The Surfaxin Trial and the Ethics of Exploitation in Global Clinical Research

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"I really love doing research . . . I look at it as a kind of detective work. I would prefer to research forever and ever. The hard part is doing the writing."[1]

- James John Patrick Murphy, author, (1947-2022)

[1] Genzlinger, Neil, Obituary, "Jim Murphy, 74, Writer of Vivid, Candid Books of History for the Young", *The New York Times*, June 9, 2022, p.B11

Capstone Abstract

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In this age of political correctness and consistent with a tenet of contemporary "woke" culture[2], namely an alertness and sensitivity to social justice, any matter within the context of clinical research that involves or suggests a transaction that takes unfair advantage of the vulnerability or weakness of another human being might elicit immediate censure from regulatory agencies, bioethicists or the general public. These groups might claim that such research is a violation of law, bioethical principles or morality. Such criticisms may be made even when the lives and well-being of research participants are ultimately improved by clinical trials and the subjects have provided their consent. There are at times objections to clinical research which is conducted in areas designated as high poverty regions including,

[2] "Woke" is a U.S. slang word defined by Merriam-Webster as "awareness of and actively attentive to important facts and issues, especially issues of racial, social justice and issues surrounding marginalized communities". Source: https://www.merriam-webster.com/dictionary/woke

but not limited to, clinical trials that are off-shored to lower- and middle-income countries.

In certain countries, usually due to economic deprivation or local regulatory deficiencies, the possibility of *exploitation*, understood as taking unfair advantage of another's vulnerability and weakness, is higher than in countries ordinarily characterized as high-income countries. In 2000, a private American startup pharmaceutical company, Discovery Labs, proposed a clinical trial in Latin America (primarily Bolivia), to test the efficacy of a new drug to treat respiratory distress syndrome (RDS) in 650 neonatal infants. The planned clinical trial involved the use of a placebo as part of the research. The design of the trial was condemned as "exploitative" after strong criticism by a consumer watchdog organization alleging that the trial contravened an article (involving use of placebos) of the Declaration of Helsinki that "new treatments should always be tested against the best current method, where they exist". The trial in Latin America was abandoned and the company instead conducted it in the USA. Known as the Surfaxin Trial, it is still often cited and debated in bioethical literature of whether the proposed clinical trial design should have been halted solely because it involved exploitation, i.e., taking advantage of the lack of baseline healthcare or effective treatment for neonatal infants with RDS in Bolivia.

Withdrawing this trial from Latin America raises the question of whether a charge of or the reality of an exploitative transaction is sufficient to deny some research participants (especially newborn infants) to treatment that they would not normally have. If taking unfair advantage of others is permissible or even advisable, we have to consider what role ethical principles such as informed consent, the use of placebos and structural injustice in clinical trial design play in determining what should be considered or require intervention.

The specter and reality of exploitation is, for better or worse, a component of clinical research in LMICs and as such, the ethical or moral weight of each transaction, especially those with a trial design like Surfaxin, must be considered before it warrants public condemnation or regulatory intervention to prohibit a trial from going forward.

Key words: *Exploitation, clinical research, off-shoring, low- and middle-income countries, informed consent, economic deprivation, regulatory deficiencies, risk, Declaration of Helsinki, Surfaxin trial, placebos, respiratory distress syndrome, morality, bioethics, structural injustice, intervention, trial design*

Ethics

What, then, is ethics? Ethics is two things. First, ethics refers to well-founded standards of right and wrong that prescribe what humans ought to do, usually in terms of rights, obligations, benefits to society, fairness, or specific virtues.

Secondly, ethics refers to the study and development of one's ethical standards. Ethics is the continuous effort of studying our own moral beliefs and our moral conduct, and striving to ensure that we, and the institutions we help to shape, live up to standards that are reasonable and solidly-based.[3]

Moral Beliefs and Moral Conduct

Moral behavior doesn't start with having the right beliefs (principles). Moral behavior starts with an act – the act of seeing the full humanity of other people. Moral behavior is not having the right intellectual concepts in your head. It's about seeing other people with the eyes of the heart, seeing them in their full experience, suffering with their full suffering, walking with them on their path. Morality starts with the quality of attention we cast upon each other.

If you look at people with a detached, emotionless gaze, it doesn't really matter what your beliefs (principles) are, because you have morally disengaged. You have perceived a person not as a full human being but as a thing, as a vague entity toward which the rules of morality do not apply.[4]

[3] Manuel Velasquez, Claire Andre, Thomas Shanks, S.J., Michael J. Meyer, "What is Ethics?", Markkula Center for Applied Ethics at Santa Clara University, https://www.scu.edu/ethics/ethics-resources/ethical-decision-making/what-is-ethics/

[4] Brooks, David, "The Southern Baptist Moral Meltdown", *The New York Times*, May 27, 2022, p.A23

1.0 Introduction

Exploitation of humans in clinical trials, i.e., taking unfair advantage of a person's vulnerability, is not usually the first ethical concern that bioethicists address. According to Dr. Alan Wertheimer, even though the word exploitation usually suggests something which is morally and ethically suspect, exploitation is not explicitly one of the four canonical principles of bioethics, namely *autonomy*, *non-maleficence*, *beneficence* and *justice*.[5] *Autonomy* means "the principle of respect for persons"; if subjects are *autonomous*, they should be given the opportunity to decide for themselves whether or not to contribute to or participate in a research project.[6] *Beneficence* denotes protecting patients and participants not only from harm, but also by making efforts to secure their well-being. The term beneficence is often understood to cover acts of kindness or charity that go beyond strict obligation.[7] The principle of *non-maleficence* can be understood as *primum non nocere* – 'above all do no harm' including physical, psychological, social and economic harm. *Justice* means 'fairness and desert' – people should be treated fairly

[5] Wertheimer, Alan, *Rethinking the Ethics of Clinical Research: Widening the Lens*, Oxford University Press, N.Y., N.Y, 2011, p.191

[6] McNeil, Paul M., *The Ethics and Politics of Human Experimentation*, University of Cambridge, Melbourne, Australia, 1993, pp.139-149.

[7] https://inside.nku.edu/rgc/research-compliance/irb/resources/ethical-principles.html accessed November 16, 2022

and disinterestedly, and should be given what they deserve in the sense of what they have earned.[8] As Dr. Erik Malmqvist[9] points out, exploitation is not a well-established part of the bioethics "toolbox", like autonomy and harm.[10] Part of the difficulty is linguistic. Some bioethicists might disagree with the above definitions of autonomy, beneficence, etc. and could demand that more precise or other language be used to describe those words. Nevertheless, bioethicists are still unsettled by the idea of human exploitation, especially among participants in clinical trials by large American and European pharmaceutical firms (and their local partners), regardless of whether these trials are conducted in countries characterized by the World Bank[11] as either high income countries (hereafter HICs) or low and middle-income countries (hereafter LMICs, see appendix #2 for a list of LMICs). Even so, exploitative transactions or allegations of wrongful exploitation in clinical research should not be the sole factor in the decision to cancel or abandon a clinical trial involving human beings. The ethical and moral weight of each transaction needs to be evaluated on a case-by-case basis before it warrants public condemnation or regulatory intervention.

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[8] McNeil, Paul M., *The Ethics and Politics of Human Experimentation*, University of Cambridge, Melbourne, Australia, 1993, pp.139-149.

[9] Senior lecturer of practical philosophy, University of Göthenburg (Sweden)

[10] Malmqvist, Erik, "(Mis)Understanding Exploitation", The Hastings Center, Volume 33, Issue 2, February 2016

[11] Founded in 1944, the International Bank for Reconstruction and Development—soon called the World Bank—has expanded to a closely associated group of five development institutions. Originally, its loans helped rebuild countries devastated by World War II. In time, the focus shifted from reconstruction to development, with a heavy emphasis on infrastructure such as dams, electrical grids, irrigation systems, and roads. Source: https://www.worldbank.org/en/about/history

Using the proposed Surfaxin clinical trial involving the lives of 650 neonatal infants in Bolivia suffering from RDS as a point of reference, this essay will introduce the reader to the various ethical and moral challenges involved with global clinical research, i.e., informed consent, use of placebos, permissible exploitation, structural injustices and complicity. RDS is a common and potentially fatal disease in premature infants, caused by insufficient surfactant in the lungs. The use of surfactant replacement therapy is the standard treatment for RDS in the developed world. It is not a viable option in many LMICs because of its high cost (>$1,000 per child.[12]

A growing concern among some contemporary bioethicists and others, is the evolution of clinical trials beyond the borders of HICs, where the possibility, based on empirical data, of abusive practices and unfair transactions in globalized clinical trials in LMICs is very real. For example, despite the availability of two vaccines that have been proven to be highly effective in preventing serious rotavirus infections in infants and young children, more than 2,000 children in a 2014 India clinical trial received placebo injections of salt water rather than one of the available effective vaccines.[13] It is often alleged that some pharmaceutical companies take

[12] Wertheimer, Alan, *Rethinking the Ethics of Clinical Research: Widening the Lens*, Oxford University Press, N.Y., N.Y, 2011, p.193

[13] Source: https://www.citizen.org/news/unethical-clinical-trials-still-being-conducted-in-developing-countries/ accessed July 22, 2022

advantage of the assumed deprivation of vulnerable people to impose the risk of health research on them for the ultimate benefit of citizens of HICs.[14] According to Dr. Sidney Wolfe, the director of Public Citizen's health research group (which lobbied against the Surfaxin Trial): "The infants who would get placebos [in the Surfaxin Trial] are being used by the company for reasons having to do with corporate bottom lines in order to get their drug approved."[15]

Starting with a general discussion of what clinical research involving human beings is and why it is necessary, this essay will then address the diverse reasons why clinical research is being "off-shored" to LMICs and some of the bioethical issues associated with or implied by global clinical research. Afterwards, the concept of exploitation and the challenges of arriving at a universal definition of exploitation and wrongful exploitation within the context of clinical research will be presented. Next, the details and background of the proposed Surfaxin trial will be described and why allegations of wrongful exploitation caused the trial to be cancelled. This essay will then focus on the response to the Surfaxin Trial by six bioethicists to highlight their different reactions to it from their own unique bioethical perspectives regarding exploitation. When it comes to understanding the

[14] Weigmann, Katrin, "The Ethics of Global Clinical Trials", *EMBO Reports*, April 2015, p.569. Katrin Weigmann is a free-lance medical journalist based in Oldenburg, Germany

[15] Source: Charatan, Fred, "Surfactant Trial in Latin American Infants Criticised", *British Medical Journal*, Volume 322, March 10, 2001, p.575

boundaries of acceptable exploitation in global clinical research, it is evident that bioethicists themselves are not necessarily "of one mind". Finally, I will present my own argument of why the Surfaxin trial, even though deemed by some bioethicists as "deeply exploitative," should nevertheless have been permitted as designed followed by a conclusion to this essay.

