



CLINICAL TRIALS IN AFRICA

THE CASES OF EGYPT, KENYA, ZIMBABWE AND
SOUTH AFRICA

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TABLE OF CONTENTS



INTRODUCTION	3
EGYPT	6
KENYA	13
ZIMBABWE	19
SOUTH AFRICA	26
CONCLUDING REMARKS	32
APPENDIX	35

INTRODUCTION



In November 2016, 60-year old cancer patient Dania was visited by representatives of the Swiss pharmaceutical giant Roche in Cairo. Several months earlier, she had joined one of their clinical cancer trials. Uninsured, Dania was eager to take the opportunity to get access to free treatment, as Egypt's cancer drugs are virtually unaffordable for the average citizen. Although Dania was grateful for getting treatment via the trial, she said she suffered from the tested drug's painful side effects: skin burns, nails falling out, and cataract.

Not long after Roche's visit though, the Swiss NGO Public Eye – which had written a report with Wemos and SOMO on clinical trials in Egypt that included Dania's story and testimony - received a legal claim signed by a Swiss lawyer stating that Dania wanted her name and pictures removed from the report, and that she did not agree anymore to have them published. During Roche's visit to Dania in November, she allegedly stated that her side effects were unrelated to the tested drug. Moreover, she had stressed that she was happy about having participated in the trial and that she would recommend it to others.

However, Public Eye had proof – a tape recording – in which Dania explicitly gives permission for her name and pictures to appear in the report. And there was more that was odd about the situation. First, Dania could have avoided the entire expensive legal route and just directly contacted Public Eye to have her name and picture removed. A journalist who interviewed her during the research and who had met Dania in September – several months after the report was published – even declared that she did not mention anything negative about her story at all. But most importantly: how and why could an average Egyptian woman with cancer – unable to afford cancer medication – have found her way to a Swiss lawyer and hired him? In fact, the lawyer turned out to be someone who had often worked for Roche. A spokesperson for Roche stated that they were very much willing to help Dania as “she was not happy with the report”. According to him, that was why they facilitated contact between the lawyer and Dania.

Even if the sudden change of attitude of Dania was perceived as doubtful, all (recognizable) pictures of Dania were removed from the report and her name was changed (Dania is not her real name) to respect her wish; and a new version of the report was eventually uploaded on NGOs' websites. Eventually, the verdict was in favour of Public Eye, since they had recorded proof of Dania's permission. And according to the Egyptian partner, Dania was uninformed about the entire ordeal, and was even told she had won the case. She never knew she had hired a lawyer and doesn't even know his name; the Roche representatives merely asked her to sign a form – which she did. What is more is that Dania now has to bear the brunt of the financial costs of the legal process, as whoever paid for the initiation of the legal case (Roche and/or the lawyer) has refused to pursue its financial support.

Why would a pharmaceutical giant push a participant to start a legal process – which costs money and manpower, and bears a huge reputational risk if the manipulation attempt became

known— over one testimony that was in fact not even all that negative? There were more testimonies in the report, so why target Dania's? Through the court documents it became clear that the drug that was tested on Dania was Perjeta: an up-and-coming breast cancer treatment for which Roche has high hopes. It is therefore likely that Roche wanted to prevent any negative publicity on its promising blockbuster.

THE EMERGENCE OF CLINICAL TRIALS IN AFRICA AND ITS CONSEQUENCES

Dania's case received extensive media attention in Switzerland and the Netherlands. We quote it at length here, because it shows how the pharmaceutical industry is very much willing to extend its powers beyond the corporate field and use jurisdiction to counter any criticism on its corporate conduct, and put obstacles on the road for NGOs. This tactic of intimidation can be seen as a new method. Nevertheless, the course of such events cannot be understood without looking at the background of the industry's emergence in developing regions like Africa.

Over the past decades, the global pharmaceutical industry has increasingly been conducting clinical trials in low- and middle-income countries. In 2005, 40% of all clinical trials took place in emerging countries¹. Several reasons for this shift from affluent regions like USA, Europe and Japan in the mid-90's to developing regions are: faster and cheaper recruitment of clinical trial participants, weak health systems, and treatment-naïve, often medically illiterate populations with a wide range of diseases. Also, it is easier to bypass ethical rules and regulations because of lack of legislation and less stringent or weak monitoring.

The African continent has attracted the global pharmaceutical industry's attention due to its unique profile: low access to quality healthcare, epidemiological transition, fast-growing population, a rising middle class, and rapid economic growth. And the expanding middle class – with its 'Westernized' lifestyle - has a concomitant effect: an increase in non-communicable diseases (NCDs), like diabetes, cardiovascular disease and cancer. This is also why the industry sees Africa's commercial potential in regard to new drugs for NCDs. 'Of all emerging locations or regions, Africa has arguably the least access to quality care, ensuring a steady stream of dedicated patients to fill trial enrolments.'²

But this shift has come with a prize. To ensure that clinical trial participants' rights are protected and safeguarded, pharmaceutical companies must adhere to guidelines like the Declaration of Helsinki or CIOMS Guidelines³. And while their policies mention adequate protection measures, reality has shown a discrepancy between what is mentioned in these policies, and what truly happens during and after clinical trials. The globalization of clinical trials has raised questions about ethics and safety, and has also resulted in cases of clinical trial participants like Dania - who are already vulnerable - being exploited.

