> over data. For example, the MERS-CoV and H5N1 outbreaks raised questions around: who ‘owns’ samples (those who collect blood / tissue samples or those who identify a virus from the sample)?; and who stands to benefit from subsequent virus samples (who can access the vaccines developed by virtue of sharing virus samples)?<sup>52</sup> Regarding the latter question, the PIP Framework was developed in the wake of Indonesia’s refusal to share H5N1 samples with the WHO, on the grounds that low-income countries (LICs) typically struggle to access vaccines resulting from the sharing of such samples.<sup>53</sup> Whilst the PIP Framework and its Global Influenza and Surveillance Response System (GISRS) now strengthens sharing of pandemic influenza viruses and LIC access to resultant vaccines, considerable room for improvement remains, particularly regarding a complex IP environment.<sup>54</sup>

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<sup>47</sup> As our discussion suggests, it is both a crucial and a rather complex task to differentiate between those interventions that are purely research and those that are purely response. We have therefore chosen to use the term ‘response’ to refer broadly to those actions that are mainly motivated by the desire to contain / mitigate / treat; and the term ‘research’ for those activities that are primarily aimed at producing generalisable knowledge. We recognise, however, that several kinds of activities might fall under both categories, or may not be easily categorised under either label.

<sup>48</sup> The WHO working group on Ebola attracted criticism on various fronts, including the legitimacy of the panellists and the failure to include key, affected actors. See, for example, The Conversation (12 August 2014) *WHO Ebola ethics panel excluded those most affected*, available at: <https://theconversation.com/who-ebola-ethics-panel-excluded-those-most-affected-30429>.

<sup>49</sup> Gostin L (2014) *Global health law* (Cambridge, Massachusetts: Harvard University Press), at page 42.

<sup>50</sup> Minja H, Nsanzabana C, Maure C, *et al.* (2011) Impact of health research capacity strengthening in low- and middle-income countries: the case of WHO/TDR programmes *PLoS Neglected Tropical Diseases* **5(10)**: e1351.

<sup>51</sup> Hameiri S (2014) Avian Influenza, ‘viral sovereignty’ and the politics of health security in Indonesia’ *The Pacific Review* **27(3)**: 333-56.

<sup>52</sup> Bollinger A (2015) E-MERS-GENCY: an application and evaluation of the Pandemic Influenza Preparedness Framework to the outbreak of MERS-COV *Temple International and Comparative Law Journal* **29(1)**:1-24; Gostin L, Phelan A, Stoto M, Kraemer J, and Reddy S (2014) Virus sharing, genetic sequencing and global health security *Science* **345(6202)**: 1295-6.

<sup>53</sup> Sedyaningsih E, Isfandari S, Soendoro T, and Supari S (2008) Towards mutual trust, transparency and equity in virus sharing mechanism: the avian influenza case of Indonesia *Annals Academy of Medicine Singapore* **37(6)**: 482-7; Mullis K (2009) Playing chicken with bird flu: ‘viral sovereignty’, the right to exploit natural genetic resources, and the potential human rights ramifications *American University International Law Review* **24(943)**: 944-55.

<sup>54</sup> Preliminary findings of the PIP Framework Review also acknowledge the need to address the ‘current disconnect’ between handling seasonal and pandemic viruses. See: WHO (2016) *PIP Review Group*



12 There has been an increase in public-private partnerships (PPPs)<sup>55</sup> (also known as ‘collaborative partnerships’ and ‘global health partnerships’) between researchers and national / international institutions. Such initiatives involve various actors, but often imply “relatively institutionalised initiatives, established to address global health problems, in which public and for-profit private sector organisations have a voice in collective decision-making”.<sup>56</sup> Examples of partnerships in the GHE context include:

- The PIP Framework (WHO, member states and various industry partners who develop vaccines based on virus samples);
- ZMapp trial for Ebola in Sierra Leone (International Medical Corps and NIH);
- Rapid diagnostic tests (International Medical Corps, WHO and Foundation for Innovative New Diagnostics); and
- in the context of AMR, the unprecedented ND4BB (New Drugs for Bad Bugs) programme launched by the European Union’s Innovative Medicine Initiative (IMI) in 2012,<sup>57</sup> which currently comprises seven PPP projects.<sup>58</sup>

13 Partnerships can bring additional ethical considerations to the fore<sup>59</sup> particularly with respect to the role of different actors in shaping the research agenda. The World Bank,<sup>60</sup> the Bill and Melinda Gates Foundation,<sup>61</sup> the GAVI Alliance,<sup>62</sup> and the Global Fund to Fight Aids, Malaria and TB<sup>63</sup> provide vast amounts of funding for research. Such organisations might also (directly and indirectly) influence the types of technology / innovation to be applied / investigated.

14 One notable way in which organisations influence the research agenda is via a ‘vertical approach’ whereby research and innovation is targeted towards specific (often funder-dictated) diseases rather than broad systemic improvements.<sup>64</sup> It has been suggested that the vertical approach leads to more easily identifiable or ‘tangible’ outputs in contrast with horizontal / systemic approaches.<sup>65</sup> This targeted approach is often achieved through ‘extrabudgetary funding’,<sup>66</sup> similar to ‘multi-bi financing’: a

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*Preliminary Findings*, available at:

[www.who.int/influenza/pip/2016review/pip\\_review\\_group\\_prelim\\_findings.pdf?ua=1](http://www.who.int/influenza/pip/2016review/pip_review_group_prelim_findings.pdf?ua=1), at page 3.

<sup>55</sup> Crane J (2010) Unequal ‘partners’: AIDS, academia and the rise of global health *Behemoth A Journal on Civilization* 3.

<sup>56</sup> Buse K and Harmer A (2007) Seven habits of highly effective global public-private health partnerships: practice and potential *Social Science & Medicine* 64(2): 259-71, at page 259.

<sup>57</sup> Nature News Blog (24 May 2012) *Europe targets superbugs with public-private effort*, available at: <http://blogs.nature.com/news/2012/05/europe-targets-superbugs-with-public-private-effort.html>.

<sup>58</sup> Innovative Medicines Initiative, New Drugs for Bad Bugs: [www.imi.europa.eu/content/nd4bb](http://www.imi.europa.eu/content/nd4bb).

<sup>59</sup> Martin M and Halachmi A (2012) Public-private partnerships in global health: addressing issues of public accountability, risk management and governance *Public Administration Quarterly* 36(2): 189-237.

<sup>60</sup> World Bank, Projects and Programs: [www.worldbank.org/en/topic/health/projects](http://www.worldbank.org/en/topic/health/projects) note, in particular, its HIV/Aids Program for Africa.

<sup>61</sup> Bill and Melinda Gates Foundation: [www.gatesfoundation.org/](http://www.gatesfoundation.org/).

<sup>62</sup> GAVI, The Vaccine Alliance: <http://www.gavi.org>.

<sup>63</sup> The Global Fund: <http://www.theglobalfund.org/en/>.

<sup>64</sup> Gostin L (2014) *Global health law* (Cambridge, Massachusetts: Harvard University Press).

<sup>65</sup> Vu A, Duber H, Sasser S, Hansoti B, Lynch C et al. (2013) Emergency care research funding in the global health context: trends, priorities, and future directions *Academic Emergency Medicine* 20(12): 1259-63.

<sup>66</sup> Walt G (1993) WHO under stress: implications for health policy *Health Policy* 24(2): 125-44.

trend in global health where donors “route non-core funding –earmarked for specific sectors, themes, countries, or regions – through multilateral agencies and to the emergence of new multistakeholder initiatives”.<sup>67</sup> This raises questions around the potential preference for disease-specific research at the expense of broader healthcare concerns<sup>68</sup> and interventions. For example, in the case of AMR, we might not yet have mechanisms to achieve a good balance between innovation and efforts to change behaviour around the use of antibiotics. Further considerations relate to power dynamics and (lack of) accountability<sup>69</sup> of funders, pharmaceutical organisations and academic institutions which increasingly play a role in PPPs.

- 15 Given the diverse ethical and governance considerations at play, the different actors, agendas and types of research, the remainder of this paper identifies and considers in more detail some of the key ethical concepts, concerns and important questions associated with research during GHEs.

## Section two: overarching ethical considerations

- 16 **Definitions:** whilst the WHO definition (PHEIC) (see paragraph 5 above) is frequently used, it raises several issues. How a PHEIC is defined, and by whom, is itself worthy of ethical attention. Given the wide array of public health and normative responses this might necessitate, it is worth asking to what extent such definitions might help sustain or overcome global divides. Are other (less powerful) actors as free to delineate PHEICs? In terms of triggering international response, to what extent would LICs be dependent on their (resource-limited) ability to muster sufficient international concern? If antimicrobial resistance were to be declared a PHEIC, what additional responsibilities and burdens might be placed on already fragile health systems? Further, events not formally recognised as PHEICs (given that definitions will necessarily be exclusionary) might themselves have potential health implications in the long term.<sup>70</sup> A key challenge lies in ensuring that events which fall outside of the WHO definition of PHEICs are still treated with the urgent attention that they often require.
- 17 **Types of research:** a wide range of activities take place during GHEs that might be classified as research, each of which carry their own ethical concerns. Research undertaken during GHEs ranges from the minimally invasive (collection of data,

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<sup>67</sup> Sridhar D (2012) Who sets the Global Health research agenda? The challenge of multi-bi financing *PLoS Medicine* **9(9)**: e1001312.

