Clinical Trials in Pandemic Settings: How Corona Unbinds Science

Mariacarla Gadebusch-Bondio and Maria Marloth

"There has never been so much knowledge
of our ignorance."

Jürgen Habermas[1]

The Pandemic Scenario

The speed with which the novel coronavirus SARS-CoV-2[2], the pathogenic agent of the lung disease COVID-19, is spreading globally has put society and science under enormous pressure. Increasing numbers of people around the world are falling victim to the disease caused by the virus, which is why effective measures to slow its spread require careful consideration, rapid decision-making and implementation. On the one hand, the scientific knowledge is currently fragmentary (Ioannidis 2020); on the other hand, on the political level there is a moral imperative to protect life. Action must therefore proceed in the face of relative ignorance.

Very little is known about the pathogen (Paules et al 2020). Evidence of this is provided by the abrupt changes of course by political decision-makers – e.g., from trivialising the virus to accepting the danger, and from the vision of achieving herd immunity by allowing the spread of infection to the lockdown of entire cities. Revisions and corrections of initial assessments have added to the uncertainty among the population. The dystopia of an infection spreading rapidly across the globe with lethal consequences for thousands of people – recalling the thriller Contagion (2011) – now appears to have become a reality.[3] The collective imagination, stirred up by the media, is haunted by the spectre of historical epidemics. The Spanish flu of 1918/1919

[1] "So viel Wissen über unser Nichtwissen gab es noch nie", in: https://www.fr.de/kultur/gesellschaft/juergen-habermas-coronavirus-krise-covid19-interview-13642491.html (Interview mit Markus Schwering am 3.4.2020).
[2] The family of corona viruses was identified in the mid-1960s. This includes a number of pathogens that usually infect either humans or animals, more rarely both. In the case of SARS-CoV (Severe Acute Respiratory Syndrome), MERS-CoV (Middle East Respiratory Syndrome) and the novel coronavirus (SARS-CoV-2: Severe Acute Respiratory Syndrome-2), coronaviruses previously infected animals and were then transmitted to humans (zoonoses). (Federal Ministry of Health: http://zusammengegencorona.de/informieren/basiswissen-coronavirus/).
[3] Films about pandemics belong to the genre of disaster films. While "The Seventh Seal" by Ingmar Bergman (1957) historically deals with the plague in the Middle Ages, a series of dystopian depictions of pandemic outbreaks have been produced since the 1990s. Examples include: "Outbreak" by Wolfgang Petersen, USA 1995; "Twelve Monkeys" by Terry Gilliam, USA 1995; "The Last Days" by David and Alex Pastor, Spain 2011; "Contagion" by Steven Soderbergh, USA 2011.

is readily evoked for comparison.[4] In March 1918, the infection first broke out at Camp Funston in Kansas, USA, and in the following weeks spread across several military facilities in the midwestern and southeastern states. As a result of the transport of American troops to Europe during World War I, the virus was able to spread swiftly through Europe. In July 1918, initial hopes of overcoming this wave of flu were dashed, when in August the first cases of a new form of the disease were detected in Brest, from where it spread by sea around the world and back to North America (Patterson and Pyle 1991). This second wave claimed many more lives than the first. It is believed that the virus had meanwhile undergone genetic mutation (ibid.). The American cities of Philadelphia and St. Louis were also struck by this second wave. The way in which they responded to the danger was markedly different – and it is precisely this which is of particular interest from today's perspective on COVID-19. While Philadelphia downplayed the appearance of the first cases in the city and did not take preventive measures to contain the spread of the disease, opting instead to allow a public parade to take place, St. Louis issued far-reaching restrictions two days after the first cases were recorded. Philadelphia reacted with similar decrees only two weeks after the outbreak of the disease. As a result, the Spanish flu claimed significantly more lives in Philadelphia than in St. Louis (Hatchett et al. 2007).

Of the many societies affected by COVID-19, some have decided to implement measures to slow down the spread of the virus, some have delayed. Regional and national approaches vary widely. The spectrum ranges from calls to reduce social contact to complete curfews. Such measures are intended to give health care systems sufficient time to prepare for the care of the burgeoning numbers of those afflicted by the disease. On top of this is the mounting expectation that researchers will arrive at a scientific breakthrough within the shortest possible time. This places them under extreme moral pressure.