2.0 Background – Clinical Research

When it comes to research experiments involving human beings, one cannot suppose that all bioethicists agree on what is and what is not ethically acceptable. No bioethicist would argue that there is any ethical justification to defend the medical or scientific knowledge or information acquired by the revolting and immoral research of the Nazi and Imperial Japanese Army experiments during WWII. American researchers were not exempt from unethical research either, as evidenced by the 1932 Tuskegee clinical trials involving Black Americans. Unfortunately, some of the information from these horrific experiments proved to be valuable nonetheless, especially to the U.S. Government.

German physicians and scientists performed experiments on prisoners in Nazi concentration camps, literally using their victims as human guinea pigs for scientific and medical research which evoked horror and repulsion after the Second

World War.[16] Likewise, Japanese researchers in occupied China during WWII deliberately and methodically infected innocent Chinese civilians with the plague to develop weapons of biological warfare. No less shocking was the 1932 "Tuskegee Study of Untreated Syphilis in the Negro Male" in the United States where Black male participants who were diagnosed with syphilis were tricked into believing that they were receiving treatment for bad blood when in fact they were not receiving any treatment at all.[17] The repugnance generated by these deeds can easily be understood when the expression "human experimentation" is seen or heard. Still, scientific and some medical knowledge was acquired by this immoral research. The Japanese scientists and American physicians involved in their experiments fared much better than their German counterparts (see footnote 15 below).

After the Second World War, the United States government agreed to give the Japanese experimenters immunity from prosecution in exchange for information about biological warfare.[18] The government of the United States admitted that "because of *scruples* [emphasis added] attached to human experimentation" it was not possible to conduct such experiments in the United States.[19] The American

[16] Of 23 German doctors and scientists tried for crimes against humanity, 20 were physicians and all but one of these held positions in the medical services of the Third Reich. 16 were found guilty and 7 of these were hanged. Source; McNeil, Paul M., *The Ethics and Politics of Human Experimentation*, University of Cambridge, Melbourne, Australia, 1993, p.22

[17] Blow, Charles, M, "How Black People Learned Not to Trust", *The New York Times*, December 7th, 2020, p. A18

[18] McNeil, Paul M., *The Ethics and Politics of Human Experimentation*, University of Cambridge, Melbourne, Australia, 1993, p.24

[19] Ibid.

Armed Forces Command gave great weight to the fact that the Japanese experiments were "the only known source of scientifically controlled experiments" showing the direct effect of biological warfare techniques on humans.[20] The information was valued for its potential to put the United States ahead in the development of its own biological warfare program and the potential deployment of this method of warfare.[21] [22]

It was not until 1970 that American physicians began to question the ethics of human experimentation without informed consent. Some of the physicians involved in the Tuskegee experiments reluctantly admitted that the trials "may" have been unethical. When details of the study were finally made public, the medical profession simply ignored it except for the *Southern Medical Journal* which exonerated the study and chastised the "irresponsible press" for bringing it to the attention of the public.[23] A number of physicians defended the study, including Vanderbilt's Rudolph Kampmeier (1898–1990), former president of the American College of Physicians (1967–1968) and editor of the *Southern Medical Journal*. Dr.

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[20] Ibid.

[21]. McNeil, Paul M., *The Ethics and Politics of Human Experimentation*, University of Cambridge, Melbourne, Australia, 1993, p.24

[22] 15 Japanese doctors who took part in fatal experiments on human subjects subsequently went on to become professors, develop their specialties with (and in some cases directors of) university medical schools and research facilities. Many of these received high honors and awards for their contribution to society. These respected and distinguished doctors referred to their victims as "*maruta*", which means "logs of wood". Only the USSR (Soviet Union) prosecuted some Japanese doctors involved in war crimes, known as the Khabarovsk Trial, but governments in the West were not interested in the findings of a Soviet military tribunal. Source: McNeil, Paul M., *The Ethics and Politics of Human Experimentation*, University of Cambridge, Melbourne, Australia, 1993, pp.26-27.

[23] Ibid., p.27

Kampmeier blamed journalists for raising "a great hue and cry," rebuked them for their "complete disregard for their abysmal ignorance," and announced that his analysis would "put this 'tempest in a teapot' into proper historical perspective".[24]

Employing terminology associated with bioethics, one might say that the victims of these German, Japanese and American research experiments were *exploited*. The victims were vulnerable and taken unfair advantage of. But these experiments go way beyond what bioethicists mean when they talk or write about exploitation. These are not examples that can occur in or be inferred by legitimate, responsible and valid clinical research which may involve "permissible" exploitative transactions. These are illustrations of horrific egregious and methodical *criminality*. This does not mean that exploitation in clinical research cannot border on criminality, because it can (see footnote 12 above). Beyond the obvious physical, emotional and psychological wounds inflicted on them, those human beings in the above-mentioned cases were routinely and intentionally abused, tortured or killed as part of scientific research. As affirmed by Paul McNeil, the main difference between the experiments by the German and Japanese researchers and experimentation on human subjects elsewhere, i.e., authentic and ethical clinical research, was in the

[24] https://www.atsjournals.org/doi/10.1164/rccm.202201-0136SO (American Thoracic Society) accessed July 30, 2022

extent of the atrocities committed and the deliberate intention to inflict brutal injury and death.[25].

Nevertheless, clinical research and experimentation involving human beings continues to be a critical fact of life. The urgent need to develop a vaccine for COVID-19, e.g., *Operation Warp Speed*[26], required clinical trials in multiple locations throughout the world, i.e., USA, Brazil, India and South Africa among others. Globalized clinical trials are necessary, among other reasons, because different trial sites are needed to guarantee and ensure that the drug or vaccine is, in most cases, safe and works in the same way in varying ethnic groups.[27]

Scientific and specifically medical research of any kind and particularly the development of a vaccine, customarily involves some level of risk, otherwise it wouldn't be an experiment. Whatever data is being sought involves a trial or test of some type to either obtain knowledge or information about something. In clinical research involving humans, there is always the risk of physical, emotional or psychological injury to the people participating in the research experiment. As part of *Operation Warp Speed* (cited above), it was reported that two subjects in the

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[25] McNeil, Paul M., *The Ethics and Politics of Human Experimentation*, University of Cambridge, Melbourne, Australia, 1993, p.23

[26] *Operation Warp Speed* was a partnership between the Departments of Health and Human Services (HHS) and Defense (DOD)—aimed to help accelerate the development of a COVID-19 vaccine. Source: U.S. Government Accountability Office (GAO), https://www.gao.gov/products/gao-21-319 accessed November 11, 2022

[27] Trudi Lan, Sisira Siribaddana, "Clinical Trials Have Gone Global: Is This a Good Thing", *PLoS Medicine*, June 2012, Volume 9, Issue 6, p.1

AstraZeneca clinical trial developed neurological symptoms.[28] It typically takes fifteen to twenty years to develop a vaccine. Paul Offit, M.D., author of *You Bet Your Life* cautions all of us who were recently vaccinated during the current pandemic that "a COVID-19 vaccine developed in only one year effectively forces people to decide between the risk of getting COVID-19 or the risk of getting a vaccine that has not been subjected to the typical research, development, testing and licensure processes".[29]

The proposed Surfaxin clinical trial to test a new drug therapy for respiratory distress system (hereafter: RDS) in neo-natal infants by Discovery Labs (hereafter: D-Labs), cited in the abstract to this essay, was initially planned to be conducted in Bolivia sometime in 2001. Public Citizen, a Washington, D.C. based, non-profit, consumer watchdog petitioned then U.S. health secretary Tommy Thompson (appointed by President George W. Bush) to have the new Office of Human Research Protections in the Department of Health and Human Services use its influence to stop the proposed study immediately.[30] Public Citizen had condemned

[28] Rebecca Robbins, et.al., "How a Vaccine Front-Runner Fell Behind", *The New York Times*, December 9, 2020, p. A 6

[29] Offit, Paul, A., M.D., *You Bet Your Life: From Blood Transfusions to Mass Vaccination, the Long and Risky History of Medical Innovation,* Basic Books, N.Y., 2021, p.8

[30] Charatan, Fred, "Surfactant Trial in Latin American Infants Criticised", *British Medical Journal*, Volume 322, March 10, 2001, p.575

the proposed study design as "exploitative" because it involved the use of a placebo when effective treatments were available.[31]

To fully understand why Public Citizen condemned D-Labs proposed clinical trial as "exploitative", we need first to examine why clinical trials are conducted in LMICs (rather than the U.S. or another HIC.). This will help us to later realize why D-Labs proposed the Surfaxin trial in Bolivia. Secondly, it's important to explore how bioethicists identify and explain exploitation and what constitutes an act as "exploitative" in clinical research.

2.1 Global Clinical Research

Clinical trials are conducted throughout the world, in both HICs and LMICs and are a necessary step in drug development (see *Operation Warp Speed* above) and the trials themselves, especially those in LMICs such as the intended Surfaxin trial, are not immoral *per se*. Sometimes it's the only way to develop and test drugs and vaccines for diseases that predominately afflict people in certain countries. As Katrin Weigmann points out, it would be futile to test the safety and efficacy of a malaria vaccine in North America or Europe.[32] Responsible clinical trials in LMICs, for example, can directly benefit people who otherwise would have little or no access to health care services. Weigmann also correctly asserts that it's a matter of striking

[31] Ibid.
[32] Weigmann, Katrin, "The Ethics of Global Clinical Trials", *EMBO Reports*, April 2015, p.569

a fine-tuned balance between the economic and research benefits of pharmaceutical companies and academia and the needs of patients in LMICs to make sure all sides benefit.[33]

Still, there are other reasons why clinical trials like Surfaxin are conducted in LMICs which may not be so obvious. According to Dr. Adriana Petryna (b. 1966, Professor of Anthropology. University of Pennsylvania), one of the key reasons American pharmaceutical companies "off shore" their clinical research is the need for larger subject cohorts.[34] U.S. regulatory authorities require that the long-term safety of a drug, especially a drug that is designed to be prescribed widely, be tested in clinical trials involving a greater number of participants including subjects from different ethnic and racial groups.[35] When drug company Moderna began enrolling 30,000 volunteers in July 2020 for its Covid-19 vaccine, the subjects weren't racially diverse enough and Dr. Anthony Fauci[36] had to "help coax and advise Moderna how to get the percentage of minorities up to a reasonable level."[37] In other words, the larger the population sample in the testing, the more likely the FDA (U.S. Food and

[33] Ibid.
[34] Petryna, Adriana, *When Experiments Travel: Clinical Trials and the Global Search for Human Subjects*, Princeton University Press, Princeton, N.J., 2009, p. 20
[35] Ibid.
[36] Anthony Steven Fauci, M.D., b.1940, director of the National Institute of Allergy and Infection Diseases (NIAID) and Chief Medical Advisor to the President of the United States
[37] Loftus, Peter, "The Partnership That Made the First U.S. Covid Vaccine, *The Wall Street Journal*, July 30-31, 2022, p.C5

Drug Administration, established 1906) will speed up the approval process.[38] As we will read later in this essay, the FDA required that D-Labs conduct the Surfaxin research trial subject to certain protocols that were not permitted in the United States.