<sup>68</sup> Gostin L (2014) *Global health law* (Cambridge, Massachusetts: Harvard University Press).

<sup>69</sup> Martin M and Halachmi A (2012) Public-private partnerships in global health: addressing issues of public accountability, risk management and governance *Public Administration Quarterly* **36(2)**: 189-237; Ng N and Prah Ruger J (2014) Global health governance at a crossroads *Global Health Governance* **3(2)**: 1-37.

<sup>70</sup> Diaz J (2011) The legacy of the Gulf oil spill: analyzing acute public health effects and predicting chronic ones in Louisiana *American Journal of Disaster Medicine* **6(1)**: 5-22.

surveillance)<sup>71</sup> and strengthening of health systems,<sup>72</sup> to more 'risky' and invasive procedures, such as the use of experimental therapeutics (unregistered, unproven or repurposed)<sup>73</sup> or innovative vaccines.<sup>74</sup> This highlights a crucial question: what kind of research questions and designs are appropriate and justified and in which contexts? For example in the case of Zika, possible research and innovation approaches range from biotechnology-oriented approaches such as GM mosquitoes,<sup>75</sup> to vector control,<sup>76</sup> to more basic (but not necessarily less efficient) approaches such as improvement of water supply.<sup>77</sup> Each approach has its own potential, anticipated advantages and disadvantages. Each type of research and associated intervention might need to be assessed in terms of justification, priority and social value, as well as public acceptance and engagement according to appropriate standards. It is important to note that these standards will be subject to change as GHEs evolve. For example, ring vaccines started gaining prominence during Ebola once unproven therapeutics failed to live up to expectations.<sup>78</sup>

**18 The rationale for conducting research:** given that ethical priority lies in responding to the safety and care needs of those affected and those potentially at risk,<sup>79</sup> it will be important to nurture sustained scrutiny of the rationale and justification for conducting research in the first place. Several direct and indirect forms of justification appear in the literature, but these might necessitate further global discussion. For example, Médecins Sans Frontières (MSF) has justified its research by emphasizing that it is focused on “reporting on the health and humanitarian consequences of conflict, investigating the feasibility and effectiveness of interventions and validating models of delivery”.<sup>80</sup> The WHO specifies that research may in no way compromise the response to an outbreak or appropriate care.<sup>81</sup> Developing ethical frameworks for urgent GHEs and potential / long-term GHEs (such as AMR)<sup>82</sup> alongside each other could add

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<sup>71</sup> Nuffield Council on Bioethics (2016) *Briefing note: Zika – ethical considerations*, available at:

<http://nuffieldbioethics.org/wp-content/uploads/NCOB-briefing-note-zika-ethical-considerations.pdf>.

<sup>72</sup> Qari S, Abramson D, Kushma J, Halverson P (2014) Preparedness and emergency response research centers: Early returns on investment in evidence-based public health systems research *Public Health Reports* **129(4)**: 1-4.

<sup>73</sup> Calain P (2016) The Ebola clinical trials: a precedent for research ethics in disasters *Journal of Medical Ethics* published online: [jme.bmj.com/content/early/2016/08/29/medethics-2016-103474.short?rss=1](http://jme.bmj.com/content/early/2016/08/29/medethics-2016-103474.short?rss=1).

<sup>74</sup> Rid A and Miller F (2016) Ethical rationale for the Ebola “Ring Vaccination” trial design *American Journal of Public Health* **106(3)**: 432-5.

<sup>75</sup> FDA (2016) *FDA releases final environmental assessment for genetically engineered mosquito*, available at: <http://www.fda.gov/AnimalVeterinary/NewsEvents/CVMUpdates/ucm490246.htm>.

<sup>76</sup> Centers for Disease Control and Prevention, Zika Virus, Mosquito Control: [www.cdc.gov/zika/vector/](http://www.cdc.gov/zika/vector/).

<sup>77</sup> Centers for Disease Control and Prevention, Zika, Mosquitoes and Standing Water, Public Health Matters Blog: <https://blogs.cdc.gov/publichealthmatters/2016/03/zikaandwater/>.

<sup>78</sup> Rid A and Miller F (2016) Ethical rationale for the Ebola “Ring Vaccination” trial design *American Journal of Public Health* **106(3)**: 432-5.

<sup>79</sup> Draft CIOMS Guidelines (10 September 2015) Guideline 20:

[http://www.cioms.ch/final\\_draft\\_CIOMS\\_guidelines-10\\_september\\_2015-WITH\\_WATERMARKS.pdf](http://www.cioms.ch/final_draft_CIOMS_guidelines-10_september_2015-WITH_WATERMARKS.pdf);

WHO (2016) *Guidance on managing ethical issues in infectious disease outbreaks*, available at: <http://apps.who.int/iris/handle/10665/250580>, guideline 8.

<sup>80</sup> Ford N, Mills E, Zachariah R, and Upshur R (2009) Ethics of conducting research in conflict settings *Conflict and Health* **3(7)**: 1-9, at page 2.

<sup>81</sup> WHO (2016) *Guidance on managing ethical issues in infectious disease outbreaks*, available at: <http://apps.who.int/iris/handle/10665/250580>, guideline 8.

<sup>82</sup> Viens A and Littmann J (2015) Is antimicrobial resistance a slowly emerging disaster? *Public Health Ethics* **8(3)**:1-15.

nuance to the discourse around rationale, by showing, for example, that the apparent normative urgency of access to experimental therapeutics need not consistently overshadow wider, long-term concerns of social value.

- 19 **Priority setting** is often used as a broad umbrella term and might in fact refer to diverse ethical considerations. Priority setting might refer to the global research agenda (in light of the fact that health concerns in LICs are often low-ranked).<sup>83</sup> The Working Group on Disaster Research Ethics (WGDRE) was formed in response to the 2004 Indian Ocean tsunami and the inadequacy of pre-existing guidelines around interventions and research in post-disaster settings. The WGDRE stresses the need to have due regard for whether research is based on local needs and priorities.<sup>84</sup>
- 20 Alternatively, priority setting might refer to immediate priority setting between response and research (as well as how each of these separate activities are to be coordinated and by whom), or setting priority between different studies according to their goals (response or potentially therapeutic, preventative, patient / victim support, enhancing future response, context-targeted innovation, capacity building, creative evidence-base). Consideration of priority will necessarily be informed by infrastructural capacity, urgency, time-related considerations, social value and funding priorities. These potentially conflicting considerations point to the need for leadership in this area as well as some form of representative and transparent deliberation.<sup>85</sup> But these tensions may be too challenging to reconcile: consider for example potential conflict between a call to make research an integral part of response,<sup>86</sup> versus the imperative not to “drain critical health-related resources”.<sup>87</sup>
- 21 **Social value** of research appears particularly important<sup>88</sup> when considering the justification for research, priority setting and research design. It is also a site of potential conflict between individual and collective interests<sup>89</sup> when research and response develop side-by-side. While the distinction may not always be clear-cut, the exercise of elucidating social value might be of ethical import regarding study design, the broader underlying reasons for conducting research, and asking whether research is valuable to those affected by the GHE (see also paragraph 37 below). Recent WHO guidelines require ensuring added social value, as with research during non-

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<sup>83</sup> Sumathipala A, Jafarey A, De Castro L, *et al.* (2010) Ethical issues in post-disaster clinical interventions and research: a developing world perspective. Key findings from a drafting and consensus generating meeting of the Working Group on Disaster Research Ethics (WGDRE) 2007 *Asian Bioethics Review* **2(2)**: 124-42.

<sup>84</sup> *Ibid.*

<sup>85</sup> Such engagement is not without its challenges, see: Bolsewicz Alderman K, Hipgrave D, and Jimenez-Soto E (2013) Public engagement in health priority setting in low- and middle-income countries: current trends and considerations for policy *PLoS Medicine* **10(8)**: e1001495.

<sup>86</sup> National Biodefense Science Board (2011) *Call to action: include scientific investigations as an integral component of disaster planning and response*, available at: <http://www.phe.gov/Preparedness/legal/boards/nprsb/Documents/nbsbrec14.pdf>.

<sup>87</sup> WHO (2016) *Guidance on managing ethical issues in infectious disease outbreaks*, available at: <http://apps.who.int/iris/handle/10665/250580>, guideline 8.

<sup>88</sup> A forthcoming special issue of *Bioethics* will be dedicated to elucidating the concept of social value.

<sup>89</sup> Calain P (2016) The Ebola clinical trials: a precedent for research ethics in disasters *Journal of Medical Ethics* published online: [jme.bmj.com/content/early/2016/08/29/medethics-2016-103474.short?rss=1](http://jme.bmj.com/content/early/2016/08/29/medethics-2016-103474.short?rss=1).

emergency situations<sup>90</sup> and social value also appears at the top of the draft revised CIOMS guidelines.<sup>91</sup> The concept, however, will necessarily be constructed and deconstructed<sup>92</sup> even within the short time frame of disaster research and therefore remains a 'shifting target' for ethical consideration.<sup>93</sup> In contrast, social value for research conducted on slow-developing, potential GHEs such as AMR<sup>94</sup> might be both long-term but also in some cases, more easily identified.

