Institution: University College London		
Unit of Assessment: 30 - Philosophy		
Title of case study: Establishing ethical standards for clinical research during public health emergencies		
Period when the underpinning research was undertaken: 2013-2020		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s): Sarah Edwards	**Role(s) (e.g. job title):** Professor of Bioethics 2018-present Senior Lecturer, 2008-2018	**Period(s) employed by submitting HEI:** 2008-2020
Period when the claimed impact occurred: 2014-2020		
Is this case study continued from a case study submitted in 2014? No		

1. Summary of the impact (indicative maximum 100 words)

Edwards' research informed the World Health Organisation's (WHO) Ethics Guidance and a Training Manual for clinical research during epidemics of emerging and re-emerging infectious diseases, for which no effective treatments or vaccines are known. The ethics guidance applied to 4955 studies undertaken into WHO's priority infectious diseases and pathogens with over 88 million participants globally. Edwards' research has benefited individuals participating in clinical research by promoting wider access to new and repurposed medicines and by protecting the rights and interests of current patients. Edwards initiated the development of an Afrocentric ethics framework for clinical research during epidemics across Africa and supervised a project for the African Union Centres for Disease Control (Africa CDC), involving wide consultation, engagement, and training. Her expertise has been consulted over clinical research for COVID-19 by organisations such as WHO, Africa CDC, and the US FDA which issued new guidelines leading to >370 early approvals of medicines and medical products with surveillance for research.

2. Underpinning research (indicative maximum 500 words)

Professor Sarah Edwards has developed a leading body of research, which examines the relationship between ethics and methodology in clinical research. She argues that trial design can be made more responsive to current patients' clinical needs without sacrificing methodological rigour or scientific gain. In 2013, she published the first article [**R1**] to define the unique moral challenges raised by, and develop ethical standards for, clinical research specifically during the circumstances of public health crises for which no known effective treatments or vaccines exist. These exceptional moral concerns, she argues, undermine the traditional precautionary assumptions that underlie the regulation of medicines. Under such approaches, access to new medicines should be initially restricted to small samples of the population in order first to establish a new treatment's safety and efficacy, often through the conventional randomised controlled trial (**RCT**), before making them more widely available. Where a particular new or repurposed treatment offers a patient the only potential chance at life, then the liberty to access that treatment directly is a significant one. During public health emergencies, such restrictive regulatory rules are more difficult to justify since they primarily seek to gain knowledge to treat future, rather than current patients whose lives could be immediately threatened. Edwards argues that science can advance successfully through 'natural experiments' which prioritise individual and current patients' interests providing direct access to potentially beneficial medicines.

Edwards hosted an international academic conference in June 2014 to review her work in [**R1**]. Representatives from regulatory agencies participated in the conference including the World Health Organization, the US Food and Drug Administration (**FDA**), and the European Medicines Agency (**EMA**). In August that year, Ebola was officially declared a public health emergency of international concern. With collaborators, Edwards secured two major awards from the European African Clinical Trials Partnership (**EDCTP**) to support research during epidemics across Africa [**i**], one specifically for Ebola to gauge local views and values [**ii**].

To help undermine the regulatory premise behind restricting access to new medicines in the way outlined above, Edwards later targeted the epistemic assumption that placebo controlled RCTs are the most efficient scientific method to gain knowledge to treat future patients. In [**R2**], Edwards with colleagues in philosophy of science, argued that robust scientific methods use data

from different sources including from wild animals which may also be susceptible to similar diseases as humans, for example Ebola in Chimpanzees and Gorillas. Methodological pluralism holds that claims regarding causality are more credible when evidence from different sources points to a similar result. Developing a range of methods for 'real-world' research, Edwards, with colleagues, developed an ethical framework for so-called pragmatic trials whose aim is to generate data on how interventions could work in practice rather than under artificial conditions of a conventional placebo-controlled trial [**R3**]. Edwards later showed that a pragmatic approach could efficiently replace the need for subsequent 'implementation studies' to establish how well clinical trial results can be applied more widely especially in the context of COVID-19 [**R4**]. Given the sheer number of new and repurposed treatment candidates available, large effects will become apparent from smaller observational or 'screening' studies especially when no formal clinical trial has (yet) been set up as in [**R5**].