There is always the risk that large pharmaceutical companies, i.e., so-called *Big Pharma*, will take advantage of the vulnerability of people who may be uneducated or have no access to any health care at all and find it easy to exploit them in clinical research trials.[39] Pharmaceutical companies can search for "host" countries (usually LMICs) for clinical research that usually have large or pockets of an impoverished population with governments that may not have the political leverage to address adverse or catastrophic events in medical research. These same governments often do not have an interest in demanding or offering adequate regulatory procedures and guaranteeing access to drugs for its population during and after clinical trials.[40] Indeed, the governments of some LMICs are often" eager to attract and "host" foreign sponsors (researchers) as part of broader strategies of economic liberalization and international competitiveness.[41]

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[38] Petryna, Adriana, *When Experiments Travel: Clinical Trials and the Global Search for Human Subjects*, Princeton University Press, Princeton, N.J., 2009, p. 20

[39] Big Pharma, a colloquial (and often pejorative) term used to describe faceless pharmaceutical corporations that push hugely overpriced drugs onto hapless and desperate consumers. Source: https://deserthopetreatment.com/addiction-guide/drug-industry-trends/ accessed November 11, 2022

[40] Petryna, Adriana, *When Experiments Travel: Clinical Trials and the Global Search for Human Subjects*, Princeton University Press, Princeton, N.J., 2009, p. 37

[41] Malmqvist, Erik, "Better to Exploit than to Neglect? International Clinical Research and the Non-Worseness Claim", *Journal of Applied Philosophy*, Volume 34, Issue 4, August 10, 2015, p. 2

Thomas Pogge, (b.1953, Austria, Director of Global Justice Program, Yale University) claims that D-Labs found in Bolivia exactly what it was looking for to conduct the Surfaxin trial: rampant RDS routinely left untreated among the poor[42] and in order to do this, the staff of D-Labs had to "scour the earth in hopes of finding RDS infants whom they could permissibly infuse with "sham" air."[43] It is beyond the scope of this essay to discuss the numerous ethical issues and questions raised by clinical trials in LMICs, or whether they should be permitted or in some cases even prohibited. Nevertheless, this theme will resurface and be addressed when the ethical and moral issues associated with the Surfaxin Trial are examined.

We read in the Background section of this essay that Public Citizen demanded the Surfaxin Trial be stopped because it was "exploitative". This leads us to our next discussion points: exploitation and exploitative transactions.

3. 0 Exploitation

Exploitation is a vast political and philosophical notion which can range from Marxist theories of the station of workers within a capitalist society to Emmanuel Kant's "Categorical Imperative" (sometimes referred to as the Formula of Universal Law or the Formula of the Kingdom of Ends), of which one formulation states that

[42] Pogge, Thomas, "Testing Our Drugs on the Poor Abroad", excerpted in Jennifer S. Hawkins and Ezekiel J. Emanuel, (editors), *Exploitation and Developing Countries: The Ethics of Clinical Research,* Princeton University Press, Princeton, N.J., 2008, p.112

[43] Ibid., p.111

one should "Act in such a way that you always treat humanity, whether in your own person or in the person of any other, never simply (merely) as a means but always at the same time as an end".[44] [45]

The word *exploitation* alone is a two-edged sword since it routinely brings to mind, as stated in the background to this essay, some activity that is morally or ethically suspect. If pressed to give a precise definition of exploitation, the average person might respond, as former U.S. Supreme Court Justice Potter Stewart (1915-1985) did, when asked if he could define pornography. Justice Stewart responded that although he couldn't precisely define pornography, "he knew it when he saw it." [46] It other words, intuition plays a critical role in discerning exploitation and bioethicists themselves are challenged when asked to give a universal definition of exploitation or even what makes an act exploitative.

The noun "exploitation", as well as its adjectival form "exploitative", can be used in a non-moral or non-derisive sense.[47] We can say, for example, that a taller

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[44] O'Neill, Onora, "A Simplified Account of Kant's Ethics", excerpted in J.E. White (ed)., *Contemporary Moral Problems*, West Publishing Co., St. Paul, MN, 1985, p.1

[45] Using someone as a *mere* means is to involve them in a scheme of action to which they could not in principle consent. According to Kant, if we act on a maxim (intent) that requires deception or coercion of others, we treat others as mere means, as things rather than as ends in themselves. If we act on such maxims, our acts are not only wrong but unjust: such acts wrong the particular others who are deceived or coerced. Source: O'Neill, Onora, "A Simplified Account of Kant's Ethics", excerpted in J.E. White (ed)., *Contemporary Moral Problems*, West Publishing Co., St. Paul, MN, 1985, p.3 (Onora O'Neill, b.1941, British philosopher, University Professor (Cambridge) and member of the House of Lords)

[46] https://www.mtsu.edu/first-amendment/article/1359/potter-stewart accessed November 12, 2022

[47]Wertheimer, Alan, *Rethinking the Ethics of Clinical Research: Widening the Lens*, Oxford University Press, N.Y., N.Y, 2011, p.191

student *exploits* their ability to jump higher than a shorter student and possibly gets preferential selection for the high school basketball team. The shorter student may also be an excellent basketball player, but he or she was not exploited in the selection process. Unfair treatment possibly, but not exploitation. If your roof gets a hole in it and it starts raining and you call a roofer to fix it, the roofer is technically *exploiting* a customer's vulnerability, yet no reasonable person would describe this transaction as *exploitation*, assuming no excessive price gouging or onerous sales terms. Human beings exploit their intellectual and creative talents every day in their lives and in their professions. In its most minimal sense "to exploit" means to use something to advantage.

Within the context of clinical research, there have been many attempts to formulate a precise or universal definition of exploitation. A boilerplate bioethical definition suggested by some bioethicists is: Exploitation means any "transaction" that does not respect and protect participants from harm or injury in the conduct of clinical research and that the participants understand the risks and potential benefits and are willing to participate and are protected against any "undue influence".[48] But what is really meant when words like "*understands*", "*respect*", "*harm*", "*willing*" and "*protected*" are used? These words may have different meanings for bioethicists

[48] Emanuel, J. Ezekiel, et.al., (editors), *Ethical and Regulatory Aspects of Clinical Research, Readings and Commentary*, The John Hopkins University Press, Baltimore, MD., 2003, p. 151

beyond their conventional usage when explaining exploitation. We will see later in this essay how a straightforward word like "understands" can present problems for some bioethicists. The Norwegian theologian and bioethicist Jan Helge Solbakk (b.1956) invokes the Biblical metaphor of the Tower of Babel[49] narrative from Genesis 11 to illustrate just how difficult and complex it is to build a universal normative language for research ethics.[50]

Linguistic challenges notwithstanding, exploitation still continues to be a diffuse and unclear ethical concept precisely because any attempt to narrowly define exploitation (including the above definition) runs the danger, as Hawkins and Emanuel put it, "of substituting a vague pile of concerns for an equally vague label – giving it the patina of coherence but without real clarity."[51]

Still, we should have some sort of wide-ranging definition of exploitation to discuss the morality and ethics of an act involving clinical research. As stated previously, the word exploitation can be used in a non-moral or non-derisive sense.

[49] Genesis 11:1-11: a tower built by Noah's descendants (probably in Babylon) who intended it to reach up to heaven; God foiled them by confusing their language so they could no longer understand one another

[50] Solbakk, Jan Helge, "In the Ruins of Babel: Pitfalls on the Way toward a Universal Language for Research Ethics and Benefit Sharing", *Cambridge Quarterly of Healthcare Ethics*, 2011, p. 341

[51] Hawkins, Jennifer S. and Ezekiel J. Emanuel, "Introduction: Why Exploitation?", excerpted in Jennifer S. Hawkins and Ezekiel J. Emanuel (editors), *Exploitation and Developing Countries: The Ethics of Clinical Research,* Princeton University Press, Princeton, N.J., 2008, p.13 (Jennifer S. Hawkins, Associate Research Professor, Department of Philosophy, Duke University, Ezekiel Emanuel, b.1957, chair Department of Medical Ethics and Health Policy, U. of Penn.)

To judge exploitation as morally problematic or unethical in clinical research requires that exploitation be understood as *wrongful exploitation*.

Erik Malmqvist and András Szigeti assert correctly that *most* [emphasis added] theories of exploitation subscribe to a two-part analysis, according to which two conditions are necessary and jointly sufficient for wrongful exploitation.[52] The first condition- the *'Vulnerability Clause'* – is that the exploiter (A) and exploitee (B) are strongly asymmetrically related. In other words, the person being exploited is vulnerable, needy, or in a weak bargaining position with no access to reasonable or non-prohibitively burdensome alternatives to transacting with the exploiter.[53] The second condition – the '*Advantage Clause'* – is that the exploiter (A) uses this very asymmetry to extract a gain from B, which is excessive or otherwise inappropriate.[54] The word inappropriate might be too ambiguous as most bioethicists writing about exploitation appear to simply use the word "unfair" (which is also difficult to quantify). Also, an "excessive" gain by (A) does not mean that the exploitee (B) has not gained *anything*, just that the exploiter's (A) gain is much greater than any gain that accrues or should accrue to the person (B) being exploited.

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[52] Malmqvist, Erik, Szigeti, András, "Exploitation and Remedial Duties", Journal of Applied Philosophy, doi: 10.1111/japp.12407, John Wiley & Sons, Oxford, U.K., 2019, p.3 (András Szigeti, Senior Associate Professor, University of Linköping, Sweden)

[53] Ibid.

[54] Ibid.

No very general definition of exploitation is applicable for every case and will not satisfy and explain every issue in research bioethics. Using intuition to explain exploitation, i.e., "one knows it when one sees it" alone is not always suitable or helpful. Nicholas Vrousalis, from the Institute of Political Science, Leiden University, the Netherlands, aptly writes that trying to distinguish between morally innocuous and morally objectionable advantage-taking is a "*trick"*. And the trick, he says, is figuring out precisely what makes a transaction between A and B wrong.[55] For the remainder of this essay, whenever the term exploitation or an act is described as exploitative is used, it will mean *wrongful exploitation*.

4. 0 The Surfaxin Trial

I have demonstrated the need for responsible clinical research involving human beings and have discussed the reasons some pharmaceutical companies might "off shore" their clinical trials. From an ethical and moral perspective, there are nuances and at times ambiguity in describing exploitation. This is a challenge for bioethicists when struggling to designate what is morally permissible or what is a morally unacceptable exploitative transaction in clinical research. We move now to examine the ethical and moral issues in the Surfaxin Trial. See Appendix #1 for a

[55] Vrousalis, Nicholas, "Exploitation: A Primer", *Philosophy Compass*, doi:10.1111/phc3.12486, John Wiley, November 2017, p.2

glossary of italicized medical terms that will be used in the background discussion of the Surfaxin trial.