How is the international research community reacting to this historic challenge? What strategies promise to lead quickly to a therapeutic treatment for SARS-Covid-2? What are the epistemic and ethical implications of the medical-political emergency?

We wish to pursue these questions in the following, in which we present the SOLIDARITY study launched by the WHO.

Rethinking research in outbreak settings

The pandemic expert, US virologist Anthony Fauci and his co-authors understand SARS-CoV-2 as

> "a stark reminder of the ongoing challenge of emerging and reemerging infectious pathogens and the need for constant surveillance, prompt diagnosis, and robust research

[4] For example, in an article of 16 March 2020 in the online edition of Forbes Magazine, available at https://www.forbes.com/sites/kionasmith/2020/03/16/a-cautionary-tale-about-social-distancing-for-st-patricks-day-and-every-day/#20e244cc1d99 [last accessed on 10 April 2020].

> to understand the basic biology of new organisms and our susceptibilities to them, as well as to develop effective countermeasures." (Fauci et al 2020).

If medicine is to be clinically effective, it must have reliable data and robust evidence. Equally, society and politics depend on scientific evidence to legitimise the sometimes drastic strategies for mitigation or suppression of virus spread (Ferguson et al. 2020). This state of affairs dynamises and accelerates research. It also provokes a lively process of critical, interdisciplinary discussion coupled to rapidly circulating scientific information, which is difficult even for experts to evaluate, thus causing further uncertainty.[5] Even science journalists complain about the "breathless" condition in which, paradoxically, they are expected to explain things that cannot yet be explained. Added to this, maintaining critical distance is scarcely possible given their personal involvement (Brost/Pörksen 2020). Virologists and epidemiologists are among the main actors not only in the scientific, but also in the socio-political and media arenas. However, their role in the public sphere is deeply ambivalent. They are required to communicate complex knowledge in an accessible way, to deal with gaps in knowledge in a transparent manner, and guard against the deceptive facticity of numbers.

Under these exceptional circumstances, medical research has a dual objective: 1. to understand the properties of the novel SARS-CoV-2 and the mechanisms of the disease triggered by it on a biomolecular, infectiological, and immunological level, and 2. to develop therapeutic approaches, and ultimately a vaccine, on this basis.

In the context of the pandemic, however, this is associated with a tension between the demand for high research standards (robust research) and the need for rapid development of an effective therapy that is almost impossible to resolve.

The established evidence regime for the quality assurance of preclinical and clinical studies to test the effect and tolerability of potential therapies is very time consuming. Even in the preclinical phases, numerous active substances fail. The complete development of a new drug would take years. In a situation in which thousands of people the world over are dying of COVID-19, healthcare systems and societies are crashing, and doctors are compelled to use triage models to allocate life-saving resources, this time is simply not available. The urgency of the situation forces us to seek alternative, shorter-term solutions. While in politics this attitude is associated with protective measures that entail more or less restrictive limitations on freedom, the normative constraints have been loosened for scientific quality assurance. To this end, the research community is pursuing two strategies in addition to the efforts to develop a vaccine: on the communication level and on the study design level.

The first strategy is the WHO response to the challenge as "Public Health Emergency of International Concern (PHEIC)"[6], which was later classified as a pandemic. Research is to be

[5] One example is the transmission simulation model developed by epidemiologists at Imperial College, London, Ferguson et al.'s 'Report 9', which was published on 16 March. A critical response to this simulation study came from Chen Shen et al. one day after its release. Chen Shen et al., 17 March 2020.
[6] https://www.who.int/blueprint/priority-diseases/key-action/novel-coronavirus/en/