3. References to the research (indicative maximum of six references)

Peer-reviewed papers

R1. Edwards SJL. Drug discovery at the bedside: ethics of clinical science during a pandemic. *American Journal of Bioethics* 2013; 13(9): 1-14 DOI: 10.1080/15265161.2013.813597; with Response to Open Peer Commentaries American Journal of Bioethics 2013; 13(9): W1-W3. (*The AJOB is the highest ranking journal in the specialist field of Bioethics*).

R2. Edwards SJL., Norell C., Illari P., Clarke B., Neuhaus C. A Radical Approach to Ebola: Saving Humans and Other Animals. *American Journal of Bioethics* 2018; 18 (10): 35-42. DOI: 10.1080/15265161.2018.1513584; with Response to Open Peer Commentaries on "A Radical Approach to Ebola: Saving Humans and Other Animals", The American Journal of Bioethics, 19:1, W8-W9, DOI: 10.1080/15265161.2018.1536770 (Funding **i**).

R3. Taljaard M., Weijer C., Grimshaw JM., Ali A., Brehaut JC., Campbell MK., Carroll K., **Edwards S**, Eldridge S., Forrest CB., Giraudeau B., Goldstein CE., Graham ID., Hemming K., Hey SP., Horn AR., Jairath V., Klassen TP., London AJ., Marlin S., Marshall JC., McIntyre L., McKenzie JE., Nicholls SG., Alison Paprica P., Zwarenstein M., Fergusson DA. Developing a framework for the ethical design and conduct of pragmatic trials in healthcare: a mixed methods research protocol. *Trials*. 2018; 19(1):525. DOI: 10.1186/s13063-018-2895-x. PMID: 30261933; PMCID: PMC6161426 (Funding **iii**).

R4. Edwards SJL, Bock T., Palm U., Wang S., Cheng G., Wang L., Pitts P. The Case for Methodological Pluralism in Medical Science. *The American Journal of Bioethics* 2020; 20(9): 39-41, DOI: 10.1080/15265161.2020.1795516 (Funding **i**).

R5. Baker, EH., Patel, K., Ball, J., **Edwards, S**., Harrison, TS., Kaul, A., Koh, M., Krishna, S., Leaver, S., Kumar, V., Forton, DM. Insights from compassionate use of tocilizumab for COVID-19 to inform appropriate design of randomised controlled trials. *British Journal of Clinical Pharmacology* 2020. https://doi.org/10.1111/bcp.14466.

Grants

i. European and Developing Countries Clinical Trials Partnership Pan African and European Network for Research, Response and Preparedness for tackling emerging and re-emerging infectious diseases (PANDORA-ID-NET). Edwards SJL is co-investigator, EUR10,000,000. Mar 2018 - Feb 2022. RIA2016E-1609-PANDORA-ID-NET.

ii. European and Developing Countries Clinical Trials Partnership Epidemic preparedness and risk assessment for Ebola virus disease outbreaks in the Republic of the Congo. Edwards SJL is co-investigator, EUR500,000. Oct 2018 - Sept 2020 (plus one-year extension). RIA2018EF-2082-EPIRISK-Ebov.

iii. Canadian Institutes of Health Research Developing a framework for the ethical design and conduct of pragmatic randomized controlled trials. Edwards SJL is co-investigator, CAD780,300 Apr 2017 – Feb 2021. PJT-153045.

4. Details of the impact (indicative maximum 750 words)

Edwards' research shaped the World Health Organisation's (**WHO**) ***Guidance For Managing Ethical Issues In Infectious Disease Outbreaks***, for clinical research during public health crises,

and also helped to inform the WHO training programme. Edwards' expertise initiated and supported the development of an Afrocentric ethics framework for clinical research during epidemics across Africa. Her expertise had been sought to help prioritise ethical and efficient research for COVID-19 by WHO, Africa CDC, and the US FDA amongst others.