4.1 Background to Trial

In 2000, D-Labs planned a clinical trial in Bolivia to demonstrate the efficacy of a new *synthetic surfactant*, brand name Surfaxin, for the treatment of RDS.[56] The company believed that Surfaxin would be easier and cheaper to manufacture with the added benefit that the side effects would be less than surfactants derived from animal tissue.[57] Most surfactants at that time were made from tissue extracted from pig and cow lungs making them extremely expensive due to the small quantities of surfactant extractable from each animal, as well as the costs of purification.[58] The drug would probably not be affordable in a country like Bolivia (or other LMICs), so the principal target market for Surfaxin was the United States and Europe.[59] D-Labs proposed a multi-centered, *double-blinded*, *randomized*, *two-arm placebo-controlled trial* (PCT) involving 650 premature infants with RDS.[60]

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[56] Wertheimer, Alan, *Rethinking the Ethics of Clinical Research: Widening the Lens*, Oxford University Press, N.Y., N.Y, 2011, p.193
[57] Ibid.
[58] Bourgeois, Mark, L., "Autonomy and Exploitation in Clinical Research: What the Proposed Surfaxin Trial Can Teach Us about Consent", *Ethics in Biology, Engineering & Medicine – An International Journal*, Begell House, Inc., 2012 p. 52
[59] Wertheimer, Alan, *Rethinking the Ethics of Clinical Research: Widening the Lens*, Oxford University Press, N.Y., N.Y, 2011, p.193
[60] Ibid., p.194

It's essential to understand why the trial was designed as a placebo-controlled trial (PCT) since it aids us in understanding why D-Labs proposed this trial in Bolivia. There were already other synthetic surfactants on the market with markedly positive results in premature infants with RDS.[61] However, the data for these synthetic surfactants comparing them to placebo varied greatly, making it difficult to determine the *exact degree* [emphasis added] to which these drugs were superior to placebo.[62] The FDA will only license a drug for use in the United States for a particular disease treatment (such as RDS) if the manufacturer is able to prove that the new drug is superior to placebo for treating a specific disease.[63] D-Labs did not necessarily expect Surfaxin to be critically superior to existing surfactants (it would just be totally synthetic and ultimately less expensive to produce) to those manufactured by its competitors, but since there was uncertainty about the degree of superiority over placebo relative to the existing treatments, it was determined that an *active-controlled trial* (ACT) comparing Surfaxin to its competitors would probably not produce any meaningful or valuable information.[64] D-Labs had no choice but to "off shore" its clinical trials because the FDA notified D-Labs that it must produce data from a PCT. At the same time, the FDA and the American

[61] Hawkins, Jennifer S., "Exploitation and Placebo Controls", excerpted in Jennifer S. Hawkins and Ezekiel J. Emanuel, eds., *Exploitation and Developing Countries: The Ethics of Clinical Research,* Princeton University Press, Princeton, N.J., 2008, p.249
[62] Ibid.
[63] Ibid., p.250
[64] Ibid., p.251

medical community agreed that it would be unethical to run a PCT in the United States because there was already widespread use of surfactants in the U.S. and it was generally thought that these were superior in their efficacy.[65]

According to Dr. Alan Wertheimer (1942-2015, Ph.D., former senior research scholar, the Department of Bioethics, National Institutes of Health and Professor Emeritus of Political Science, University of Vermont), D-Labs initially proposed to provide endotracheal tubes, ventilators and antibiotics to all trial participants which these patients would not have had access to outside of this clinical trial.[66] The parents of infants of RDS would have to give their consent for their babies to participate and after intubation with an endotracheal tube, half the infants (325) would receive air suffused with Surfaxin (or another surfactant) and the other 325 infants would receive ("sham") air without any drug.[67] As unfair or cruel as this sounds, it should be pointed out that ventilator support with "sham" air was known to improve survival and was superior to the treatment generally available to Bolivian infants with RDS.[68] In other words, the *baseline* for Bolivian infants with RDS was effectively no treatment at all.

[65] Ibid.
[66] Wertheimer, Alan, *Rethinking the Ethics of Clinical Research: Widening the Lens*, Oxford University Press, N.Y., N.Y, 2011, p.194
[67] Ibid.
[68] Ibid.

Public Citizen, a consumer watchdog organization cited above, argued that the proposed trial was exploitative because it violated a Declaration of Helsinki[69] ordinance against testing using a placebo which states: "The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current *prophylactic*, diagnostic and therapeutic methods."[70] Public Citizen also alerted U.S. health secretary Tommy Thompson that internal FDA documents showed that the new Bush administration was against placebo controlled trials of surfactants in *idiopathic* RDS in the United States because "we have available approved surfactants that are the standard of care."[71] Before the FDA issued any decision to approve or not approve the trial, due to the "complex issues that the trial raised",[72] D-Labs voluntarily abandoned the trial in Bolivia and conducted an ACT trial in the United States.

Complex issues, indeed. To this day, bioethicists debate and publish papers on the moral and ethical issues associated with the Surfaxin trial. As I said above,

[69] The Declaration of Helsinki was created in 1964 by the World Medical Association (WMA). The WMA was established seventeen years before in 1947, and was created to handle the growing concern of unethical medical practice which became more apparent during and after World War II. While the WMA is a well-respected body which is cited by health organizations around the world, it does not have any legal authority. Therefore, the Declaration of Helsinki is an ethical guideline, rather than a document with international legal implications. The Declaration set the standard for ethical human experimentation conducted by researchers. Source: https://inside.tamuc.edu/research/compliance/IRB-Protection of Human Subjects/irbDocuments/Declaration of Helsinki accessed November 12, 2022

[70] Charatan, Fred, "Surfactant Trial in Latin American Infants Criticised", *British Medical Journal*, Volume 322, March 10, 2001, p.575

[71] Ibid.

[72] Ibid.

bioethicists are not always of "one mind". I will now briefly examine how some contemporary bioethicists assessed, from their personal ethical and moral perspective, what the key exploitative problems in the trial were. I will then offer my own argument of why I believe the trial should not have been abandoned and relocated to the United States.

4.2 Response to the Surfaxin Trial by 6 Bioethicists

Alan Wertheimer
"*Permitted Exploitation Principle (PEP)*"

Dr. Alan Wertheimer implies that the Surfaxin Trial should have been permitted in Bolivia. He did not claim that the trial was not exploitative. Wertheimer coined an innovative term which he labeled the *Permitted Exploitation Principle* (PEP). PEP means that a transaction should be allowed whenever it would be better for all parties to the transaction and *worse for no one else* (emphasis added).[73] My understanding of Wertheimer's PEP theory is illustrated as follows: If a Bolivian parent (B), having been properly informed, consents to allow her baby into an unfair transaction with D-Labs (A), (unfair because D-Labs uses a placebo in the trial when there is an available alternative surfactant treatment), there is, according to Wertheimer, no ethical reason the transaction should be prohibited. This is because

[73] Wertheimer, Alan, *Rethinking the Ethics of Clinical Research: Widening the Lens*, Oxford University Press, N.Y., N.Y, 2011, p.219

the *baseline* for the Bolivian infants selected for the trial is no treatment at all and as described above, "sham" air (effectively the placebo) and ventilator support were known to have some efficacy and improve the chances of survival.[74] Wertheimer described this as a *mutually beneficial* transaction, unique to LMICs, since both the pharmaceutical company D-Labs and the trial subjects benefit from it (information and improved health respectively). The reason Wertheimer thought that a *mutually beneficial* transaction was unique to a LMIC is because he felt it would be irrational for a parent in a HIC to make the same choice as a parent in a LMIC because they (the citizens of a HIC) already have access to the best available therapy.

Wertheimer believed that the moral default position should be not to prevent, but to positively enable transactions that are beneficial to the disadvantaged and to which they consent.[75] He admitted that the consent of a trial subject (in this case, a Bolivian parent) did not automatically render the Surfaxin trial non exploitative. He insisted, however, that such consent might ethically justify not *interfering* with the Surfaxin study.[76] He believed that from an *ex-ante* (based on forecasted rather than actual results) perspective, one could argue that the a PCT such as the Surfaxin trial was actually beneficial to all participants. Every Bolivian baby in the trial would (at least) have had a 50% chance of receiving beneficial treatment and even those not

[74] Ibid., p. 227
[75] Ibid., p.222
[76] Ibid, p. 232

getting the drug would have profited from intubation and better all-around care and treatment.[77]

Wertheimer emphasized in his writings that PEP does not refer to the *morality of the transactions* themselves, but to the *morality of regulating transactions*. He asked rhetorically whether there was any justification in interfering with the Surfaxin trial because it was a *mutually advantageous* (for D-Labs and Bolivian infants) and *consensual transaction* (by Bolivian parents), if interference or prohibiting the trial is ultimately better for no one?[78] Wertheimer's crucial point is that PEP is a justification to *permit* mutually advantageous and consensual transactions even when they are *unfair*[79] [emphasis added].

Mark L. Bourgeois[80]
"*Informed Consent*"

Dr. Mark L. Bourgeois states emphatically that the Surfaxin trial should be rightly characterized as "deeply exploitative".[81] He believes that the first canonical principle of ethics, namely autonomy, was violated. Dr. Paul McNeil defines

[77] Ibid., p.228
[78] Ibid., p.218
[79] Ibid., p.241
[80] Dr. Mark L. Bourgeois is a Visiting Associate Professor and philosopher associated with the Technology Ethics Center at the University of Notre Dame.
[81] Bourgeois, Mark, L., "Autonomy and Exploitation in Clinical Research: What the Proposed Surfaxin Trial Can Teach Us about Consent", *Ethics in Biology, Engineering & Medicine – An International Journal*, Volume 3, Number 1 – 3, Begell House, Inc., 2012 p. 55

autonomy as "the principle of respect for persons", i.e., if subjects are *autonomous* (within the context of a clinical study), they should be given the opportunity to decide for themselves whether or not to contribute to a research project.[82]

Bourgeois interprets the Surfaxin trial through the second formulation of Immanuel Kant's Supreme Principle of Morality, a.k.a. the *Categorical Imperative* which was a core principle of Kant's ethics, namely, to treat people as ends and never merely as means (see introduction to exploitation above).[83] Since the intent of the proposed Surfaxin trial was not to benefit the babies involved (even though some would have benefitted); the purpose, as we have seen above, was to obtain data (using a placebo) to support the approval application of the drug by the FDA.[84] The infants (and their incidental benefit) are *means* to this end; they are in no ways *ends* in themselves.[85]

Bourgeois concedes that if treating research participants as means to an end is morally objectionable in itself, then it would appear that all medical research would

[82] McNeil, Paul M., *The Ethics and Politics of Human Experimentation*, University of Cambridge, Melbourne, Australia, 1993, p.139

[83] The first formulation of the *Categorical Imperative* is to "Act only according to that maxim (intent) whereby you can at the same time will that it should become a universal law without contradiction". This not a reformulation of the Golden Rule, i.e., to do unto others as you would have them do unto you. Kant grounded his ethics in reason through an appeal to its sheer logical self-consistency. Kant holds that unethical conduct would actually violate logic were it to be universalized as a prescription (law). Source: Bourgeois, Mark, L., "Autonomy and Exploitation in Clinical Research: What the Proposed Surfaxin Trial Can Teach Us about Consent", *Ethics in Biology, Engineering & Medicine – An International Journal*, Volume 3, Number 1 – 3, Begell House, Inc., 2012, p.54

[84] Ibid., p.53

[85] Ibid.