supported by "data sharing" and access to relevant research data even before publication. The "International Committee of Medical Journal Editors" endorses this initiative (Moorthy et al. 2020). Many publications will be available even before they have gone through a peer review process. A critical evaluation of the literature must therefore be carried out by the readers, which entails increased personal responsibility. The idea is to provide collective and cooperative access to data and preliminary results. Finally, the unimpeded flow of all this data promises a more comprehensive understanding of the disease itself and allows for the development and adaptation of ongoing research to be accelerated. An integral part of this accelerated, 'open' scientific exchange is a willingness to compromise, operating on the basis of ever-changing data sets, and to accept public criticism and correction. Similarly, political and social decision-making processes can be progressively adjusted. Validated evidence is already being made available in well-known databases, such as the Chochrane Library[7] or the Oxford COVID-19 Evidence Service of the Oxford Centre for Evidence-Based Medicine.[8] Many medical journals have special sections on COVID-19 that are updated daily (e.g. NEJM, Lancet, etc.). This acceleration of communication is proving to be increasingly problematic in two domains: at the interface between science and media and between science and politics (Brost/Pörksen 2020). Scientists have been thrust into the limelight alongside politicians. Among other things, they report on preliminary results and ongoing studies. This carries with it the risk of a skewed response.

The second strategy is the SOLIDARITY clinical trial. On 27 March 2020, the Director-General of the WHO, Tedros Adhanom Ghebreyesus, announced the start of SOLIDARITY with the following words:

> "One of the most important areas of international cooperation is research and development. A vaccine is still at least 12 to 18 months away. In the meantime, we recognize that there is an urgent need for therapeutics to treat patients and save lives. Today we are delighted to announce that in Norway and Spain, the first patients will shortly be enrolled in the Solidarity Trial, which will compare the safety and effectiveness of four different drugs or drug combinations against COVID-19. This is a historic trial which will dramatically cut the time needed to generate robust evidence about what drugs work."[9]

SOLIDARITY has been working on the rapid testing of therapies for COVID-19 The prospect of a "dramatic" reduction in the time required to develop these therapies is, in the eyes of Ghebreyesus, unprecedented and therefore of "historical" significance. The "megatrial" includes 45 countries with a correspondingly large number of patients (Kupferschmidt/Cohen 2020), where drugs to treat COVID-19 are being tested. These are not new drugs developed specifically for COVID-19, but rather the so-called "repurposing" or "drug repositioning"

[7] https://www.cochranelibrary.com/covid-19
[8] https://www.cebm.net/covid-19/
[9] https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---27-march-2020.

procedure is used (Hanging et al 2018; Newman 2018). This means that existing drugs, some of which have been approved for other diseases or are close to approval, are tested for their efficacy against COVID-19. Specifically, the SOLIDARITY trial involves the following drugs or drug combinations:

1. The antiviral Remdesivir, which was developed to combat the Ebola virus and is administered intravenously; 2. The antimalarial drugs Chloroquine and Hydroxychloroquine, 3. The HIV combination Lopinavir/Ritonavir – known as Kaletra – and 4. This combination supplemented by beta-interferon (WHO 2020).

The method used by SOLIDARITY is not new. A glance at the pandemic history of the last 40 years shows comparable precursors. Particularly impressive is the fact that as early as the mid-1980s, in connection with the HIV/AIDS pandemic, clinical research successfully tested so-called drug repurposing (Killen 2008). Even today, drug repurposing is still a good alternative in identifying effective therapies for emerging diseases. The fact is that biomedical research has achieved only modest success in the last three decades in terms of developing new drugs (Strittmatter 2014). With a virtually unchanged total of 25-30 novel molecules among the approximately 50 new drugs approved by the FDA each year, only 12% of drug candidates that make it into Phase I clinical trials receive the final green light. This means that of 5,000 to 10,000 compounds from traditional drug development, probably only one will be approved. According to Pizzorno et al., the reasons for this include the focus of research on complex diseases, the limitations of experimental models for reproducing biological complexity ("reductionist experimental models"), high regulatory control measures and, of course, the question of tolerability and unexpected side effects (Pizzorno et al. 2019). On average, it takes 13-15 years to develop a new drug. This makes drug repurposing all the more attractive as a means of filling the innovation gap. The precondition is an excellent understanding of the active pharmacological mechanism of the respective substances. If it is possible to identify drugs for which a new therapeutic application can be validated, long, risky and cost-intensive preclinical and early clinical phases can be avoided. Pushpakom et al. describe three steps that are needed to identify substances that are suitable for repurposing: 1. the relevant molecules for a given therapeutic application must be identified (hypothesis generating); 2. an assessment and evaluation of the effect in preclinical models must have been carried out; 3. an evaluation of the efficacy in Phase II studies must be carried out. The first step in particular is critical, which is why systematic approaches are increasingly being developed (Pushpakom et al. 2019).