Shaping global ethical standards for clinical research during public health emergencies

The numbers of clinical research studies internationally, especially in developing countries, are increasing as more public health crises arise, and emerging and re-remerging infectious diseases, especially zoonoses (infectious diseases caused by pathogens jumping from animals to humans), become increasingly problematic with human populations encroaching on wildlife and engaging in intensive farming. In turn, this has led to changes in the ways in which clinical research is conducted, particularly by ensuring the use of a robust ethical framework for evaluating study designs and methodology. Edwards' research has benefited individuals participating in clinical research by promoting wider access to new and repurposed medicines and by protecting the rights and interests of current patients. In so doing, the research has helped to address the problem of designing and recruiting participants for clinical research during public health emergencies.

Edwards' research informed training of healthcare workers and researchers by WHO and other organisations. Edwards's 2013 paper [**R1**] was reviewed by WHO and international regulators including the FDA and EMA at the conference she held in June 2014. The **WHO Training Manual, Ethics in epidemics, emergencies and disasters: research, surveillance and patient care** [**A**]**,** was published in 2015 and later translated into Chinese. It had been downloaded >4,000 times by 31-12-2020 [**A**]. The Manual discusses [**R1**] under three of its seven core competencies, including the "Ability to define adequate processes for ethics review in public health interventions, surveillance and research in emergencies". It also contains a case study based on [**R1**] [in **A**, pp.70-71]. Edwards' [**R1**] is cited ten times in the Manual, and other papers by Edwards a further five times [**1**]. The Manual thus seeks to illustrate the ethical problems and putative solutions identified in [**R1**] to encourage more consideration and critical thought on why new medicines are restricted and how health research can progress in context. Edwards also served as a named reviewer of this Manual for WHO. The Manual addresses what it calls a "lack of international consensus" on some aspects of research, surveillance and patient care in emergencies and is designed to "give participants a certain proficiency in ethical reasoning and awareness of the main ethical dilemma that can arise in emergencies" [**A**]. Consequently, it has been regularly used by WHO in training workshops run globally. In addition, the course has been taken 16,795 times on The Global Health Network (a digital platform that delivers training, skills and career development to healthcare workers and researchers) alone [**B**]. Participants commented that they would now consider all the issues raised in the course before making decisions and they would seek to disseminate the Guidance further by including it in their own courses [**B**]. Healthcare workers and researchers are, as a result, better equipped to use innovative trial designs, natural experiments, and real-world data to respond to epidemics and improving access to and standards for clinical care along the way.

Edwards is a named participant who contributed to the writing of **WHO *Guidance For Managing Ethical Issues In Infectious Disease Outbreaks***, published in 2016 and later translated into Chinese, Farsi and Faroese [**C**]. Edwards' paper [**R1**] identified the ethical problems associated with restricting access to clinical trials during epidemics for which no proven treatment had been established at the outset of the outbreak. It also sought to resolve these problems using innovative trial designs and natural experiments and use of "real-world" data. The WHO Guidance [**C**] specifically gives guidance on innovative study designs to help promote the interests of current patients while gaining knowledge through research. WHO facilitates research on diseases posing public health threats of international concern and is legally authorised under the International Health Regulations (**IHRs**). The IHRs is a legally binding agreement governing questions of global health particularly public health emergencies of international concern. WHO guidance is technically referred to as "soft" or quasi-law. While not legally binding as a code of practice, adherence by signatories of the IHRs is expected to enable WHO to discharge its legal function. When a public health emergency is declared, WHO has greater legal powers and adherence to guidance is more critical. Since the Guidance was published, a total of 4955 studies with over 88 million participants have been publicly recorded (on clinicaltrials.gov) to address WHO's priority infectious diseases and pathogens including Ebola, Marburg Virus, Crimean-Congo haemorrhagic

fever, Rift Valley Fever, Lassa Fever, and Zika. Through endorsement of Edwards' research in [**R1**], WHO Guidance governed the above studies of which 4397 studies were specifically related to Covid-19 with 87,024656 participants. The Guidance was downloaded 28,300 times in the period April-October 2020 alone, predominantly in the United States (14,300 downloads) [**C**]. Edwards' research has thus benefited the many individual patients treated during outbreaks by promoting wider access to new and repurposed medicines, and future patients by protecting standards for clinical research.