have to be outlawed on principle.[86] Since this is not practicable or can even be considered, Bourgeois thinks that there has to be something that moderates this problem. Since treating people as means to your own end ignores their autonomy, Bourgeois suggests that obtaining their fully *informed consent* affirms their autonomy and is *the* [emphasis added] moderating principle that removes the moral objection. [87]He doesn't use Wertheimer's term *mutually beneficial,* but he infers that there should theoretically be no obstacle to allowing the Bolivian parents (even if they were completely aware there was no better alternative), to enroll their infants in the Surfaxin trial if both parties have consented to the arrangement.[88]

Still, since Bolivian parents were being asked to choose between a poor or a reasonable chance at the survival of their babies, Bourgeois imagines that such consent is for all intents and purposes compelled.[89] He also poses the question if it is truly possible for a person to autonomously consent to being treated as means to someone else's end (in this case D-Labs using the parents' permission to use their infants to obtain data). To answer that question, he refers to Kant once again who claimed that a rational agent cannot autonomously consent to being used as a means and at the same time remain a rational agent.[90] For Kant, such a scenario is a logical

[86] Ibid., p.54
[87] Ibid.
[88] Ibid.
[89] Ibid., p. 53
[90] Ibid., p.54

paradox – *autonomy subverting itself* - therefore truly consenting to be a means to an end is impossible. What this implies is that a research subject cannot autonomously enroll in a trial where they will be treated as a means to an end, even if they do so by seeking their own end.[91]

Moving beyond the Kantian philosophical arguments about autonomy and consent, Bourgeois characterizes the Surfaxin trial as "deeply exploitative" because the baseline for a Bolivian parent was no treatment at all, with a far less latitude for "choice" and the real possibility of making an autonomous decision. From Bourgeois' perspective, even the most altruistic of trial subjects are at a disadvantage because ultimately the burden of research risk falls on them even if and when they have no expectation of benefit. The moral default should be to design clinical trials (where feasible) in such a way that the study offers some prospect of benefit on those who participate in the study.[92] .

Jennifer S. Hawkins
"*Good Samaritan Obligations*"

Dr. Jennifer S. Hawkins writes that a basic premise of morality, accepted by moral philosophers and ordinary people, is that everyone has a positive obligation

[91] Ibid.

[92] Bourgeois, Mark, L., "Autonomy and Exploitation in Clinical Research: What the Proposed Surfaxin Trial Can Teach Us about Consent", *Ethics in Biology, Engineering & Medicine – An International Journal*, Begell House, Inc., 2012 p. 56

to assist others in need (she admits, though, that it's a limited obligation).[93] She labels this responsibility the *Good Samaritan*[94] *Obligations* and she argues that, like explaining exploitation itself, there appears to be an element of *intuition* [emphasis added] in understanding what a Good Samaritan obligation is, even if defining such obligations "are notoriously difficult to pin down and make precise."[95]

In clinical trials likes Surfaxin, being conducted in a LMIC and involving a placebo, Hawkins asserts that researchers, just like the rest of us, have Good Samaritan obligations and are flouting that obligation when they fail to perform easy rescues.[96] An "easy rescue" in the Surfaxin trial means that the researchers have access to life-saving medicines for all the infants and they should all receive it. She says that when researchers go to LMICs, they knowingly enter an environment where people they could easily save are dying all around them. She says further, like in the Surfaxin trial, that researchers are sometimes the *only ones* in the local environment who could help.[97] She insists furthermore that the cost to sponsors, i.e.,

[93] Hawkins, Jennifer S., "Exploitation and Placebo Controls", excerpted in Jennifer S. Hawkins and Ezekiel J. Emanuel, (editors)., *Exploitation and Developing Countries: The Ethics of Clinical Research,* Princeton University Press, Princeton, N.J., 2008, p.266

[94] Good Samaritan: one who voluntarily renders aid to another in distress although under no duty to do so. From the good Samaritan in the New Testament parable (Luke 10:30–37)

[95] Hawkins, Jennifer S., "Exploitation and Placebo Controls", excerpted in Jennifer S. Hawkins and Ezekiel J. Emanuel, (editors)., *Exploitation and Developing Countries: The Ethics of Clinical Research,* Princeton University Press, Princeton, N.J., 2008, p.268

[96] Ibid., p.267

[97] Ibid.

D-Labs, of additional medical supplies is (usually) not too expensive and would not be a big sacrifice to them.[98]

Hawkins is not against all placebo trials. She concedes that PCT trials are sometimes necessary to obtain useful data and the data themselves are not morally significant in the sense that Good Samaritan obligations are being ignored.[99] There are three conditions, when, according to Hawkins, that researchers may depart from their Good Samaritan Obligations in a PCT trial. First, the aim of the research must be morally weighty, i.e., there must be a need for the information. Second, a PCT must be the only way to obtain the information that is required and third, the community from which the subjects will be drawn must greatly benefit, and is also reasonably likely to benefit, from the research.[100] There is probably no weighty moral obligation is a clinical trial testing and developing a new cold or allergy medicine. She claims that it's the design of a PCT trial itself which determines whether researchers have moral obligations to their subjects.

Hawking asserts that the PCT design of the Surfaxin trial rendered it immoral. Her reasoning is that D-Labs was developing and testing a "me-too"[101] drug (since there were already other surfactants on the market) and consequently

[98] Ibid.
[99] Ibid., p.267
[100] Ibid., p.273
[101] A "me-too" drug is a drug manufactured by pharmaceutical companies to mimic so-call blockbuster drugs (Viagra, Nexium, Prozac, etc.) even if the pharmaceutical or therapeutic gain is minimal.

there was no *need* for the drug.[102] The data obtained from the trial was to make Surfaxin cheaper to manufacture because it would be entirely synthetic. This reduction in costs would merely aid D-Labs to earn a larger share of the profits of a lucrative industry. Also, the Bolivian community would not "greatly" benefit from the new drug, presuming it was successful.

On page vi of this essay, an article by David Brooks of the *New York Times* was cited in which he wrote that morality is about seeing other people with the eyes of the heart, seeing them in their full experience, suffering with their full suffering, walking with them on their path. Morality starts with the quality of attention we cast upon each other.[*103*] Compounding the moral issue in the Surfaxin trial design, Hawkins also says that the parents of the infants in the control group (infants receiving "sham" air) also experience an additional layer of psychological suffering.[104] If their babies died, they knew (after the fact) that there was something (the new surfactant drug) that *might* have helped their baby and they had a chance at it, but did not get it. They lost the lottery, so to speak. The consent process itself illustrates even more clearly for the Bolivian parents what they do not have and a

[102] Hawkins, Jennifer S., "Exploitation and Placebo Controls", excerpted in Jennifer S. Hawkins and Ezekiel J. Emanuel, (editors)., *Exploitation and Developing Countries: The Ethics of Clinical Research,* Princeton University Press, Princeton, N.J., 2008, p.267

[103] Brooks, David, "The Southern Baptist Moral Meltdown", *The New York Times*, May 27, 2022, p.A23

[104] Hawkins, Jennifer S., "Exploitation and Placebo Controls", excerpted in Jennifer S. Hawkins and Ezekiel J. Emanuel, eds., *Exploitation and Developing Countries: The Ethics of Clinical Research,* Princeton University Press, Princeton, N.J., 2008, p.266

PCT trial and the blindness of the randomization process offers them hope that is later dashed which for Hawkins appears to be a clear violation of the ethical principle of benevolence.[105]

For Hawkins, Good Samaritanism is her *moral* argument and she emphatically states that Good Samaritan obligations, including not inflicting additional emotional or psychological harm, must be enforced and she advocates that whenever these obligations are being contravened, the study should be forbidden.[106]

Erik Malmqvist, Silvia Camporesi,[107] Matteo Mameli[108]
"*Justice & Complicity*"

The first sentence in the abstract of this essay referred to a tenet of contemporary "woke" culture, namely an alertness and sensitivity to social justice. For some bioethicists, social justice is *the* critical issue in global clinical research involving LMICs.

Dr. Erik Malmqvist thinks that clinical research that is off-shored to LMICs evokes unease partly because of the precarious structural conditions in which it is

[105] Ibid., p.271
[106] Hawkins, Jennifer S., "Exploitation and Placebo Controls", excerpted in Jennifer S. Hawkins and Ezekiel J. Emanuel, eds., *Exploitation and Developing Countries: The Ethics of Clinical Research,* Princeton University Press, Princeton, N.J., 2008, p.267
[107] Silvia Camporesi, Reader in Bioethics and Health Humanities in the Department of Global Health & Social Medicine, Kings College, London
[108] Matteo Mameli, Reader, Department of Philosophy, Kings College, London

carried out. People who live in poverty and lack access to healthcare are vulnerable to exploitation. He sees the Surfaxin trial as a prime example of where the circumstances of their lives could easily weaken the bargaining position of a Bolivian parent to such an extent that the parent cannot reasonably refuse an unfair, but potentially beneficial offer.[109]

For Malmqvist, poverty and the lack of access to healthcare are background circumstances that are *themselves unjust*.[110] According to Malmqvist, justice requires access to at least some minimum level of healthcare. He points out that surfactants are not luxury drugs and the World Health Organization (WHO) lists surfactants as essential medicines. Since drugs like surfactants are thought to satisfy priority healthcare needs, access to them should be considered part of the human right to health.[111] He asserts further that since a Bolivian parent would not agree to participate on D-Labs terms even in *just* circumstances, i.e., if they had access to these treatments – sponsor companies like D-Labs can rightly be said to *take advantage of injustice* when they conduct clinical research in some LMICs.[112]

Malmqvist accepts that exploitation is usually understood as a feature of discrete exchanges, i.e., transactions (see Malmqvist/Szigeti explanation of

[109] Malmqvist, Erik, "Better to Exploit than to Neglect? International Clinical Research and the Non-Worseness Claim", *Journal of Applied Philosophy*, Volume 34, Issue 4, August 10, 2015, p. 7
[110] Ibid.
[111] Ibid., p.8
[112] Ibid.

wrongful exploitation, pages 18 - 19, above). He feels, however, that a focus on transactional fairness in explaining exploitation is too narrow. According to Malmqvist, when researchers (like D-Labs) take advantage of structural injustice like poverty and the lack of healthcare, they become complicit in perpetuating injustice.[113]

Drug companies (research sponsors) are complicit in perpetuating structural injustices when they create incentives to slow structural reform. Malmqvist claims that research sponsors have a vested interest in continued lack of access to healthcare in poor countries because such lack of access provides opportunities to conduct future research on terms highly favorable to them.[114] If the Bolivian parents had adequate access to healthcare, they would not enroll in research like the Surfaxin trial and companies like D-Labs would have to design trials in costlier ways.[115] Once a research trial begins, research sponsors prefer that treatment remain inaccessible for the duration of the trial (months or years). Research sponsors have an incentive to actively oppose efforts to increase healthcare access. Malmqvist points out that large drug companies have considerable economic and legal muscle to influence policy making. Therefore, if a research sponsor's trial depends on unjust

[113] Malmqvist, Erik, "Better to Exploit than to Neglect? International Clinical Research and the Non-Worseness Claim", *Journal of Applied Philosophy*, Volume 34, Issue 4, August 10, 2015, p. 8
[114] Ibid., p. 10
[115] Ibid.

inaccessibility to healthcare, the sponsor has an additional incentive to exercise its influence to preserve that injustice.[116]