**22 Roles and conflict of relevant actors (regarding response and research in GHEs):** we have considered above how different funding models might influence the research and priority setting agenda. Concerns relating to roles and obligations in response *and* research arise when we consider the wide array of actors implicated by GHEs and their potentially conflicting roles and duties.

23 These potential conflicts can, for example, arise between local / international humanitarian workers versus local / international researchers, and the dual role of NGOs such as MSF, which "initiates, sponsors or participates in numerous research projects in multiple field sites".<sup>95</sup> A separate but related problem is that those actors (or research institutions) with expertise in developing and conducting research are often far removed (geographically and culturally)<sup>96</sup> from those humanitarian actors who have the infrastructure and established relationships with the affected community.<sup>97</sup>

24 Finally, while both conventional care ethics and research ethics have developed sophisticated accounts for key actors involved in these endeavours, as well as their roles and obligations, GHEs (especially during acute phases) can attract many responders (and the media), many of whom may not be adequately trained in either care, or research ethics. This involves risk to privacy<sup>98</sup> (e.g. sharing photos in the media and social media) and other potential harms. Attending to these adds yet a further layer of burden to response activity and coordination.

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<sup>90</sup> WHO (2016) *Guidance on managing ethical issues in infectious disease outbreaks*, available at: <http://apps.who.int/iris/handle/10665/250580>, guideline 8.

<sup>91</sup> Council for International Organizations of Medical Sciences (2015) *Draft CIOMS guidelines*, available at: [www.cioms.ch/final\\_draft\\_CIOMS\\_guidelines-10\\_september\\_2015-WITH\\_WATERMARKS.pdf](http://www.cioms.ch/final_draft_CIOMS_guidelines-10_september_2015-WITH_WATERMARKS.pdf), guideline 1.

<sup>92</sup> Ganguli Mitra A, Dove E, Laurie G, and Taylor-Alexander S (Forthcoming) Reconfiguring social value in health research through the lens of liminality *Bioethics*.

<sup>93</sup> Eckenwiler L, Pringle J, Boulanger R, and Hunt M (2015) Real-time responsiveness for ethics oversight during disaster research *Bioethics* **29(9)**: 653-61.

<sup>94</sup> Viens A and Littmann J (2015) Is antimicrobial resistance a slowly emerging disaster? *Public Health Ethics* **8(3)**: 1-15.

<sup>95</sup> Médecins Sans Frontières *Ethics Review Board*: [www.msf.org/en/msf-ethics-review-board](http://www.msf.org/en/msf-ethics-review-board).

<sup>96</sup> Curry D, Waldman R, and Caplan A (2014) *An ethical framework for the development and review of health research proposals involving humanitarian contexts: project final report*, available at: [http://www.elrha.org/wp-content/uploads/2015/01/FINAL-R2HC-Ethical-Framework\\_Final-Report\\_24-January-2014\\_0.pdf](http://www.elrha.org/wp-content/uploads/2015/01/FINAL-R2HC-Ethical-Framework_Final-Report_24-January-2014_0.pdf).

<sup>97</sup> Levine A (2016) Academics are from Mars, humanitarians are from Venus: finding common ground to improve research during humanitarian emergencies *Clinical Trials* 1-4.

<sup>98</sup> MacIntyre R and Travaglia J (2015) Heightened vulnerability, reduced oversight, and ethical breaches on the internet in the West African Ebola epidemic *The American Journal of Bioethics* **15(4)**: 65-8.

### Section three: conceptualisations of research and their ethical relevance

Research in the context of GHEs can be conceptualised or categorised in various ways. Each approach might have distinct ethical nuances and foci. In the following section we consider some of the ethical implications associated with different categories.

#### (i) Research as response (and response as research)

25 One approach is to describe research as response (and response as research), for those cases where the activities of response and research are so closely intertwined that they must be considered together in terms of broad ethical scrutiny. For example, at the height of the Ebola crisis a WHO Working Group came together to approve the use of unproven and investigational therapeutics as potential therapeutics for the disease.<sup>99</sup> This was considered a research activity (with data on use being systematically collected) and titled MEURI (Monitored Emergency use of Unregistered and Experimental Interventions), clearly distinguished from ‘compassionate use’, which takes place in the care context.<sup>100</sup> Research as response, and vice versa, represents the most challenging conceptualisation given the long-standing distinctions between ethics of care and ethics of research.

#### (ii) Anticipatory research (in anticipation of future care)

26 Another way of conceptualising and categorising research is by distinguishing questions and study designs that aim to anticipate the care and response needs for future GHEs. As the draft CIOMS guidelines point out: “disasters can be difficult to prevent and the evidence base for effectively preventing or mitigating their public health impact is limited”.<sup>101</sup> For example, there is a dearth of evidence for response mechanisms, e.g. on the management of crush victims during earthquakes or successful protocols for pandemics.<sup>102</sup> The need to develop evidence bases<sup>103</sup> and standards for regulatory, clinical and public health decision-making in the epidemic context might be one of the strongest ethical rationales for conducting research in GHEs.

27 Anticipating future care enables improved preparedness for future emergencies.<sup>104</sup> Careful consideration of pre-approved designs and protocols<sup>105</sup> might also constitute

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<sup>99</sup> WHO (2014) *Ethical issues for related to study design for trials on therapeutics for Ebola Virus Disease*, available at: [http://apps.who.int/iris/bitstream/10665/137509/1/WHO\\_HIS\\_KER\\_GHE\\_14.2\\_eng.pdf](http://apps.who.int/iris/bitstream/10665/137509/1/WHO_HIS_KER_GHE_14.2_eng.pdf), at page 2.

<sup>100</sup> *Ibid.*

<sup>101</sup> Council for International Organizations of Medical Sciences (2015) *Draft CIOMS guidelines*, available at: [www.cioms.ch/final\\_draft\\_CIOMS\\_guidelines-10\\_september\\_2015-WITH\\_WATERMARKS.pdf](http://www.cioms.ch/final_draft_CIOMS_guidelines-10_september_2015-WITH_WATERMARKS.pdf), guideline 20.

<sup>102</sup> Levine A (2016) Academics are from Mars, humanitarians are from Venus: finding common ground to improve research during humanitarian emergencies, *Clinical Trials* 1-4.

<sup>103</sup> Lurie N, Manolio T, Patterson A, Collins F, and Frieden T (2013) Research as a part of public health emergency response *New England Journal of Medicine* **368**: 1251-5.

<sup>104</sup> Bhan A (2010) Ethical issues arising in response to disasters: need for a focus on preparation, prioritisation and protection *Asian Bioethics Review* **2(2)**: 143-7.

<sup>105</sup> Calain P (2016) The Ebola clinical trials: a precedent for research ethics in disasters *Journal of Medical Ethics* published online: [jme.bmj.com/content/early/2016/08/29/medethics-2016-103474.short?rss=1](http://jme.bmj.com/content/early/2016/08/29/medethics-2016-103474.short?rss=1).

a means of anticipating potential power and engagement gaps to be overcome before the next GHE. Calls to ensure appropriate training for local healthcare professionals in responding to GHEs also point to the need to develop research alongside response endeavours.<sup>106</sup>

28 The very nature of GHEs such as H5N1, SARS, Ebola, environmental disasters, disasters related to climate change (e.g. floods) and the burden these place on the health systems of the Global South suggest that there may be an ethical imperative to address the North-South divide by involving all relevant voices now, in advance of future GHEs. This is so that the needs of those most disadvantaged are not left to fate or to unpredictable decisions taken in emergency contexts.

### (iii) Research as capacity building

29 Closely related to anticipatory research, are research questions / study designs aimed at building capacity and strengthening health systems: for example, fragile local healthcare systems have been identified as a central factor in the escalation of Ebola.<sup>107</sup> It is worth distinguishing between anticipatory research and research into capacity building because the latter may be primarily aimed at strengthening health systems, while the prevention or improved control of GHEs is a welcome (but subsidiary) result of such endeavours.

30 In turn, these issues are closely related to questions of sustainability (when planning research), fairness, justice in global research agendas, and the need to develop research partnerships ahead of humanitarian crises.<sup>108</sup> All of these considerations apply, regardless of the type of GHE arising. Building coalitions around less imminent disasters such as AMR might also provide a useful base to draw from in the case of more immediate outbreaks. Moreover, allowing for capacity building in one context might pave the way for horizontal learning across the board (e.g. low-cost, low-power electronic diagnostics in acute pandemics used as preventative or routine healthcare measure in the context of natural disasters and armed conflicts). Research undertaken during GHEs may provide the opportunity to further consolidate the crucial, currently often missing,<sup>109</sup> capacity for research review in these contexts.<sup>110</sup>

### (iv) Ethically problematic research

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<sup>106</sup> Lurie N, Manolio T, Patterson A, Collins F, and Frieden T (2013) Research as a part of public health emergency response *New England Journal of Medicine* **368**: 1251-5.

<sup>107</sup> O'Hara B (2015) Weak health systems and Ebola *The Lancet: Global Health* **3(2)**: e71-2.

<sup>108</sup> Sumathipala A, Jafarey A, De Castro L, *et al.* (2010) Ethical issues in post-disaster clinical interventions and research: a developing world perspective. Key findings from a drafting and consensus generating meeting of the Working Group on Disaster Research Ethics (WGDRE) 2007 *Asian Bioethics Review* **2(2)**: 124-42.

<sup>109</sup> Levine A (2016) Academics are from Mars, humanitarians are from Venus: finding common ground to improve research during humanitarian emergencies *Clinical Trials* 1-4.