For repurposing procedures, "sleeping candidates" may also be considered. These are drugs that have been abandoned during the development process and at advanced stages of clinical trials (Phase II and III) because they have proven to be insufficiently effective for the originally intended medical application or have side effects. A new therapeutic application could potentially revive such candidates (Hernandez et al 2017). An example of such a "sleeping candidate" is AZT (zidovudine). AZT was initially developed as a potential cancer drug, but proved to be ineffective. However, a placebo-controlled study in 1986 confirmed the assumption that it could be effectively used against AIDS. In 1987, AZT was approved as the first antiretroviral drug (Fauci 2006). The urgency of a pandemic situation, in which a

potentially deadly "plague" – be it HIV/AIDS, Ebola or COVID-19 – confronts scientists with the task of developing a therapy under time pressure, provides a favourable context for testing sleeping candidates or drugs already established for other diseases (Bai/Hsu 2019; Zhou et al 2020). The SOLIDARITY study design has been streamlined to allow hospitals overburdened by the pandemic to participate without having to substantially increase their workload. To enroll a patient in the study, clinicians must first check whether the COVID-19 diagnosis has been confirmed and then enter the patient's data on a website, including any previous illnesses such as diabetes or HIV. Once the patient has been informed and has agreed to participate in the study, their consent is transmitted electronically to the WHO, along with details of the drugs available to the hospital. The website then randomises the patient to one of the drugs and the Standard of Care (SoC) or only SoC for COVID-19. This means that patients included in the study will always receive SoC. Finally, the doctor has to document the day the patient was discharged or died, how long the treatment in hospital lasted and whether oxygen therapy or ventilation was necessary.

From an epistemic perspective, it should be stressed that, due to the urgency and the rapidly increasing number of victims, the WHO has decided not only on a streamlined but also a dynamic study design. Adjustments are possible at any time during the course of the study. This is a randomised controlled trial, but without a blinded and placebo group, which is a limitation. During the course of the study, a committee will monitor the data collected and, if necessary, remove one of the four agents from the test if it is shown to have no effect. There is also the possibility of including further drugs in the course of the study.[10]

The dynamic study design is subordinated to the goal of providing patients with effective therapy as quickly as possible. From an ethical point of view, the orientation towards this goal legitimises the generation of weaker evidence. The WHO study coordinators are aware of this, as the authors of a report on SOLIDARITY published online in Science underline: "The design is not double-blind, the gold standard in medical research, so there could be placebo effects from patients knowing they received a candidate drug. But WHO says it had to balance scientific rigor against speed." (Kupferschmidt/Cohen 2020). In addition to accepting the increased risk of systematic bias in the results due to the lack of blinding, the time pressure means that not all possible data are collected as would be usual. For example, parameters such as virus load are not monitored. This allows the study to be conducted in different contexts. The heterogeneity of the study population invalidates an objection that is often raised against randomised controlled trials. In favour of comparability, the selected study participants usually form a very homogeneous group, whose characteristics do not correspond to those of the actual patients who will eventually receive the therapy. For example, study participants show fewer or less severe comorbidities (Campbell-Scherer 2010). The focus on male study participants has also led to recurring debates in medical practice and medical ethics (Gadebusch Bondio

[10] https://www.aerzteblatt.de/nachrichten/111267/WHO-testet-in-globaler-Studie-4-Therapeutika-auf-Wirkung-bei-COVID-19; A similarly designed randomised controlled trial – DISCOVERY – is being conducted in France (INSERM research centre), which is limited to a few European countries but also includes hospitalised patients treated with COVID-19 and tests all the same drugs apart from chloroquine.

2014). The SOLIDARITY study design is not subject to these limitations. Knowledge of the potential side effects of the treatments favours a more liberal practice of inclusion.

Science Unbound

Finally, strategies, adaptations and compromise solutions that enable clinical trials to be conducted in the context of a pandemic outbreak represent a field that has been little researched in terms of research ethics. This makes the scientific and ethical criteria for conducting studies on experimental therapies for HIV and Ebola, which Lane and co-authors have formulated on the basis of a previous study by Emanuel, all the more valuable at this point:

1. Attention to careful patient education as the basis for consent to participate in the study; 2. Clear definition of the primary endpoints in the study design; 3. good communication and cooperation between the participating countries; 4. Establishment of a body to monitor the scientific work; 5. Transparency and timely dissemination of data to treating clinicians and affected communities (Lane et al 2016; Emanuel 2004).