Malmqvist says that when a research sponsor turns injustice into profit, it encourages and legitimizes similar behavior on the part of other research sponsors that they may conduct trials that involve withholding treatment.[117] He implicitly criticizes Dr. Wertheimer's theory of *mutually beneficial* transactions when he writes that research participants like the Bolivian parents, acting as consenting proxies for their infants, contribute to the message to research sponsors that trials that withhold treatment have an air of legitimacy.[118]

He says that only by testing the Surfaxin drug against an existing surfactant therapy (vs. a placebo), could D-Labs have avoided being complicit in structural injustice because it would have avoided taking advantage of that same injustice when interacting with its victims.[119] For Malmqvist, any interaction in clinical research in LMICs must be on terms that the participants would accept if background conditions were *just*.[120]

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[116] Ibid., p. 11
[117] Malmqvist, Erik, "Better to Exploit than to Neglect? International Clinical Research and the Non-Worseness Claim", *Journal of Applied Philosophy*, Volume 34, Issue 4, August 10, 2015, p. 12
[118] Ibid.
[119] Ibid.
[120] Ibid, p.13

Dr. Silvia Camporesi and Dr. Matteo Mameli, both Readers in Bioethics and Philosophy at Kings College, London, echo most of Malmqvist's arguments and they argue, like Malmqvist, that the unfairness of background conditions of prospective subjects needs to be taken into account when evaluating the ethical justifiability of a trial.[121] Camporesi and Mameli argue that if a pharmaceutical company is taking advantage of unjust background conditions, like the lack of access to healthcare, then it's necessary to intervene to prevent a clinical trial like Surfaxin from taking place.[122]They believe that when research sponsors like D-Labs recruit subjects from economically disadvantaged backgrounds, it contributes to and perpetuates the status quo and exacerbates social inequalities.[123]

4.3 Capstone-Thesis Argument

"Whoever saves a single life is considered by scripture to have saved the whole world." – Talmud (Sanhedrin 37a)

I agree with all six bioethicists that the proposed Surfaxin trial was exploitative. The *degree* of exploitation from their individual perspectives varies greatly however – from Wertheimer's simple admission that the trial was

[121] Camporesi, S. & Mameli, M., "Trading participation for access to health-care: A morally relevant feature of participation in clinical research", *JOSHA – Journal of Science, Humanities and Arts*, 2016, vol.3., no. 4., p.9
[122] Ibid., p. 10
[123] Ibid.

exploitative to Bourgeois' characterization of the trial as "deeply exploitative". Bourgeois, Hawkins, Malmqvist, Camporesi and Mameli offer persuasive bioethical and philosophical arguments as to why, in their opinion, they either explicitly or seem to suggest that if the trial design had been allowed to move forward, intervention of some sort or prohibition would have been warranted. Nevertheless, I would argue that the Surfaxin trial should have been permitted to be conducted as designed and that their arguments in the Surfaxin case were not practical.

It may appear at first glance that I'm endorsing *carte blanche* Wertheimer's concept of Permitted Exploitation Principle. While it is true that I'm sympathetic with his openness to the permissibility of [some] exploitation in global clinical research, I can easily see the possibility of serious ethical issues in mutually beneficial transactions that simply mask desperate access to some form of health care by disadvantaged people via their voluntary clinical trial participation. While I would not go as far as Camporesi and Mameli who sarcastically characterize Wertheimer's Permitted Exploitation Principle (PEP) as the Principle of *Encouraging* Exploitation (PEE), I'm very much aware of the potential ethical dangers in sanctioning any degree of exploitation in clinical research[124]. I believe that bioethicists should, if possible, be receptive to reasonable solutions to ethical

[124] Camporesi, S. & Mameli, M., "Trading participation for access to health-care: A morally relevant feature of participation in clinical research", *JOSHA – Journal of Science, Humanities and Arts*, 2016, vol.3., no. 4., p.5

problems in what may be described as legitimate and responsible clinical research and at times should perhaps "widen the lens" beyond the boundaries of their own philosophies. My thinking is strongly influenced by the late bioethicist, philosopher and one-time Jesuit priest, Dr. Albert Rupert Jonsen who died in 2020. Jonsen once compared the bioethicist to a balloonist floating high above the earth and able to see what lies ahead and sees below him/her a frantically pedaling bicyclist, the physician [or the researcher] who is negotiating the ethical curves and potholes that suddenly appear in clinical practice [or research].[125] For Dr. Jonsen, philosophy was like a hot-air balloon that gave a serene, grand view of an expanse. But most people, as we know, do not live in balloons. Dr. Jonsen's idea was that the philosopher in the balloon would somehow shout down to the bicyclist, like a navigator from above, giving her/him sage advice and direction.[126] Jonsen showed philosophers and bioethicists a way to shift from the "intoxicating" heights of theory to managing the muddy, messy and often nebulous challenges in medicine and clinical research.[127] For example, in a 2004 interview with the Office of Human Research Protections (U.S. Department of Health and Human Services), Dr. Jonsen stressed that in global clinical research, the ethical principle of autonomy, i.e. respect for persons, should be understood not merely on an isolated individual basis but on a community basis

[125] Kolata, Gina, "Obituary: Dr. Albert R. Jonsen, 89, An Academic Who Brought Medical Ethics to the Bedside", *The New York Times*, November 19, 2020, p. B 10
[126] Ibid.
[127] https://bioethicstoday.org/blog/a-tribute-to-albert-r-jonsen-1931-2020/ accessed August 2, 2022

as well. He pointed out that in some cultures, especially Hispanic communities, the link of the individual and the community is much more powerful than in "our" culture.[128] He was not speaking about the Surfaxin Trial per se, but this practical consideration needs to be addressed when an issue like "consent" is sought in clinical research involving groups of people in non-Western cultures like the Quechua and Aymara peoples of Bolivia. Bourgeois, et.al offer us intoxicating theories, but no practical solutions. Even in the presence of an exploitative transaction, I believe that bioethicists are pragmatists and often are faced with dealing and navigating the messiness of the reality of life in clinical trials like Surfaxin which may deeply offend their ethical philosophies. At the end of the day, 650 neo-natal infants in Bolivia and countless other infants in Latin America may have died because the Surfaxin Trial was abandoned.

I would maintain that the argument of Bourgeois (and implicitly Wertheimer) regarding *informed consent* as a moderating principle to removing a moral objection to exploitation is *partially* flawed. Informed consent implies understanding and as I wrote in the discussion on exploitation, even a straightforward word like *understands* can be problematic for a bioethicist. In other words, by acknowledging the risks and benefits of the trial to them personally, participants nevertheless accept

[128]https://www.hhs.gov/ohrp/education-and-outreach/luminaries-lecture-series/belmont-report-25th-anniversary-interview-ajonsen/index.html

those risks and freely give their permission to be part of an experiment using their (or as in the Surfaxin trial, their children's') bodies. On the surface, there doesn't appear to be any ethical or moral obstacle here. But as the late Franz J. Ingelfinger (1910-1980), a physician, researcher and journal editor wrote: "the trouble with informed consent is that it is not *educated consent*".[129] He asserted that providing information to prospective research participants does not mean that they understand the information. To further complicate matters, Ingelfinger contends that besides being impractical, it's probably unethical to list and provide all possible contingencies since extensive detail usually heightens the subject's confusion.[130] Bourgeois' argument regarding informed consent is not without merit because consent has to be obtained by participants in a trial. But the principle of informed consent alone is not enough to remove a moral objection to exploitation, it has to be more. It has to incorporate some sort of educated consent, and that's the real practical challenge for bioethicists how to define what educated consent means and how not to overwhelm participants with too much information. As Dr. Ingelfinger observed, when a clinical trial subject is uneducated or uncomprehending, the process of obtaining informed consent with all its regulations and conditions is no more than

[129] Emanuel, J. Ezekiel, et.al., (Editors), *Ethical and Regulatory Aspects of Clinical Research, Readings and Commentary*, The John Hopkins University Press, Baltimore, MD., 2003, p. 190

[130] Ingelfinger, Franz J., "Informed (But Uneducated) Consent", excerpted in Ezekiel J. Emanuel, et.al. (editors), *Ethical and Regulatory Aspects of Clinical Research, Readings and Commentary*, the John Hopkins University Press, Baltimore, MD, 2003, p. 202

an elaborate ritual, a device which confers no more than the semblance of propriety on human experimentation.[131]

As a possible solution, Bourgeois appears to offer the practicality of true autonomous and informed consent without violating Kantian ethics if a clinical study makes *mutually sought ends*, i.e., some form of *collaboration* between both researchers and trial participants possible. In other words, the trial would have to offer some prospect of benefit to participating subjects[132]. I would argue that in the Surfaxin trial case that the participants were receiving some prospect of benefit which I discuss in more detail below when I address the issue of Good Samaritan Obligations. I think that Bourgeois is in effect approximating the thinking of Dr. Paul Formosa[133] who maintains and allows that human vulnerabilities play a role within Kantian ethics since human bodies have rational capacities and as such are highly vulnerable, especially in some sub-groups of persons, e.g., the parents of and the children suffering from RDS.[134] Formosa affirms that there is a perfect duty to undertake extra measures to ensure that researchers do not intentionally or inadvertently play on the *allocational vulnerabilities* of others just to benefit

[131] Ibid.p.203

[132] Bourgeois, Mark, L., "Autonomy and Exploitation in Clinical Research: What the Proposed Surfaxin Trial Can Teach Us about Consent", *Ethics in Biology, Engineering & Medicine – An International Journal*, Begell House, Inc., 2012 p. 56

[133] Associate Professor of Philosophy, Macquarie University, Sydney, Australia

[134] Formosa, Paul, "The Role of Vulnerability in Kantian Ethics", excerpted in Catriona Mackenzie, Wendy Rogers and Susan Dodds (editors), *Vulnerability: New Essays in Ethics and Feminist Philosophy*, Oxford University Press, New York, N.Y., 2014, p.106

themselves. Allocational vulnerabilities occur when a subject's only ready access to important goods or services is through participation in a study (like Surfaxin).[135] Formosa acknowledges that the duty to obtain the free and informed consent (and avoid exploitation and define mutually sought ends) of members of highly vulnerable sub-populations by researchers is therefore much more onerous.[136] I see it as positive that both Bourgeois and Formosa seem to allow for optional alternatives within their interpretation of Kantian ethics but the difficulty for both of them, as well as for most bioethicists, is determining exactly how this can practically be achieved.