Development of an Afrocentric ethics framework for clinical research during epidemics of infectious diseases and training research ethics committee and regulators in central Africa
Through PANDORA-ID NET [**i**], a consortium of organisations across Africa and Europe supporting research in emerging and re-emerging infectious diseases, Edwards was enlisted in 2018 to support the newly formed **Africa Centres for Disease Control (Africa CDC)**, part of the African Union, to initiate the development of an **authoritative African ethics framework for research during epidemics** across Africa [**D**]. To help develop the Framework, and drawing on her expertise in **R1**, Edwards hosted a series of physical and virtual meetings with the Africa CDC to help consult and engage African communities of ethics committees, medical scientists, and public health practitioners [**D**]. This included a "Workshop for research ethics committees across the whole Continent" attended by over 200 delegates, which "was the first event of its kind designed to facilitate shared discussion of an exchange of views on research ethics" [**E**]. As the Director of Africa CDC, explains, "the information gained from the consultative work to date has already informed our approach to integrating research into outbreak responses in ethical ways", including consideration of "repurposing vast numbers of existing therapies in an attempt to manage cases of Covid-19". [**D**] They confirm, "Edwards' work helped to systematize these efforts with research goals in mind, bringing them into line with WHO guidance on ethics and study design during public health emergencies" [**D**]. Three quarters of respondents (from 51 African countries) felt that in the absence of available standard treatments, patients with confirmed infection during epidemics could benefit from unregistered interventions for which there is some scientific rationale. Regarding conventional placebo-controlled trials during outbreaks with high case fatality rates, there were three times the number of respondents who considered such trials to be unethical than ethical [**D**]. While the resulting Framework is yet to be finalised by the African Union, the Head of Public Health Institutes and Research for Africa CDC, who leads their public health research programme, has already put the approach to ethics and evidence into practice, for example through collaboration with some 800 senior first responders and integrating research into outbreak response, supported by Edwards [**D**]. Edwards mentored the Head of Public Health Institutes and Research by supervising the project, from which the above survey results are drawn, through the **Chatham House African Leaders' Fellowship** 2018/19 [**F**]. Their collaboration is being used as a model by the Africa CDC: "to help strengthen National Public Health Institutes in each African Union Member State, we continue these conversations in ways first illustrated in Taj's Chatham House work with Edwards" [**D**].

As a member of PANDORA-ID NET, Edwards has contributed to the training of over 300 members of research ethics committees and regulators in central Africa, drawing on her expertise in **R1.** In April 2018, Edwards organised training **in Congo Brazzaville during the 9th Outbreak of Ebola** at the request of the Minister of Health [**E**]. There were over 300 participants, including members of the national ethics committees and regulators from central Africa. In light of reviewing [**R1**] and the WHO Guidance, participants drafted standard operating procedures for research ethics committees and a Community Engagement and Risk Communication Strategy for WHO AFRO, which adopts clinical research in a broader sense than clinical trials [**E**]. As the PANDORA-ID NET coordinator confirms "These documents were used for a preparedness response exercise across these countries then considered at high risk of Ebola, and were subsequently used to expand community consultation and engagement [regarding clinical research] during the 10th and 11th outbreaks of Ebola in DRC" [**E**]. During the **10th Outbreak of Ebola in Democratic Republic of Congo**, "Edwards' expertise in clarifying the ethical implications for clinical decision-making of using unregistered medical interventions" contributed to a workshop for small teams of specialist first responders in Uganda and a training event held in October 2018 in Kinshasa, DRC [**E**]. Both events were specifically designed to support the availability and off-label use of four then experimental drugs for Ebola and detail the requirements for consent in so doing. They were also

designed to prepare the teams for recruiting to clinical trials that were later organised in the DRC to randomly allocate patients to these four drugs respectively without a placebo-only control.