<sup>110</sup> For example, the WHO calls for the involvement of international non-governmental organisations (INGOs) in consolidating collaborative reviews. See: WHO (2016) *Guidance for managing ethical issues in infectious disease outbreaks*, available at:

<http://apps.who.int/iris/bitstream/10665/250580/1/9789241549837-eng.pdf?ua=1>, guideline 8.

31 The central concern in this case is that if review and standards are not rigorous enough, this might lead to opportunistic, unethical research. While it is unlikely that much purely opportunistic research would filter through the review process (although a high number of cases of non-approved research have been reported),<sup>111</sup> it is worth illustrating that the distinction between valuable research (see paragraph 37 above, and paragraph 21 below) and research that is not relevant might become blurred unless there is sustained ethical attention to several considerations: choice (especially with regards to study location, fair participant selection, and research question), adequate evidence-base, and considerations of timeliness.<sup>112</sup>

#### Section four: key ethical concepts

32 **Fairness / justice / inequality:** the ethical concerns under these three broad labels will be heavily tied to various specific ethical issues, including: priority setting; selection of participants; choice of study location; power, voice and say; sustainability; and access to the benefits of research. As overarching questions, we may want to consider to what extent existing and developing ethical frameworks overcome or enable inequality and injustice (especially systemic, social and structural injustice)? For example, to what extent might mechanisms that are, by design or coincidence, gender blind, further exacerbate problematic social norms (such as the care burden on women during GHEs, or their livelihood)? What might the status be of an “aim to reduce health inequalities”?<sup>113</sup> How might research itself contribute to inequalities perpetuated or exacerbated by GHEs?<sup>114</sup> Which benefit-sharing models might help overcome inequalities rather than sustain them? How might previous work done by the Nuffield Council feed into these considerations?<sup>115</sup>

33 **Context sensitivity:** the discussion on this matter is noteworthy since it goes beyond the paradigmatic ‘clash of culture’ often associated with research conducted by researchers from the global North with participants from the global South. A more nuanced approach to these issues will point to a broader and multi-dimensional understanding of potentially conflicting cultures, values, norms and perspectives: those between responders and researchers,<sup>116</sup> between local responders and non-local responders or researchers, between professional actors and volunteers,

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<sup>111</sup> Sumathipala A, Jafarey A, De Castro L, *et al.* (2010) Ethical issues in post-disaster clinical interventions and research: a developing world perspective. Key findings from a drafting and consensus generating meeting of the Working Group on Disaster Research Ethics (WGDRE) 2007 *Asian Bioethics Review* **2(2)**: 124-42.

<sup>112</sup> *Ibid.*

<sup>113</sup> Nuffield Council on Bioethics (2016) *Briefing note: Zika – ethical considerations*, available at:

<http://nuffieldbioethics.org/wp-content/uploads/NCOB-briefing-note-zika-ethical-considerations.pdf>.

<sup>114</sup> Sumathipala A, Jafarey A, De Castro L, *et al.* (2010) Ethical issues in post-disaster clinical interventions and research: a developing world perspective. Key findings from a drafting and consensus generating meeting of the Working Group on Disaster Research Ethics (WGDRE) 2007 *Asian Bioethics Review* **2(2)**: 124-42.

<sup>115</sup> Particularly with regards to the Council’s attention on global and social justice in its work on research conducted in LICs, public health and global health. Nuffield Council on Bioethics: (2002) *The ethics of research related to health care in developing countries*; (2011) *Global health symposium: responsibility, ethics and policy – report: anniversary symposium*; and (2007) *Public health: ethical issues*.

<sup>116</sup> Levine A (2016) Academics are from Mars, humanitarians are from Venus: finding common ground to improve research during humanitarian emergencies, *Clinical Trials* 1-4.



between local state actors and community members and the international community, and between researchers, research ethics committees (RECs) and participants.<sup>117</sup>

34 **Trust and trustworthiness:** the need to build trust with affected individuals and populations is critical, as increasingly acknowledged within the literature and guidelines. At the same time, building trust might be particularly difficult when there are no pre-existing relationships or engagement, and where the presence of outsiders may further exacerbate the distrust of others or the trauma resulting from the situation of conflict or disaster (e.g. when conducting research in refugee camps).<sup>118</sup>

35 A key ethical concern may be the need to establish trust mechanisms that ensure that participants are truly heard and respected and that trust is not imposed as a further burden in order to facilitate research in emergency contexts. It might be worthwhile considering whether 'building trust' is the ideal ethical term or whether a more appropriate approach might be that of openness and mutual respect, or even the concept of trustworthiness.<sup>119</sup> The latter concept focuses ethical attention on the behaviours that engender trust and places the moral onus for developing trust on the research community rather than the participants, especially given that participants might already be overburdened in various other ways.

36 As with research conducted within different social and cultural settings, the recent Ebola outbreak demonstrated the need to engage with key community figures whom community members were more likely to listen to (i.e. to explain the link between handling dead bodies and the spread of the disease).<sup>120</sup> However, this also points to the need to listen to dissenting or marginalised voices within those communities, and to direct particular moral attention towards those who might bear the brunt of the care work (in the case of Ebola, for example, women were heavily burdened with both formal and informal care work that is often 'invisible' to governance frameworks).<sup>121</sup>

37 **Responsiveness:** prior to the development of research ethics in the disaster context, the concept of responsiveness was most often associated with the literature on research ethics in low-income countries. Popularised by London,<sup>122</sup> responsiveness to host community health needs was developed as an answer to controversies around

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<sup>117</sup> Eckenwiler L, Pringle J, Boulanger R, and Hunt M (2015) Real-time responsiveness for ethics oversight during disaster research *Bioethics* **29(9)**: 653-61; Sumathipala A, Jafarey A, De Castro L, *et al.* (2010) Ethical issues in post-disaster clinical interventions and research: a developing world perspective. Key findings from a drafting and consensus generating meeting of the Working Group on Disaster Research Ethics (WGDRE) 2007 *Asian Bioethics Review* **2(2)**: 124-42.

<sup>118</sup> Eckenwiler L, Pringle J, Boulanger R, and Hunt M (2015) Real-time responsiveness for ethics oversight during disaster research *Bioethics* **29(9)**: 653-61.

<sup>119</sup> As highlighted by the Council in the context of children in clinical research. See: Nuffield Council on Bioethics (2015) *Children and clinical research: ethical issues*, available at: <http://nuffieldbioethics.org/project/children-research/>.

<sup>120</sup> National Geographic (30 January 2015) *How the fight against Ebola tested a culture's traditions*, available at: <http://news.nationalgeographic.com/2015/01/150130-ebola-virus-outbreak-epidemic-sierra-leone-funerals/>.

<sup>121</sup> Harman S (2016) Ebola, gender and conspicuously invisible women in global health governance *Third World Quarterly* **37(3)**: 524-41.

<sup>122</sup> London A (2008) *Responsiveness to host community health needs*, in Emanuel *et al* (Editors) *The Oxford textbook of clinical research ethics* (Oxford and New York: Oxford University Press), pp737-44.

benefit-sharing, the global research agenda, concerns around ‘helicopter research’<sup>123</sup> and general permissibility of research in LICs. Responsiveness in the context of GHEs has been further developed to encompass other kinds of considerations, as discussed further below in terms of attention to local context and actors, sustained ethical scrutiny, and in ways comparable to the concept of ‘reflexivity’.<sup>124</sup>

38 **Vulnerability** as a concept within research ethics has been both broadly and narrowly defined<sup>125</sup> to such an extent that it has been criticised for losing either its normative force or its normative appeal. Nevertheless, vulnerability remains a frequently invoked concept in the context of GHEs.<sup>126</sup>

39 Whilst reference has been made to the ‘resulting vulnerability’<sup>127</sup> from GHEs, or to a state of ‘heightened vulnerability’,<sup>128</sup> there is a lack of consensus around robust conceptual and theoretical underpinnings for its use. Levine, for example, argues that participants should not be automatically considered vulnerable unless legally designated so. Rather, beyond legally defined vulnerability and threats to informed consent, she argues for specific attention to the risk of exploitation, and the effect of prior research (including social science research) on the potential participants.<sup>129</sup> While Levine uses the example of children as a paradigmatic example of vulnerability, this label has been challenged elsewhere, notably by the Nuffield Council’s report on children and clinical research.<sup>130</sup> Similarly, a report by Berman et al. for UNICEF largely avoids the category of vulnerability in relation to children, but rather speaks of the heightened emotional and social vulnerability arising from security issues, volatility and instability.<sup>131</sup>

40 Despite its conceptual and normative vagueness, and the historical problems associated with vulnerability as a category in research ethics, the term persists both in research ethics and in regulation. It might, therefore, deserve further scrutiny in the

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<sup>123</sup> Conducting research in a location and then leaving without establishing long-term collaborative relationship or pathways to access. See: Emanuel EJ (2008) Benefits to host countries, in *The Oxford textbook of clinical research ethics* (Emanuel EJ et al., editors) (Oxford: Oxford University Press).

<sup>124</sup> As developed in Nuffield Council on Bioethics (2015) *Children and clinical research: ethical issues*, available at: <http://nuffieldbioethics.org/project/children-research/>.