Hawkins' philosophy of Good Samaritan Obligations on the part of researchers in laudable, but I have the sense she is blurring the ethics of medicine with that of clinical research. It's easy to understand why this can occur given that researchers are often physicians and the ethics governing the practice of medicine and clinical research often conflict. There is a natural tension between physicians and clinical researchers, especially those researchers who are physician-scientists. Just as bioethicists are not always of "one mind" on ethical issues, neither are physicians when defining their role in clinical research. Physicians are to provide diagnosis, preventative treatment and therapy to individuals to enhance their health

[135] Ibid., p.104
[136] Ibid., p.106

and well-being with a reasonable expectation of success.[137] Research describes an activity designed to test a hypothesis, permit conclusions to be drawn and contribute to generalized knowledge.[138] As stated by Dr. Anthony Fauci (see footnote # 36 above), the goals of the randomized clinical trial are not to deliver therapy but to answer a scientific question so that the drug can be available for everybody once you've established safety and efficacy.[139] Dr. Samuel Hellman, M.D., writing in the New England Journal of Medicine, states that *randomized clinical trials* (see glossary) force physicians to simultaneously become scientists thereby creating an unsustainable ethical conflict for them. Randomized clinical trials, in Hellman's mind, expose the conflicting moral demands between rights-based[140] moral theories and utilitarian[141] ones. According to Hellman, Fauci is suggesting that randomized clinical trials expect physicians to sacrifice the interests of their particular patients for the sake of the study and that of the information that it will make available for the benefit of society.[142] Hellman does allow for some randomization in clinical

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[137] The Belmont Report, "Ethical Principles and Guidelines for the Protection of Human Subjects of Research", The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, excerpted in Ezekiel J. Emanuel, et.al., (editors), *Ethical and Regulatory Aspects of Clinical Research, Readings and Commentary*, The John Hopkins University Press, Baltimore, MD., 2003, p. 33

[138] Ibid.

[139] Hellman, Samuel, M.D., Hellman, Deborah S., "Sounding Board: Of Mice but Not Men", *The New England Journal of Medicine*, vol 324 no 22, 1991, pp. 1585-1586

[140] Rights based moral theories depend on the moral theory of Immanuel Kant which states that human beings, by virtue of their unique capacity for rational thought, are bearers of dignity and ought not to be treated [merely] as means to an end. They must always be treated as ends in themselves. See above references to *Categorical Imperative*

[141] Utilitarianism defines what is right as the greatest good for the greatest number (social utility) – the morally correct act is the act that produces the most pleasure and the least pain overall

[142] Hellman, Samuel, M.D., Hellman, Deborah S., "Sounding Board: Of Mice but Not Men", *The New England Journal of Medicine*, vol 324 no 22, 1991, p.1586

research as ethical but only when the physician has no preference for a particular drug or therapy or a specific treatment and the physician believes that the severity and likelihood of harm and good are evenly balanced. In other words, the trial is in a state of equipoise.[143] There are different interpretations of the clinical equipoise doctrine, but the central tenet is that conducting a clinical trial is only justified when there is uncertainty about which of the trial interventions is better.[144] In other words, clinical trial equipoise exists when on the basis of available data, a community of competent physicians would be satisfied to have their patients pursue any of the treatment strategies being tested in a randomized trial, since none of them have been clearly established as preferable.[145] Even if a patient signs an informed consent document or wishes to participate in a clinical trial for altruistic reasons, Hellman says the right to be treated as an individual deserving the physician's best judgement and care cannot be waived or abrogated.[146] His reasoning appears to echo that of Bourgeois who says that altruistic trial participants bear the burden of research risk. Writing in the same journal, however, Dr. Eugene Passamani, M.D., argues that randomized clinical trials are the most scientifically sound and ethically correct

[143] Hellman, Samuel, M.D., Hellman, Deborah S., "Sounding Board: Of Mice but Not Men", *The New England Journal of Medicine*, vol 324 no 22, 1991, p.1586
[144] Malmqvist, Erik, "(Mis)Understanding Exploitation", The Hastings Center, Volume 33, Issue 2, February 2016, p.1
[145] Passamani, Eugene, M.D., "Sounding Board: Clinical Trials – Are They Ethical", *The New England Journal of Medicine*, vol 324 no 22, 1991, p.1590
[146] Hellman, Samuel, M.D., Hellman, Deborah S., "Sounding Board: Of Mice but Not Men", *The New England Journal of Medicine*, vol 324 no 22, 1991, p.1586

means of evaluating new therapies.[147]Passamani writes that randomization tends to produce treatment and control groups that are evenly balanced in both known and unrecognized prognostic factors.[148] He believes that randomization will provide a more accurate estimate of treatment effect in groups of patients assigned to experimental and standard therapies.[149] Passamani asserts that many physicians are aware that the evidence supporting many common therapies is often weak and this is precisely why properly performed randomized clinical trials have profound effects on medical practice.[150] He says that most physicians recognize the scientific importance of randomized controlled trials in safeguarding current and future patients from the therapeutic passions of physicians.[151]When he refers to therapeutic passions, Passamani is implicitly taking aim at Hellman's emphasis that the judgement and hunches of the physician take precedence and are more valuable in patient care than clinical trial findings. Passamani is not oblivious to potential ethical gulfs that exist between proved therapies and possible effective therapies but he maintains that the only reliable way to make the distinction between proved and possible effective therapies is to experiment – experimentation that will increasingly involve randomized clinical trials.[152] Passamani affirms that physicians owe their

[147] Passamani, Eugene, M.D., "Sounding Board: Clinical Trials – Are They Ethical", *The New England Journal of Medicine*, vol 324 no 22, 1991, p.1589
[148] Ibid., p.1590
[149] Ibid.
[150] Ibid.
[151] Ibid.
[152] Ibid., p.1591

patients involved in the assessment of new therapies the best that science and ethics can deliver and for most unproved treatments, a properly performed randomized clinical trial is the way to achieve that. When Hawkins talks about "easy rescue" (because the researchers have access to medicine) her sentiments seem to lean towards the reasoning of Dr. Hellman who ends his article declaring that "we must develop and use alternative methods for acquiring clinical knowledge".[153] Nevertheless, physician-scientists are not an extension of *Doctors Without Borders*.[154] I applaud her compassion, but in this imperfect world where alternative methods for acquiring clinical knowledge are not yet available or developed and she really believes that the role of researchers is to provide treatment in every case, then no clinical research can effectively or ever be done.

Dr. Hawkins acknowledges that defining Good Samaritan Obligations can be difficult to pin down and make precise and she concedes that in some circumstances randomized trials using placebos are the only way to obtain important data. She might lessen her ethical objection to the Surfaxin trial by not considering the children in the control group as strictly receiving a placebo. By definition, a placebo has no therapeutic effect, but that was not technically the case in the Surfaxin trial. It was

[153] Hellman, Samuel, M.D., Hellman, Deborah S., "Sounding Board: Of Mice but Not Men", *The New England Journal of Medicine*, vol 324 no 22, 1991, p.1589

[154] Doctors Without Borders/Médecins Sans Frontières (MSF) – founded 1971, France, cares for people affected by conflict, disease outbreaks, natural and human-made disasters, and exclusion from health care in more than 70 countries Source: https://www.doctorswithoutborders.org/ accessed November 12, 2022

known that the so-called "sham" air, plus the medical devices, e.g., ventilators, endotracheal tubes and antibiotics would be given to ALL children in the trial. Granted, the children in the control group would receive an inferior treatment relative to the children in the active control group (who would receive the surfactant drug). Even so, some bioethicists would not necessarily consider this to be unethical and there is a precedent promulgating that participants receive an inferior (less promising) intervention than other participants in a clinical trial. Bioethicists Dr. Nir Eyal of Rutgers University and Dr. Marc Lipsitch, a professor in the Department of Epidemiology at Harvard University, believed that it was not only acceptable, but should have been widely accepted, that some participants in clinical research in the course of Covid-19 vaccine testing in 2020 receive less-promising interventions than those offered to other participants.[155] Their thinking was driven by the then looming global public health emergency in early 2020. Clearly, RDS and Covid-19 have different weight in terms of urgency and allocation of resources for global societies. Still, on a much smaller scale, isn't it possible that Hawkins might consider RDS to be a public health emergency of sorts not only in Bolivia but in surrounding Latin American countries as well? Perhaps Hawkins or another bioethicist who shares her philosophy of Good Samaritan Obligations might see those very obligations as being

[155] Nir Eyal and Marc Lipsitch, "It's ethical to test promising coronavirus vaccines against less-promising ones", P*roceedings of the National Academy of Sciences (PNAS)*, Vol. 117, no. 32, August 11, 2020, p.18900

fulfilled to some degree in the Surfaxin trial if they can overcome the belief that the inferior treatment in the control arm of the trial was just a placebo in the classic understanding of the word. At the same time, if one considers the inferior treatment (not using the surfactant drug) as, at a minimum, a prospect for some benefit (for all) in the Surfaxin trial design, might this not satisfy Dr. Bourgeois' moral default requirement?

Dr. Hawkins explicitly writes that the Surfaxin trial should have been forbidden and Drs. Camporesi and Mameli believe that in some cases intervention is required to prevent research participants from participating in clinical trials.[156] Dr. Malmqvist, when writing about the duties of research sponsors, i.e., D-Labs, not to be complicit in contributing to structural injustices argues that if the sponsors themselves cannot fulfill these duties, that *somebody* has such a duty.[157] The difficulty with proposing interventions either by governments or regulatory agencies on ethical or humanitarian grounds suggests explicit criminality on the part of clinical researchers and by extension, that clinical trial subjects are being victimized. Dr. Charles R. Beitz[158]asserts that we have a duty to protect the innocent and vulnerable people from harms to which they are vulnerable but he questions whether

[156] Camporesi, S. & Mameli, M., "Trading participation for access to health-care: A morally relevant feature of participation in clinical research", *JOSHA – Journal of Science, Humanities and Arts*, 2016, vol.3., no. 4., p.2
[157] Malmqvist, Erik, "Better to Exploit than to Neglect? International Clinical Research and the Non-Worseness Claim", *Journal of Applied Philosophy*, Volume 34, Issue 4, August 10, 2015, p. 12
[158] Charles R. Beitz, b. 1949 teaches contemporary political philosophy and the history of modern political philosophy at Princeton University. Source: https://politics.princeton.edu/people/charles-beitz

considerations of humanity require us to act in every case where we are permitted to do so.[159]Beitz rejects what he calls injudicious talk about a "duty to intervene" if it obscures the fact that there might be other, competing considerations that should also be taken into account since we have no way of knowing what other moral considerations might be in play in any particular case.[160] Furthermore, he affirms that it will often be unrealistic, both ethically and politically, to consider an intervention successful if it alleviates the immediate causes of distress but leaves the underlying causes intact.[161] One could reasonably ask what good it would do in the Surfaxin trial if the government of Bolivia stopped the trial from going forward instead of D-Labs voluntarily abandoning the trial under pressure from American regulatory agencies. In both cases, the underlying cause of distress, namely children in Bolivia dying from RDS would remain intact. I would argue it is not sufficient for bioethicists to demand or advocate intervention on strictly humanitarian grounds alone since what constitutes humanitarian can be ambiguous. It's possible that a bioethicist could insist on intervention simply because the trial conflicts with his or her particular ethical philosophy. In addition, bioethicists need to give concrete specifics of how such intervention is to be done and by whom. Dr. Beitz correctly asks who that "competent authority" might be and how the goals of that authority

[159] Beitz, Charles R., "Humanitarian Intervention", excerpted in Hugh LaFollette (ed), *Ethics in Practice: An Anthology*, Fourth Edition, John Wiley & Sons, Inc., Malden, Massachusetts, 2014, pp.660-661
[160] Ibid., p.661
[161] Ibid., p.663

will be achieved.[162] Indeed, Drs. Camporesi and Mameli openly admit that they themselves do not have the skills to determine how prevention and/or intervention can be enforced.[163]

The reality in the Surfaxin trials is that many infants would have survived. We know that D-Labs was required by the FDA to conduct a placebo test which could not be conducted in the United States. Thomas Pogge's assertion that D-Labs had to "scour the earth in hopes of finding RDS infants whom they could permissibly infuse with "sham" air" [164]appears to me to be overkill and is a lame attempt to portray the company as if it were a sinister predator. At the time of the proposed trial, D-Lab's president, Dr. Robert Capetola, asserted that D-Labs had made a large commitment to not only a Latin American study, but also an international one. While it is true that a placebo would be involved in one of the control arms, the two other control arms would have Surfaxin and another known surfactant drug (beractant).