These criteria also provide a valuable ethical framework for the current situation in the context of the pandemic outbreak. However, due to the complexity of these exceptional circumstances, which are historically unprecedented on this scale, additional criteria are indicated, which primarily concern the communication between science, politics and the media. With the global spread of the virus, the rapid, global communication channels are a challenging new departure. Moreover, the relaxation of the usual control mechanisms within research communication due to the urgency of the situation and the media exposure of scientists makes the evaluation and examination of information in circulation more difficult. Rules governing the prudent and fair transfer of data, information and interpretations appropriate to the circumstances of the crisis should be laid down at this point. Clarification of the degree of certainty or uncertainty of what is communicated would go a long way towards enhancing quality assurance. In respect of the ongoing study, it can be said that SOLIDARITY is benefiting from the coordination and support of the WHO. The broad inclusion of patients and the flexible architecture of the study, which allows the rapid withdrawal or replacement of the tested substances, are promising features. The pragmatic trials for the development of urgently needed therapies that preceded SOLIDARITY are historical proof that research designed in this way can yield results faster. If it is possible to make the data obtained and the information extrapolated from it available to clinicians and decision-makers and to release all publications – as planned – in open-access format, the international community stands to benefit. It is also possible that decisions will then be made more quickly and more reliably. In principle, the outbreak of the pandemic should serve, on the one hand, to stimulate those epistemic virtues that would also be desirable in 'normal' research contexts: instead of interest-based competition and waste of time and resources, targeted cooperation, solidarity, and transparency and openness in communication now predominate in the research. On the other hand, the loosening of habitual control mechanisms and standardisation grids presents a challenge to science. Researching in high-

speed mode, evaluating interim results, communicating in a differentiated way with sensation seeking media outlets, and coping with everyday life in exceptional situations – all this must be learned. This demands moral backbone from all those involved.

References

Bai JPF, Hsu CW (2019). Drug Repurposing for Ebola Virus Disease: Principles of Consideration and the Animal Rule. *J Pharm Sci.* 108(2):798-806. doi: 10.1016/j.xphs.2018.09.010

Brost M, Pörksen B (2020): Angesteckt. Warum der Journalismus in der Corona-Krise besonders gebraucht wird – und vor welchen Problemen er steht. DIE ZEIT 8. April (16): 8.

Campbell-Scherer D (2010). Multimorbidity: a challenge for evidence-based medicine. *BMJ Evidence-Based Medicine*, 15(6):165-166.

Emanuel EJ, Wendler D, Killen J, Grady C (2004). What makes clinical research in developing countries ethical? The benchmarks of ethical research. *J Infect Dis.* 189(5):930-7.

Fauci AS (2020). Covid-19 - Navigating the Uncharted. *N Engl J Med* 382 (13): 1268-1269.

Fauci AS: HIV and AIDS (2003). 20 years of science. NATURE MEDICINE VOLUME 9 | NUMBER 7 : 839-843.

Gadebusch Bondio M (2014). Mann und Frau, ganz individuell. Entwicklung eines neuen medizinischen Denkens, in: *Gendermedizin. Krankheit und Geschlecht in Zeiten der Individualisierten Medizin*, ed. M. Gadebusch Bondio and E. Katsari, Bielefeld: 9-18.

Hanging Xue, Jie Li, Haozhe Xie, Yadong Wang (2018). Review of Drug Repositioning Approaches and Resources. *Int J Biol Sci.* 14(10): 1232–1244. doi: 10.7150/ijbs.24612

Hatchett RJ, Carter EM, Lipsitch M (2007). Public health interventions and epidemic intensity during the 1918 influenza pandemic. *PNAS*; 104(18):7582-7587.