<sup>125</sup> Levine C, Faden R, Grady C, Hammerschmidt D, Eckenwiler L, et al. (2004) The limitations of ‘vulnerability’ as protection for human research participants *American Journal of Bioethics* **4(3)**: 44-9.

<sup>126</sup> Mezinska S, Kakuk P, Mijaljica G, Waligóra M, and O’Mathúna D (2016) Research in disaster settings: a systematic qualitative review of ethical guidelines *BMC Medical Ethics* **17(62)**: 1-11.

<sup>127</sup> Sumathipala A, Jafarey A, De Castro L, et al. (2010) Ethical issues in post-disaster clinical interventions and research: a developing world perspective. Key findings from a drafting and consensus generating meeting of the Working Group on Disaster Research Ethics (WGDRE) 2007 *Asian Bioethics Review* **2(2)**: 124-42.

<sup>128</sup> Schopper D, Dawson A, Upshur R, Ahmad A, Jesani A et al. (2015) Innovations in research ethics governance in humanitarian settings *BMC Medical Ethics* **16(10)**: 1-12; MacIntyre R and Travaglia J (2015) Heightened vulnerability, reduced oversight, and ethical breaches on the internet in the West African Ebola epidemic *The American Journal of Bioethics* **15(4)**: 65-8.

<sup>129</sup> Levine C (2004) The concept of vulnerability in disaster research *Journal of Traumatic Stress* **17(5)**: 395-402.

<sup>130</sup> Nuffield Council on Bioethics (2015) *Children and clinical research: ethical issues*, available at: <http://nuffieldbioethics.org/project/children-research/>.

<sup>131</sup> Berman G, Hart J, O’Mathúna D, Mattellone E, Potts A et al. (2016) What we know about ethical research involving children in humanitarian settings: an overview of principles, the literature and cases studies *UNICEF Office of Research, Innocenti Working Paper*.

context of GHEs, especially given conflicting uses in the literature. Possible conceptual ways forward can be based on current approaches and theories of vulnerability, which aim to characterise vulnerability beyond a category or label, and its links with structural and social privilege and inequality, as well as with theories of exploitation.<sup>132</sup>

41 Scholars speak of considering the varying states of vulnerability, arising from physical and material hardship arising from disasters, displacement and the erosion of social cohesion<sup>133</sup> and the potential of researchers contributing to a heightened vulnerability.<sup>134</sup> In the context of potential vulnerability, both in the case of children and otherwise, strong conceptual and analytical links could be made between approaches to partnership<sup>135</sup> and pathways to trust / trustworthiness (see paragraph 34 above) which focus moral attention on partnership rather than protectionism.

### Section five: the ethics of research design

42 Whilst the lines between research and response / care / practice can become blurred,<sup>136</sup> it has also been suggested that traditional research ethics are inadequate for research conducted alongside humanitarian responses. For example, the model is not always that of conventional randomised control trials (RCTs) of novel medicines but may, for example, relate to the use of ring vaccination, which, approved as a study design during the Ebola outbreak, involved tracing and vaccinating the contacts of Ebola patients.<sup>137</sup> This section illustrates some of the key ethical considerations associated with research design.

43 **Adaptive trial designs (ATDs)** are trial designs which are adapted during a study according to interim results about the (in)effectiveness of an intervention (rather than a fixed, pre-determined protocol). ATDs may offer the flexibility required during GHEs: the Global Forum on Bioethics in Research reports that in ATDs, “a much higher percentage of patients receive some kind of treatment and study arms are dropped if interim analysis shows another arm is better. In all cases, therefore, fewer patients are assigned to an arm that is believed “currently” to be the inferior arm”.<sup>138</sup> The need

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<sup>132</sup> Mackenzie C, Rogers W and Dodds S (2014) *Vulnerability: new essays in ethics and feminist philosophy* (New York: Oxford University Press); Hurst S (2008) Vulnerability in research and health care; describing the elephant in the room? *Bioethics* **22(4)**: 191-202.

<sup>133</sup> Eckenwiler L, Pringle J, Boulanger R, and Hunt M (2015) Real-time responsiveness for ethics oversight during disaster research *Bioethics* **29(9)**: 653-61.

<sup>134</sup> Browne K and Peek L (2013) Beyond the IRB: an ethical toolkit for long-term disaster research *International Journal of Mass Emergencies and Disasters* **31(3)**: 82-120.

<sup>135</sup> Nuffield Council on Bioethics (2015) *Children and clinical research: ethical issues*, available at: <http://nuffieldbioethics.org/project/children-research/>.

<sup>136</sup> WHO (2009) *Research ethics in international epidemic response: WHO technical consultation* (Geneva, Switzerland).

<sup>137</sup> Rid A and Miller G (2016) Ethical rationale for the Ebola “Ring vaccination” trial design *American Journal of Public Health* Published online: e1–e4.

<sup>138</sup> Global Forum on Bioethics in Research (2015) *Meeting report: emerging epidemic infections and experimental medical treatments*, available at: <http://www.gfbr.global/wp-content/uploads/2016/03/GFBR-2015-meeting-report-emerging-epidemic-infections-and-experimental-medical-treatments.pdf>, at page 15.

for “expanding research methodologies”,<sup>139</sup> the acknowledgment (in the context of Ebola) that no single approach “is ethically required”<sup>140</sup> and the fact that the scientific value of ATDs has been called into question<sup>141</sup> all suggest that ATDs may merit further consideration.

- 44 Another potential approach is that of ‘wedged cluster’/ ‘stepped wedge’ trial designs, whereby patients are grouped together (depending upon geographical location) and treated at intervals, and participants awaiting treatment act as the control group.<sup>142</sup> Cluster / wedge trials also present ethical challenges, particularly around inequality in timeliness and access. Whichever approach is taken to study design, distinct ethical issues will arise.<sup>143</sup> To what extent can we, or should we, allow ‘prudent transgression’<sup>144</sup> from conventional models of research ethics?
- 45 A further approach might be the use of pre-approved ‘advance protocols’ or ‘model protocols’ which “can be submitted for full review to the IRB [institutional review board] or ERC [ethics review committee], omitting items that are specific to the time and place of the predicted outbreak. When the outbreak occurs, investigators can complete the specific information for review by the committee”.<sup>145</sup> WHO *Guidance for managing ethical issues in infectious disease outbreaks* explicitly refers to such advance generic protocols, suggesting that these would necessitate “early discussion and collaboration with local research ethics committees”.<sup>146</sup>
- 46 **Participant selection:** several sources point to the importance of fair selection of participants. The phrasing used in relevant discussions and documents often echoes the selection concerns which exist in traditional research ethics. Beyond that, it remains unclear whether this consideration is: (i) mostly procedural (ensuring scientific validity and minimising risk);<sup>147</sup> (ii) whether it should merely follow existing research ethics guidelines such as the CIOMS Guidelines; or (iii) whether this always also represents an appeal to substantive considerations of fairness such as choice of research context and global research agenda, added social value for participants,

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<sup>139</sup> WHO (2014) *Ethical issues related to study design for trials on therapeutics for Ebola Virus Disease* WHO Ethics Working Group Meeting: summary of discussion (20-21 October 2014).

<sup>140</sup> Presidential Commission for the Study of Bioethical Issues (2015) *Ethics and Ebola: public health planning and response*, available at: [http://bioethics.gov/sites/default/files/Ethics-and-Ebola\\_PCSBI\\_508.pdf](http://bioethics.gov/sites/default/files/Ethics-and-Ebola_PCSBI_508.pdf).

<sup>141</sup> Cohen J and Enserink M (2016) As Ebola epidemic draws to a close, a thin scientific harvest *Science* **351** (6268): 12-3.

<sup>142</sup> Doussau A, and Grady C (2016) Deciphering assumptions about stepped wedge designs: the case of Ebola vaccine research *Journal of Medical Ethics*: Published online: <http://jme.bmj.com/content/early/2016/10/17/medethics-2015-103292.abstract>.

<sup>143</sup> Liu J (2015) Considerations for clinical trial design in public health emergencies *Applied Clinical Trials* 1-4.

<sup>144</sup> Calain P (2016) The Ebola clinical trials: a precedent for research ethics in disasters *Journal of Medical Ethics*: Published online: [jme.bmj.com/content/early/2016/08/29/medethics-2016-103474.short?rss=1](http://jme.bmj.com/content/early/2016/08/29/medethics-2016-103474.short?rss=1).

<sup>145</sup> Macklin R and Cowan E (2009) Conducting Research in Disease Outbreaks *PLoS Neglected Tropical Diseases* **3**(4): e335.

<sup>146</sup> WHO (2016) *Guidance on managing ethical issues in infectious disease outbreaks*, available at: [apps.who.int/iris/bitstream/10665/250580/1/9789241549837-eng.pdf?ua=1](http://apps.who.int/iris/bitstream/10665/250580/1/9789241549837-eng.pdf?ua=1), at page 31.

<sup>147</sup> Schopper D, Upshur R, Matthys F, Singh J, Bandewar S, *et al.* (2009) Research ethics review in humanitarian contexts: the experience of the Independent Ethics Review Board of Médecins Sans Frontières *PLoS Medicine* **6**(7): e1000115.

responsiveness, and non-exploitation claims. These considerations become particularly acute when research becomes, or is perceived as, the only way to access services / potential treatment. It is not clear that the ethical discourse has achieved an ideal equilibrium between the demands of scientific rigour (risk / benefit, randomisation), informed consent (voluntary and free from therapeutic misconception) and the arguably entirely rational choice people might make to participate in risky research if that represents their only means of accessing care or potentially life-saving treatment.