Shaping Covid-19 responses through research ethics advice

Edwards participated in the **WHO R&D Blueprint meeting on COVID-19** in Geneva in February 2020 where she helped identify important gaps in knowledge in the social sciences and in ethics regarding limits to extrapolating social and cultural acceptability of new therapeutics and vaccines from other contexts such as Influenza or Ebola and from other countries in which previous study had been undertaken [**G**]. Soon thereafter, Edwards was invited "as a member and key advisor" to join the APANDEMIC initiative, which aims to "inform and support real-world evidence for Covid-19 research and decision-making", with the aim of encouraging "regulators and researchers to design studies which are methodologically efficient and ethical" [**H**]. As the President of the Center for Medicine in the Public Interest and member of APANDEMIC reports "Edwards' research on ethics and methodology [**R1** and **R4**] informed our [APANDMICS'S] **debate with US FDA**". He explains "the pandemic has forced the US FDA to acknowledge the value of using real-world evidence mainly as surveillance of medicines which have been approved for widespread use earlier than usual" and the FDA has "now issued guidance on using real-world data to support regulatory decisions", allowing medicines to be approved early for widespread use subject to later surveillance rather than waiting until after the traditional stages of clinical trials have been fully completed. [**H**] >370 products (Vaccines; Drug and Biological Therapeutic Products; In Vitro Diagnostic Products; Personal Protective Equipment and Related Medical Devices; Ventilators and Other Medical Devices) have currently been approved under this guidance for COVID-19 [**H**]. Edwards helped set up a **compassionate access to medicines** programme at St George's Hospital NHS Trust and Medical School establishing access to the drug Tocilizumab which turned out to be life-saving. In 2020, in addition to the consultative workshop for the Africa CDC (see above), she participated in a joint webinar hosted by PANDORA-ID Net, The Global Health Network and ALERRT on research ethics during public health emergencies (particularly COVID-19) attended by over 300 delegates [**E**]. Edwards was also invited to give a keynote lecture in November 2020 to help shape and formalise **early approval of new or repurposed medicines and vaccines for COVID-19 in Israel** which has seen the first mass population vaccine programme for Covid-19 in the world with extensive "real-world" research [**I**]. 110 participants from 19 countries attended and the Deputy Academic Director explains that: "From my own perspective as an ethicist and a lawyer specializing in public health policy, medical risk management and clinical care in Israel, these issues had been largely unclear and Edwards helped develop our thinking on the topic". She "helped consolidate views on the therapeutic rationales and evidence for different treatments, as well as developing procedures for off label monitoring for research. In this way, we are able to offer a practical framework to provide access to new or repurposed treatments ethically and lawfully in hospitals with suitably trained healthcare staff" [**I**].

5. Sources to corroborate the impact (indicative maximum of 10 references)

[**A**] Citations in WHO Training Manual, "Ethics in epidemics, emergencies and disasters: Research, surveillance and patient care", published in 2015. https://bit.ly/38lzafF *case study based on [**R1**] on pp.70-71; Contributions to "core competencies" pp.51-66; pp.109-131; pp.165-189.* Downloads of manual.

[**B**] Google Analytics data and qualitative feedback from The Global Health Network.

[**C**] WHO Guidance For Managing Ethical Issues In Infectious Disease Outbreaks, 2016. https://bit.ly/3t4AR9r Downloads of guidance.

[**D**] Testimonial from the Director of Africa CDC, African Union and addendum, Head of Public Health Institutes and Research, Africa CDC.

[**E**] Testimonial from the host of the event on WHO AFRO campus Congo Brazzaville.

[**F**] Testimonial from Fellowship Director, Centre for Universal Health, Chatham House.

[**G**] Confirmation of attendance and remit of WHO R&D Blueprint priorities for Covid-19 meeting 2020. https://bit.ly/2PyIaaL https://bit.ly/3v3VaW5

[**H**] Testimonial evidence confirming membership of APANDEMIC and impact on US FDA; FDA authorisation of products during Covid-19: https://bit.ly/301uA1P

[**I**] Testimonial evidence regarding invitation to advise Israeli hospitals on early access to medicines and vaccines for COVID-19.