Hernandez JJ, Pryszlak M, Smith L, Yanchus C, Kurji N, Shahani VM, et al. (2017). Giving drugs a second chance: overcoming regulatory and financial hurdles in repurposing approved drugs as cancer therapeutics. *Front Oncol*. 7:273. doi: 10.3389/fonc.2017.00273

Institut National de la Santé Et de la Recherche Médicale, France (2020). Trial of Treatments for COVID-19 in Hospitalized Adults (DisCoVeRy) *ClinicalTrials.gov Identifier*: NCT04315948.

Ioannidis JPA (2020). In the Coronavirus Pandemic, We're Making Decisions without Reliable Data. STAT (blog), 17 March 2020, https://www.statnews.com/2020/03/17/a-fiasco-in-the-making-as-the-coronavirus-pandemic-takes-hold-we-are-making-decisions-without-reliable-data/, (last accessed April 29, 2020).

Killen YJ (2008). HIV Research. In: *The Oxford Textbook of Clinical Research Ethics* ed. E J Emanuel, C C. Grady, R A. Crouch, R K. Lie, F G. Miller, D D. Wendler Oxford University Press: 97-109.

Kupferschmidt K, Cohen J (2020). WHO launches global megatrial of the four most promising coronavirus treatments. *Science* doi: 10.1126/science.abb8497

Lane HC, Marston AD, Fauci AS (2016). Conducting Trials in Outbreak Settings: Points to consider. *Clin Trials* 13 (1), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4767673/pdf/ nihms-738356.pdf (last accessed April 29, 2020).

Moorthy V, Restrepo AMH, Preziosi M-P, Swaminathan S (2020). Data sharing for novel coronavirus (COVID-19). *Bull World Health Organ.* 98:150. doi: http://dx.doi.org/10.2471/BLT.20.251561

Newman SP (2018). Delivering drugs to the lungs: The history of repurposing in the treatment of respiratory diseases. *Advanced Drug Delivery Reviews* 133: 5-18. https://doi.org/10.1016/j.addr.2018.04.010

Patterson KD, Pyle GF (1991). The Geography and Mortality of the 1918 Influenza Pandemic. *Bulletin of the History of Medicine*;Vol 65(1):4-21.

Paules CI, Marston HD, Fauci AS (2020): Coronavirus Infections - More Than Just the Common Cold. *JAMA* 323 (8): 707-708.

Pushpakom S, Iorio F, Eyers PA, Escott KJ, Hooper S, Wells A, Doig A, Guilliams T, Latimer J, McNamee C, Norris A, Sanseau P, Cavalla D, Pirmohamed M (2019). Drug repurposing: progress, challenges and recommendations. *Nature Reviews* 18(1);41-58. doi:10.1038/nrd.2018.168

Strittmatter SM (2014). Overcoming drug development bottlenecks with repurposing: old drugs learns new tricks. *Nat.Med* 20: 590-1. doi: 10.1038/nm.3595

WHO (2020). Public health emergency SOLIDARITY trial of treatments for COVID-19 infection in hospitalized patients. *ISRCTN registry*, doi: https://doi.org/10.1186/ISRCTN83971151

Zhou Y, Hou Y, Shen J, et al (2020). Network-based drug repurposing for novel coronavirus 2019-nCoV/SARS-CoV-2. *Cell Discovery* 6, Article number: 6,14 https://doi.org/10.1038/s41421-020-0153-3

Mariacarla Gadebusch Bondio heads the Institute for the Medical Humanities at the University Hospital of Bonn since 2017. She is currently guest professor at Department of History of Science and Ideas, Uppsala University (Research award of the Alexander von Humboldt-Stiftung and Stiftelsen Riksbankens Jubileumsfond| 29th Swedish prize award 2020). Her main research interests lie in the following areas: intersections between medicine and philosophy, norm and deviance in medical discourses, medical fallibility, ethical dimensions of predictive knowledge in medicine, patient narratives, and ethics and cancer.

Dr. med. Maria Marloth, M.Phil. is Research Assistant and Assistant Doctor at the Department of Psychiatry and Psychotherapy, University of Cologne. After studying philosophy (Ludwig-Maximilians-University of Munich) and human medicine (Ludwig-Maximilians-Uninersity of Munich, Technical University of Munich, University of Tor Vergata in Rome), she worked as

Research Assistant the Institute for History and Ethics of Medicine at the Technical University of Munich, where she obtained her doctorate degree in 2018.