**47 Community involvement and representation** encompasses several considerations. For example: (i) building relationships of trust with potential participants (see paragraph 34 above); (ii) the involvement of patient groups, community members and representatives in all aspects of research design and throughout all stages of research; and (iii) the involvement of local RECs during the review process.<sup>148</sup> Bearing in mind the added burden of research on an already strained health system,<sup>149</sup> the link between “good community engagement practice” and “sensitivity to important local variation”<sup>150</sup> – beyond cultural sensitivity – is also important. For example, the WHO discussion on emergency use of experimental interventions during Ebola was sensitive to the fact that RCTs may not be acceptable to the local community if the intervention in the active arm was the only potential therapeutic intervention.<sup>151</sup> On the other side of the risk spectrum, it has been pointed out that there is a lack of empirical evidence on attitudes of stakeholders in low- and middle-income countries (LMICs) (often the hotspots of GHEs), towards individual-level data sharing in the public health research context.<sup>152</sup>

**48 Review processes:** ethical concerns arising from reviews of research conducted during, or in the aftermath of, public health emergencies have given rise to a subtopic within research ethics.<sup>153</sup> This focus places crucial emphasis on the review process and the obligations of RECs in these contexts. A prime task is weighing urgency<sup>154</sup>

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<sup>148</sup> WHO (2016) *Guidance on managing ethical issues in infectious disease outbreaks*, available at: [apps.who.int/iris/bitstream/10665/250580/1/9789241549837-eng.pdf?ua=1](https://apps.who.int/iris/bitstream/10665/250580/1/9789241549837-eng.pdf?ua=1).

<sup>149</sup> Sumathipala A, Jafarey A, De Castro L, *et al.* (2010) Ethical issues in post-disaster clinical interventions and research: a developing world perspective. Key findings from a drafting and consensus generating meeting of the Working Group on Disaster Research Ethics (WGDRE) 2007 *Asian Bioethics Review* **2(2)**: 124-42.

<sup>150</sup> Parker M and Bull S (2009) Ethics in collaborative global health research networks *Clinical Ethics* **4(4)**: 165-9.

<sup>151</sup> WHO (2014) *Ethics Working Group meeting: ethical issues related to study design for trials on therapeutics for Ebola Virus Disease - summary of discussion* (20-21 October 2014).

<sup>152</sup> Bull S, Roberts N, and Parker M (2015) Views of ethical best practices in sharing individual-level data from medical and public health research: a systematic scoping review *Journal of Empirical Research on Human Research Ethics* **10(3)**: 225-38.

<sup>153</sup> Collogan L, Tuma F, Dolan-Sewer R, Borja S, and Fleischman A (2004) Ethical issues pertaining to research in the aftermath of disaster *Journal of Traumatic Stress* **17(5)**: 363-72; O’Mathúna D (2012) Roles and challenges for IRBs with disaster research *Research Practitioner* **13(5)**: 167-74; Rosenstein D (2004) Decision-making capacity and disaster research *Journal of Traumatic Stress* **17(5)**: 373-81; Mfutso-Bengo J, Masiye F, and Muula A (2008) Ethical challenges in conducting research in humanitarian crisis situations *Malawi Medical Journal* **20(2)**: 46-9 (as cited by Eckenwiler *et al.*).

<sup>154</sup> The WHO speaks of a moral obligation to learn as much as possible as quickly as possible. See: WHO (2016) *Guidance on managing ethical issues in infectious disease outbreaks*, at page 30: [apps.who.int/iris/bitstream/10665/250580/1/9789241549837-eng.pdf?ua=1](https://apps.who.int/iris/bitstream/10665/250580/1/9789241549837-eng.pdf?ua=1).

(for example, calls have been made for flexible approaches to ethics review, including fast-track options and a balance between electronic and in-person communication by REC members<sup>155</sup>) versus rigour.<sup>156</sup> Hunt et al<sup>157</sup> have pointed to three key considerations in review governance: timeliness, responsiveness, and rigour.

- 49 **Real time responsiveness (RTR)** has been suggested as one approach to lessen the potential for disaster research “to create, perpetuate, or exacerbate vulnerabilities and contribute to injustices suffered by disaster-affected populations.”<sup>158</sup> This approach demands ‘sustained ethical attention’ throughout the research process given that no amount of rigour can fully account for the evolution of ethical concerns. RTR calls for review processes to be “sustained, iterative and cyclical”, potentially including research ethics consultants when there is no operating REC and developing research ethics capacity over time.<sup>159</sup> Without pre-delineating what will be at stake ethically, RTR would focus attention towards those actors who might highlight ethical concerns and who had not initially been appointed as community representatives.<sup>160</sup> This is where the concepts of trustworthiness, attentiveness and responsiveness may create a space to reduce vulnerability to further wrong or harm in the context of research in GHEs.
- 50 MSF has established a separate research ethics board (REB) to review its research work. Additionally, it has established models of review exemption (for a *posteriori* analyses of routinely collected medical data),<sup>161</sup> as well as pre-approval for generic protocols.<sup>162</sup> Such models may or may not be transposable to a wide variety of GHEs.
- 51 The WHO has suggested that authorisation of advanced review of generic protocols for conducting research during outbreaks may be appropriate and necessary in certain cases.<sup>163</sup> Others have pointed to the need for more stringent ethical oversight overall.<sup>164</sup> In other words, there are calls for acute attention to the special circumstances of disasters and the need for sustained rigour and attention to

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<sup>155</sup> WHO (2009) *Research ethics in international epidemic response: WHO technical consultation* (Geneva, Switzerland).

<sup>156</sup> Sumathipala A, Jafarey A, De Castro L, et al. (2010) Ethical issues in post-disaster clinical interventions and research: a developing world perspective. Key findings from a drafting and consensus generating meeting of the Working Group on Disaster Research Ethics (WGDRE) 2007 *Asian Bioethics Review* **2(2)**: 124-42.

<sup>157</sup> Hunt et al. speak here in particular about natural disasters (hurricanes, floods etc.). See: Hunt M, Anderson J, and Boulanger R (2012) Ethical implications of diversity in disaster research *American Journal of Disaster Medicine* **7(3)**: 211-21.

<sup>158</sup> Eckenwiler L, Pringle J, Boulanger R, and Hunt M (2015) Real-time responsiveness for ethics oversight during disaster research *Bioethics* **29(9)**: 653-61, at page 653.

<sup>159</sup> *Ibid*, at page 656.

<sup>160</sup> *Ibid*.

<sup>161</sup> Schopper D, Dawson A, Upshur R, Ahmad A, Jesani A et al. (2015) Innovations in research ethics governance in humanitarian settings *BMC Medical Ethics* **16(10)**: 1-12.

<sup>162</sup> *Ibid*.

<sup>163</sup> WHO (2016) Guidance on managing ethical issues in infectious disease outbreaks, available at: <http://apps.who.int/iris/bitstream/10665/250580/1/9789241549837-eng.pdf?ua=1>, at page 31.

<sup>164</sup> Sumathipala A, Jafarey A, De Castro L, et al. (2010) Ethical issues in post-disaster clinical interventions and research: a developing world perspective. Key findings from a drafting and consensus generating meeting of the Working Group on Disaster Research Ethics (WGDRE) 2007 *Asian Bioethics Review* **2(2)**: 124-42.

unpredictable concerns on the one hand, and there are ethically justified reasons for developing quick review processes or pre-approved generic protocols to aid rapid research development on the other. This apparent tension points to two important (and potentially conflicting) ethical dimensions and might require further conceptual and empirical work.<sup>165</sup> This does not preclude the possibility that pre-approved protocols might in fact enhance the rigour of ethical oversight, as well as ease the burden of RECs.

52 The situation might be different in the case of non-infectious diseases, or slowly developing future GHEs. For example, the threat of global AMR might be no less urgent in moral terms, but still offers greater flexibility in terms of developing responses than there would be in the context of an infectious outbreak. It may be that review processes in these cases are in keeping with those of traditional research ethics (for example where there is little need for pre-approved study designs).

53 Alternatively, new models arising from current outbreaks, such as a *posteriori* approval for research of collected tissue may be applicable to both future infectious and non-infectious GHEs. It is also important to consider that, at a local level, those with dual roles (either researchers / responders or REC members / responders) may be engaged in response activities (treatment / care) and therefore unavailable for rapid REC consideration.<sup>166</sup>

54 **Consent** remains a core concept within research ethics and raises particularly challenging questions in the context of research during GHEs, especially given that consent may often be sought during and for activities that stand at the intersection of response and research. There are many varieties of consent (e.g. explicit, implied, informed, broad, blanket, dynamic) and it is important to consider which form of consent will be most appropriate in order to obtain valid consent. This, in turn, will be relative to which function consent is being asked to perform. For example, is consent being sought for 'informedness', or is it (merely) being sought to avoid deception or coercion?<sup>167</sup> Several documents point to the difficult interaction between the response-setting and the research setting, as well as its many actors, and the potential danger of perpetuating humanitarian / therapeutic misconception around participation,<sup>168</sup> or unrealistic hope around experimental therapeutics. Important questions include:

- What do you seek consent for?