In addition, D-Labs intended to provide training, support, equipment, and eventually (if proved successful) Surfaxin at a very low cost to Bolivia and several

[162] Ibid., p.662

[163] Camporesi, S. & Mameli, M., "Trading participation for access to health-care: A morally relevant feature of participation in clinical research", *JOSHA – Journal of Science, Humanities and Arts*, 2016, vol.3., no. 4., p11

[164] Pogge, Thomas, "Testing Our Drugs on the Poor Abroad", excerpted in Jennifer S. Hawkins and, and Ezekiel J. Emanuel, Editors, *Exploitation and Developing Countries: The Ethics of Clinical Research,* Princeton University Press, Princeton, N.J., 2008, p.112

other countries (Ecuador, Peru and Mexico) for 10 years.[165] This is a crucial point. What Capetola was offering was a possible remedy suggested by Thomas Pogge, namely a modified form of a *differential-pricing*[166] strategy. This means that D-Labs (and other pharmaceutical companies) would offer their proprietary drugs to different customers at different prices. This would result in them realizing a large profit margin from sales to the more affluent without giving up sales to poorer buyers at a much lower margin. Whether such a strategy is practical or not, it was a promise on the part of D-Labs to at a minimum share the benefits of the (presumably successful) research to save or improve the lives of numerous infants in poor countries suffering from RDS.

I am cognizant of the healthcare structural injustices that exist in poorer nations and am sympathetic to the concerns raised by bioethicists like Malmqvist, Camporesi and Mameli. Nevertheless, even their writings on the subject of clinical research in a LMIC acknowledge a certain unease with prohibiting an exploitative transaction in a LMIC *just* because structural injustice exist.[167] Likewise, they concede that if a research subject gives their consent to participate in a trial, even

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[165] Charatan, Fred, "Surfactant Trial in Latin American Infants Criticised", *British Medical Journal*, Volume 322, March 10, 2001, p.575

[166] Pogge, Thomas, "Testing Our Drugs on the Poor Abroad", excerpted in Jennifer S. Hawkins and Ezekiel J. Emanuel, Editors, *Exploitation and Developing Countries: The Ethics of Clinical Research,* Princeton University Press, Princeton, N.J., 2008, p.127

[167] "How, it is asked, can it be worse to exploit the global poor than to neglect them when exploitation is voluntary and makes them better off?", Malmqvist, Erik, "Better to Exploit than to Neglect? International Clinical Research and the Non-Worseness Claim", *Journal of Applied Philosophy*, Volume 34, Issue 4, August 10, 2015, p. 1

though the transaction is exploitative, they ask rhetorically how they can morally object to that person's autonomy. They are not contradicting their ethical principles, they are, like most bioethicists, pragmatists and deal with the actual state of the world even when it challenges their principles.

Still, I am not convinced by the arguments of Malmqvist, Camporesi and Mameli which, explicitly (Malmqvist) and implicitly (Camporesi, Mameli), claim that it's a better world ethically and morally when deprived people in a LMIC are better off neglected rather than exploited. It was estimated that of the 325 infants in the control arm of the trial, at least 140 would have lived (keep in mind, that these infants had no access to healthcare and even the "sham" air was known to have benefits). By abandoning the trial and moving it back to the United States, perhaps most of the 650 infants with RDS who would have been included in the trial died. Nobody knows for sure. While it may be truthful that from an ethical and moral perspective that the Surfaxin trial was being conducted in an environment of structural injustice and was considered by Dr. Bourgeois as "deeply exploitative", nothing good came to the Bolivian infants and their parents by forcing D-Labs to abandon the trial.

Yes, the Surfaxin trial was exploitative but that was not the original *intent* of D-Labs. It was not criminal research as cited in the examples at the beginning of this essay. In the Surfaxin trial, there was, as Wertheimer believed, the possibility

that all the participants could have benefitted (even marginally) given that their baseline was no access to either a surfactant or "sham" air at all. The proposed Surfaxin trial design gave rise to many legitimate ethical conflicts. It was, as Dr. Jonsen may have characterized it - a messy, muddy and conscious-raising problem. But it was a problem that needed a resolution. At the end of the day, if none of the babies survived because the trial was abandoned, then all the bioethical arguments against the Surfaxin trial were, in my opinion, just academic, ethereal, "intoxicating" theories.

5. 0 Conclusion

My objective is not to invalidate or discredit the legitimate bioethical principles of the above bioethicists nor to suggest that their consideration when evaluating proposed clinical trial designs be disallowed. Nor should it be taken that I am endorsing utilitarianism, advocating that as long as most of the babies in the Surfaxin trial survived then it was for a greater societal good. The Talmudic precept about saving even one life is a plea for bioethicists to be pragmatists and try to find some common ground which involves flexibility and compromise to make the world a better place. Perhaps this is really the "trick" that Nicholas Vrousalis was referring to – how do bioethicists navigate the ethical potholes, curves and the roadblocks in clinical research, global clinical research and the challenges of dealing with exploitation, human vulnerability and competing ethical philosophies to ensure that

the weight of their own bioethical philosophies and beliefs do not cause them to look at their fellow human beings with what David Brooks describes as a "detached, emotionless gaze".

Bioethicists recognize that some degree of flexibility and compromise in their attitudes and viewpoints, however disconcerting, is sometimes essential for the greater good of humanity. Dr. Malmqvist concedes that sometimes the only way feasible clinical research and improvement in people's lives can be conducted and achieved is by relying on poor people's lack of access to healthcare in LMICs.[168] As he says, in some cases, complicity may be considered a necessary evil.[169].

Andrew W. Siegel, Ph.D., Research scholar, Berman Institute of Bioethics at John Hopkins University, sums up the entire ethical dilemma of exploitation and off-shoring to LMICs best. He writes that the vulnerabilities that researchers exploit exist in large measure because of our collective failure to fulfill the ethical duty of *beneficence*.[170] Our indifference to the true needs of the poor often sows much of the ground of exploitation.[171]

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[168] Malmqvist, Erik, "Better to Exploit than to Neglect? International Clinical Research and the Non-Worseness Claim", *Journal of Applied Philosophy*, Volume 34, Issue 4, August 10, 2015, p.14
[169] Ibid.
[170] Siegel, Andrew W., "Kantian Ethics, Exploitation, and Multinational Clinical Trials", excerpted in Jennifer S. Hawkins and Ezekiel J. Emanuel (editors), *Exploitation and Developing Countries: The Ethics of Clinical Research,* Princeton University Press, Princeton, N.J., 2008, p.201
[171] Ibid.

Still, he warns us that we must be cautious when we propose or support legislation against exploitation [in clinical research]. His thinking appears to echo my argument that an exploitative transaction alone should not be the sole factor in the decision to cancel or abandon a clinical trial involving human beings. He tells us that in this imperfect world, the *perverse reality* [emphasis added] is that the best prospect some persons currently have for improving their lives is to submit to exploitative exchanges.[172]

[172] Ibid.

Appendix #1 **Glossary**

Active Control Trial: an active control trial is one in which an investigational drug is compared with an established treatment that has a known degree of effectiveness, with the aim of either demonstrating that the test treatment is as good as or is superior to the active treatment.

Control arm: some study participants will be assigned to a "control arm" or "control group" in the study. Those who are in the control arm will not receive the new medication, device or treatment that is under study, to provide a comparison to see how the innovation compares against no treatment or an old treatment.

***Discovery Labs*:** an American startup company which was set up in 1992 and now is based in Warrington, Pennsylvania, developing drug products (pulmonary medicine) for patients with respiratory disease. In 2016, Discovery Laboratories changed its name to Windtree Therapeutics, Inc. Nasdaq: WINT

Double-blinded: a type of clinical trial in which neither the participants nor the researcher knows which treatment or intervention the participants are receiving until the clinical trial is over. This makes results of the study less likely to be biased

Idiopathic: relating to or denoting any disease or condition which arises spontaneously or for which the cause is unknown

Placebo: a substance that has no therapeutic effect, used as control in testing new drugs

Prophylactic: a medicine or course of action used to prevent disease

Synthetic: products made from artificial substances through *chemical synthesis* (the combination of one or two or more compounds, known as reagents or reactants, that will experience a transformation when subjected to certain conditions), often copying a natural product

Surfactant: a fluid secreted by the cells of the alveoli (the tiny air sacs in the lungs) that serves to reduce the surface tension of pulmonary fluids; surfactant contributes to the elastic properties of pulmonary tissue, preventing the alveoli from collapsing

Two-arm randomized controlled trial: a two-arm randomized trial where patients are equally randomized to either a control or a treatment arm. The primary endpoint is overall survival (OS) measured from the date of randomization to the date of death from any cause or last follow-up

Appendix # 2

Low and Lower-Middle Income Countries (LMICs)

GNI (Gross National Income) per capita between $1,036 and $4,045; and upper middle-income economies - those with a GNI per capita between $4,046 and $12,535 (2021).

Following is a list of the current countries that comprise the: Department for International Development (DFiD) priority countries, and World Bank Low and Lower-Middle Income countries.

Afghanistan Angola Armenia Bangladesh Benin Bhutan Bolivia Burkina Faso Burundi Cambodia Cameroon Cape Verde Central African Republic Chad, Republic China Comoros Cote d'Ivoire Democratic Republic of Congo Djibouti Egypt, Arab Rep. El Salvador Eritrea Ethiopia Gambia, The Georgia Ghana Guatemala Guinea Guinea-Bissau Haiti Honduras India Indonesia Iraq Jordan Kenya Kiribati Korea, Dem. People's Rep. Kosovo Kyrgyzstan Lao PDR Lebanon Lesotho Liberia Madagascar Malawi Mali Mauritania Micronesia, Fed. Sts. Moldova Mongolia Morocco Mozambique Myanmar Nepal Nicaragua Niger Nigeria Occupied Palestinian Territories Pakistan Papua New Guinea Philippines Rwanda Sao Tome and Principe Senegal Sierra Leone Solomon Islands Somalia South Africa South Sudan Sri Lanka Sudan Swaziland Syria Tajikistan Tanzania Timor-Leste Togo Tonga Tunisia Uganda Ukraine Uzbekistan Vanuatu Vietnam West Bank and Gaza Yemen Zambia Zimbabwe

Source: https://asm.org/ASM/media/Events-PDFs/NGS-Travel-Award_Low-and-Low-Middle-Income-Countries-List.pdf

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