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<sup>165</sup> Collogan L, Tuma F, Dolan-Sewer R, Borja S, and Fleischman A (2004) Ethical issues pertaining to research in the aftermath of disaster *Journal of Traumatic Stress* **17(5)**: 363-72; O'Mathúna D (2012) Roles and challenges for IRBs with disaster research *Research Practitioner* **13(5)**: 167-74; Rosenstein D (2004) Decision-making capacity and disaster research *Journal of Traumatic Stress* **17(5)**: 373-81; Mfutso-Bengo J, Masiye F, and Muula A (2008) Ethical challenges in conducting research in humanitarian crisis situations *Malawi Medical Journal* **20(2)**: 46-9 (as cited by Eckenwiler *et al.*).

<sup>166</sup> Sumathipala A, Jafarey A, De Castro L, *et al.* (2010) Ethical issues in post-disaster clinical interventions and research: a developing world perspective. Key findings from a drafting and consensus generating meeting of the Working Group on Disaster Research Ethics (WGDRE) 2007 *Asian Bioethics Review* **2(2)**: 124-42.

<sup>167</sup> O'Neill O (2003) Some limits of informed consent *Journal of Medical Ethics* **29(1)**: 4-7.

<sup>168</sup> Schopper D (2014) Research ethics governance in disaster situations, in O'Mathuna D, Gordijn B and Clarke M, (Editors) *Disaster bioethics: normative issues when nothing is normal* (Dordrecht: Springer).

- What should you seek consent for?
- When do you seek consent?
- Who do you seek consent from? (e.g. if the participant is unable to consent)
- What form of consent do you seek?
- When is consent necessary / sufficient?<sup>169</sup>

55 A challenging task is determining how much information is necessary in order to ensure that the participant sufficiently understands the nature of the research and the risks involved (particularly with experimental procedures / medicines). Further, consent is a narrow term but one which nonetheless encompasses broader considerations of decision-making capacity.<sup>170</sup> For example, barriers to informed consent in the GHE research context can include: fear and desperation, linguistic and cultural barriers between researchers and participants, and power dynamics (participants are often quarantined / isolated from support networks).<sup>171</sup> The question of broad consent for future use of samples collected during GHEs is also problematic,<sup>172</sup> and provides a further interesting contrast and tension to the centrality and normative strength of individual consent for trials. Added to this is question of the feasibility of giving full effect to consent / withdrawal particularly in the context of future use of samples and data, especially where these are anonymised / pseudonymised in large-scale repositories.

56 **Access and post-research benefits:** the question of access in research conducted during GHEs raises ethical questions at various levels. In the first instance, the question of access is similar to the one raised around benefit sharing when conducting research in LICs. Lessons may be learned from previous discussions on research ‘off-shored’ to LICs in an effort to exploit “loosely enforced or poorly elaborated ethical guidelines”,<sup>173</sup> and without rigorous consideration of post-trials access and benefit sharing. In this case too, questions around relevance, social value (see paragraph 21 above) and responsiveness (see paragraph 37 above) will be closely tied to access and benefit-sharing, since it is not impossible that, for example, vaccines might be tested under GHE conditions, which adhere to all existing ethical standards but which, when marketed, will only be available as travel vaccines to residents of high-income countries.

57 Can research be truly justified in the context where those who most need access to the subsequent benefits will not necessarily have access post-trial or post research?

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<sup>169</sup> For example, in the context of secondary data use for data linkage purposes, obtaining consent may not be legally required nor possible / practicable.

<sup>170</sup> Sumathipala A, Jafarey A, De Castro L, *et al.* (2010) Ethical issues in post-disaster clinical interventions and research: a developing world perspective. Key findings from a drafting and consensus generating meeting of the Working Group on Disaster Research Ethics (WGDRE) 2007 *Asian Bioethics Review* **2(2)**: 124-42.

<sup>171</sup> WHO (2016) Guidance on managing ethical issues in infectious disease outbreaks, available at: [apps.who.int/iris/bitstream/10665/250580/1/9789241549837-eng.pdf?ua=1](https://apps.who.int/iris/bitstream/10665/250580/1/9789241549837-eng.pdf?ua=1).

<sup>172</sup> Global Forum on Bioethics in Research (2015) *Meeting report: emerging epidemic infections and experimental medical treatments*, available at: <http://www.gfbr.global/wp-content/uploads/2016/03/GFBR-2015-meeting-report-emerging-epidemic-infections-and-experimental-medical-treatments.pdf>.

<sup>173</sup> Ford N, Mills E, Zachariah R, and Upshur R (2009) Ethics of conducting research in conflict settings *Conflict and Health* **3(7)**.



This is a standard question asked in the context of global research. The PIP Framework (see paragraph 11 above) was established partly in response to the need to ensure that virus sharing and benefit sharing are placed on “an equal footing” and the preliminary findings of the review of the framework suggest that such a balance “can be successfully implemented”.<sup>174</sup> The PIP Framework has established a ‘benefit sharing system’ comprised of partner contributions and standard material transfer agreements (SMTA)<sup>175</sup> and it may be worthwhile considering how this model and other benefit-sharing approaches<sup>176</sup> might be implemented in other research and access contexts, whilst also having due regard to the potential impact of implementing benefit-sharing obligations.<sup>177</sup>

58 We might also want to ask whether the use or availability of experimental treatments in RCTs are in fact perceived as last resort, or last hope, potential therapies. This relates to existing literature in global research around standards of care and placebo-controlled trials, but equally to debates around compassionate use. If access to experimental therapy become the only means to treatment, we might need to ask whether the research / care distinction is being blurred and whether parallels might be drawn with literature on compassionate access in cancer or other life-threatening conditions that do not have established treatments. To what extent is the use of experimental (unproven, unregistered, repurposed, investigational, untested for safety and efficacy in human) therapeutics in GHEs meaningfully compared to, or distinguished from, the debate around compassionate use / access?<sup>178</sup>

59 **Data sharing and management** can strongly impact research<sup>179</sup> before, during and after GHEs. Technological developments in data collection and analysis<sup>180</sup> and the changing nature of clinical trials present new opportunities for research. Rapid, accurate and accessible data during GHEs is crucial not only in the early stages of detection, but for mapping the development of GHEs and for identifying, developing, and assessing efficacy of interventions, particularly in terms of future outbreaks.<sup>181</sup> The WHO policy identifies three categories of data sharing: (i) surveillance, epidemiology and emergency response; (ii) genetic sequence data / information; and

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<sup>174</sup> WHO (2016) *PIP Review Group Preliminary Findings*, available at:

[http://www.who.int/influenza/pip/2016review/pip\\_review\\_group\\_prelim\\_findings.pdf?ua=1](http://www.who.int/influenza/pip/2016review/pip_review_group_prelim_findings.pdf?ua=1), at page 2.

<sup>175</sup> WHO PIP Framework: benefit sharing: [www.who.int/influenza/pip/benefit\\_sharing/en/](http://www.who.int/influenza/pip/benefit_sharing/en/).

<sup>176</sup> Hughes R (2012) Individual risk and community benefit in international research *Journal of Medical Ethics* **38(10)**: 626-9.

<sup>177</sup> For example, consider concerns around the implementation of the Nagoya Protocol for global health: *The Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization (ABS) to the Convention on Biological Diversity* :

<https://www.cbd.int/abs/doc/protocol/nagoya-protocol-en.pdf>; Wellcome Trust (2014) Response to consultation on implementing the Nagoya Protocol, available at: <https://wellcome.ac.uk/sites/default/files/wtp056334.pdf>.

<sup>178</sup> Calain P (2016) The Ebola clinical trials: a precedent for research ethics in disasters *Journal of Medical Ethics*: Published online: [jme.bmj.com/content/early/2016/08/29/medethics-2016-103474.short?rss=1](http://jme.bmj.com/content/early/2016/08/29/medethics-2016-103474.short?rss=1).

<sup>179</sup> Nuffield Council on Bioethics (2015) *The collection, linking and use of data in biomedical research and health care: ethical issues*, available at: [http://nuffieldbioethics.org/wp-content/uploads/Biological\\_and\\_health\\_data\\_web.pdf](http://nuffieldbioethics.org/wp-content/uploads/Biological_and_health_data_web.pdf).

<sup>180</sup> Sethi N (2014) The promotion of data sharing in pharmacoepidemiology *European Journal of Health Law*, **21(3)**: 271-96.

<sup>181</sup> Liu J (2015) Considerations for clinical trial design in public health emergencies *Applied Clinical Trials* **1-4**.

(iii) observational studies and clinical trials.<sup>182</sup> Beyond overarching practical implications of facilitating coordinated data collection and sharing at an international level, each category will bring its own distinct questions to the fore. For example, in the context of genetic sequence data, the question of who might have the capacity to conduct the sequencing is important, as well as considerations around context-sensitivity in the retention of blood and tissue samples for research purposes.<sup>183</sup> With regards to observational studies and clinical trials, “protocols often preclude the disclosure of data before predefined interim or final assessments”, yet rapid access to these data is paramount, particularly for emergency response.<sup>184</sup>

60 An important example of the importance of data management in the context of GHEs relates to pandemic influenza. The PIP Framework (see paragraphs 11 and 57 above) plays an important role in the sharing of pandemic influenza virus samples. Preliminary findings of the PIP Framework review suggest that a broader interpretation of IHR Article 6 (on data sharing) could encourage sharing of non-influenza related pathogens.<sup>185</sup> However, concerns have been raised that an expansion of the PIP Framework may endanger its viability with respect to the current work that it does regarding pandemic influenza altogether. Thus, work remains to be done in terms of identifying feasible and effective frameworks for diseases not already supported by pre-existing systems.

61 On a more general level, whilst guidance states that there is a moral obligation on researchers to share data once quality controlled,<sup>186</sup> this can be in tension with issues such as the ownership of data samples, dissemination of results, and access to treatments developed by virtue of data / sample sharing.<sup>187</sup> It has been reported that empirically grounded evidence on the various ethical and practical challenges associated with data sharing in LICs is lacking<sup>188</sup> and further work remains to be done in identifying and tackling these challenges.

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<sup>182</sup> WHO (2016) Policy statement on data sharing by the World Health Organization in the context of public health emergencies, available at: [http://www.who.int/ihr/procedures/SPG\\_data\\_sharing.pdf](http://www.who.int/ihr/procedures/SPG_data_sharing.pdf).

<sup>183</sup> Bhan A (2010) Ethical issues arising in response to disasters: need for a focus on preparation, prioritisation and protection *Asian Bioethics Review* **2(2)**:143-7.

<sup>184</sup> WHO (2016) Policy statement on data sharing by the World Health Organization in the context of public health emergencies, available at: [http://www.who.int/ihr/procedures/SPG\\_data\\_sharing.pdf](http://www.who.int/ihr/procedures/SPG_data_sharing.pdf).

<sup>185</sup> PIP Framework Review, at page 3: [www.who.int/influenza/pip/2016review/pip\\_review\\_group\\_prelim\\_findings.pdf?ua=1](http://www.who.int/influenza/pip/2016review/pip_review_group_prelim_findings.pdf?ua=1).

<sup>186</sup> WHO (2015) *Developing global norms for sharing data and results during public health emergencies*, available at: [http://www.who.int/medicines/ebola-treatment/blueprint\\_phe\\_data-share-results/en/](http://www.who.int/medicines/ebola-treatment/blueprint_phe_data-share-results/en/).

<sup>187</sup> Bollinger A (2015) E-MERS-GENCY: an application and evaluation of the Pandemic Influenza Preparedness Framework to the outbreak of MERS-COV *Temple International and Comparative Law Journal* **29(1)**: 1-24; Gostin L, Phelan A, Stoto M, Kraemer J, and Reddy S (2014) Virus sharing, genetic sequencing and global health security *Science* **345(6202)**: 1295-6.

<sup>187</sup> Sedyaningsih E, Isfandari S, Soendoro T, and Supari S (2008) Towards mutual trust, transparency and equity in virus sharing mechanism: the avian influenza case of Indonesia *Annals Academy of Medicine Singapore* **37(6)**: 482-7; Mullis K (2009) Playing chicken with bird flu: ‘viral sovereignty’, the right to exploit natural genetic resources, and the potential human rights ramifications *American University International Law Review* **24(943)**: 944-55.

<sup>188</sup> Bull S, Roberts N, and Parker M (2015) Views of ethical best practices in sharing individual-level data from medical and public health research: a systematic scoping review *Journal of Empirical Research on Human Research Ethics* **10(3)**: 225-38.

62 **Risk** is a fluid concept, particularly in the GHE context.<sup>189</sup> The nature of risk, the potential of its manifestation, and the severity of consequences should risk manifest, are constantly shifting. Risk not only requires pre-consideration, but also ethically-grounded attention throughout the GHE and any research / interventions envisioned. Whilst risk-benefit assessment is a fundamental component of research ethics review, and risk-based approaches to health research regulation are common,<sup>190</sup> conducting risk assessments in disaster contexts<sup>191</sup> (particularly where the rate of mortality is high<sup>192</sup>) poses its own distinct challenges. One such challenge is how to handle the greater uncertainties associated with research during GHEs. The potential acceptability of different risks will vary, depending on numerous factors including the type of research and the context in which it takes place.<sup>193</sup> Higher risk associated with experimental therapies raises especially challenging questions. Even where steps are taken towards risk minimisation,<sup>194</sup> the risks associated with new / experimental interventions may still be relatively high. An additional consideration is how to achieve a balance between risk identification, risk elimination, risk-management, and risk perception. It must be recognised that a 'one-size-fits-all' approach towards the management of risks may not be appropriate (potential risks associated with experimental medicines will be very different to those associated with data-sharing). From a governance perspective, holistic risk assessments which are based on as much accurate information as possible and the concept of proportionality may merit consideration in terms of offering flexible approaches which avoid "excessive and overly cumbersome procedures whilst paying due regard to real risks and seeking appropriate measures where fundamental obligations must be met."<sup>195</sup> An additional consideration lies in determining who bears the burden of the risks associated with research.

## Section six: key challenges

### (i) Tensions between 'response' and 'research'

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- <sup>189</sup> Aven T (2016) Risk assessment and risk management: review of recent advances on their foundation *European Journal of Operational Research* **253(1)**: 1-13; Eckenwiler L, Pringle J, Boulanger R, and Hunt M (2015) Real-time responsiveness for ethics oversight during disaster research *Bioethics* **29(9)**: 653-61.
- <sup>190</sup> The ICH takes a risk-based approach in its updated Good Clinical Practice (including decision-making traceability, data integrity). ICH GCP E6 (R2): [www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2015/08/WC500191488.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/08/WC500191488.pdf).
- <sup>191</sup> WHO (2013) Emergency risk management for health overview, available at: [http://www.who.int/hac/techguidance/preparedness/risk\\_management\\_overview\\_17may2013.pdf](http://www.who.int/hac/techguidance/preparedness/risk_management_overview_17may2013.pdf).
- <sup>192</sup> Calain P (2016) The Ebola clinical trials: a precedent for research ethics in disasters *Journal of Medical Ethics* published online: [jme.bmj.com/content/early/2016/08/29/medethics-2016-103474.short?rss=1](http://jme.bmj.com/content/early/2016/08/29/medethics-2016-103474.short?rss=1).
- <sup>193</sup> Rid A and Wendler D (2011) A framework for risk-benefit evaluations in biomedical research *Kennedy Institute of Ethics Journal* **21**: 141-79; Rid A and Emanuel E (2014) Ethical considerations of experimental interventions in the Ebola outbreak *The Lancet* **384(9957)**:1896-9; Russek-Cohen E, Rubin D, Price D *et al.* (2016) A US Food and Drug Administration perspective on evaluating medical products for Ebola *Clinical Trials* **1-5**.
- <sup>194</sup> Sumathipala A, Jafarey A, De Castro L, *et al.* (2010) Ethical issues in post-disaster clinical interventions and research: a developing world perspective. Key findings from a drafting and consensus generating meeting of the Working Group on Disaster Research Ethics (WGDRE) 2007 *Asian Bioethics Review* **2(2)**: 124-42.
- <sup>195</sup> Sethi N and Laurie G (2013) Delivering proportionate governance in the era of eHealth: making privacy and linkage work together *Medical Law International* 2013 **13(2-3)**: 168-204, at page 191.

- Given that research should not be conducted at the expense of care / aid, how do we strike a balance between the moral obligation to provide care and the moral obligation to learn as much (as quickly) as we can?
- How can treatment, conducting research and innovation fit together in an efficient and ethically robust manner? Do we need to try to develop an ethics of 'research and response' to close the gap between care ethics and research ethics?
- How do we engage with and scrutinise systems and models of innovation, research and collaboration? Such systems require ethical scrutiny and ethically robust pathways to develop respectful collaboration at the local level, including direct engagement with research communities through partnerships that do not perpetuate North-South divides.

### **(ii) The tensions arising within research**

- How do we balance the competing demands of: (i) time and severity-related urgency; (ii) scientific and ethical rigour; and (iii) scientific and ethical flexibility? (Particularly given the uncertainties when testing novel medicines / during experimentation.)
- How do we make the most of the possibilities of "anticipatory" ethical and regulatory frameworks for research during epidemics, particularly where early collaboration might help to identify responsibilities? Equally, how do we tend to the limits of anticipatory frameworks which can only take us so far?
- What potential benefits and limitations might adaptive trial design bring?

### **(iii) Setting priorities and challenges of collaboration**

- How do we set priorities at the global level (especially with regards to health concerns which fall outside current definitions of PHEIC e.g. antimicrobial resistance)?
- What responsibilities might different parties (e.g. pharmaceutical companies or charitable foundations have to collaborate (and with whom))?
- How do we establish collaboration and engage voices at all levels in a way that aims to overcome the North-South divide now, ahead of future GHEs?
- Which actors are best placed to fulfil the dedicated role of facilitating coordination between research and response actors? How do we better accommodate the need to develop partnerships ahead of crises?
- What are the longer term impacts of funding models in shaping research agendas and how do we balance vertical and horizontal approaches and address the need for targeted funding for research and innovation for tangible and intangible overheads?
- How do we set priorities at the level of a specific GHE? How do we set priorities at the participant level (the tension between fair selection, access and 'desperate' access to experimental therapies)?
- How do we respond to the need to listen to dissenting or marginalised voices within communities and direct particular ethical attention towards those who might be bearing the brunt of the care work?
- How do we approach value differences (real and perceived) between the academic research community and the humanitarian community as an impediment to carrying out research - where the former can be portrayed as 'disconnected' and the latter as 'missionaries'?