In this report, we have compiled our four country reports on the clinical trials industry: Egypt, Kenya, Zimbabwe, and South Africa. For these reports, we worked with partner organizations as well as local organizations and journalists. Most of the research was based on desk and field research, and interviews with researchers, health experts, academics, company representatives, contract research organization representatives, members of ethics committees and research councils. Our findings clearly show the global scope of the problem, namely that

1 Special edition: Human guinea pigs on the cheap: clinical trials, Berne Declaration (2013).

2 Cutting Edge Information (CEI) website: a US-based pharmaceutical and biotech industry source for business research

3 See Appendix.

unethical practices are common in clinical trials in developing countries. Pharmaceutical companies do not adhere to leading ethical guidelines as these countries often do not have robust legislative and regulatory frameworks in place, so this permits companies to easily cross the line. Those who participate in clinical trials in these countries are thus easily exploited, and their rights easily violated. Why should people in low- and middle-income countries risk their health and lives for the development of medicines they probably will never have access to or be able to afford? ♦





NO UNIFIED LEGISLATION ON CLINICAL TRIALS, CANCER MEDICATION IS EXTREMELY EXPENSIVE AND THEREFORE UNAFFORDABLE FOR THE GENERAL EGYPTIAN POPULATION.

EGYPT

Based on the report 'Industry-sponsored clinical drug trials in Egypt: ethical questions in a challenging context' (Wemos, SOMO and Berne Declaration, 2016)

As a lower middle-income country with a population of 90 million people, Egypt has a large population of poor people as well as a large pool of patients with different diseases. A well-functioning health system is crucial for the Egyptian population, but the system is in fact heavily fragmented. Just half of the population is insured, and patient satisfaction with health services is extremely low. Government's health expenditure is less than 1.5 per cent of GDP, and out-of-pocket expenditure on health care is about 72 per cent of total expenditure on health.

For those who can afford it and want an alternative to public sector facilities, private hospitals have a good reputation and are therefore attractive. Unfortunately, for the average Egyptian family, medical treatment is beyond their budget. Because there is no comprehensive insurance coverage and the cost of treatment is high, the poor patient in particular is vulnerable to be exploited. Those who cannot afford necessary treatment are likely to join clinical trials so they can have access to the health care they need. Some professionals view clinical trials as beneficial to the health system, regardless of whether treatment is for free or not. *'Trials provide free treatment for patients who cannot afford paying for it. If it weren't for clinical trials, the government would have to bear the cost of their treatment,'* says Hamdy Abdul Azim, Professor of Oncology and Founder of Oncology Clinical Trials Center at Cairo University.

THE CHALLENGE OF DISEASE

Hepatitis C

Egypt has the highest prevalence of viral hepatitis C worldwide. This is due to the Egyptian government's mass campaign of intravenous anti-schistosomiasis treatment in the 1960s-1980s. At the time of writing the original report, an estimated six million people were infected; the annual incidence was estimated at 150,000. The chronic infection rate was estimated at 10 per cent among 15-59-year-olds; some estimates were even higher (14 per cent). The Egyptian government endeavours to drive the country's infection rate below 2 per cent by the year 2025. »

Cancer

The incidence of cancer is rising rapidly in Egypt. Among women, breast cancer is the most common, whereas liver cancer affects men the most. It is thought that Egypt's liver incidence is related to its high Hepatitis C incidence. It is projected that by the year 2050, there will have been a three-fold increase in cancer on 2013 levels.



Why is Egypt attractive for pharmaceutical companies?

Egypt is second only to South Africa on the African continent in terms of the number of international pharmaceutical companies' sponsored clinical trials it hosts. Between 2008 and 2011, the number of trials in Egypt nearly tripled. Why is Egypt popular?

- fast-growing, largely uninsured and treatment-naïve population
- large pool of diseases within population
- attractive research infrastructure
- lower costs for conducting trials
- no official national law on clinical trials

REGULATORY FRAMEWORK AND FLAWS IN THE SYSTEM

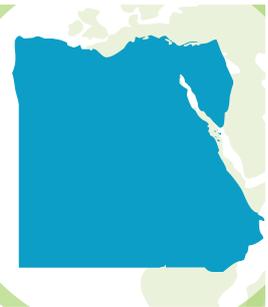
Egypt has no single, national legislation to regulate clinical trials. There are several regulatory authorities that oversee clinical trials. For example, Research Ethics Committees (REC) give approval for a trial and verify if it is ethically sound. Institutional review boards (IRBs) also approve and monitor trials, and provide training to the trial's researchers and doctors. In addition, Contract Research Organizations (CROs) are increasingly being hired by pharmaceutical companies to not only perform (parts of) the trial, but to also monitor and oversee the process. Nevertheless it is still the company that is responsible for trial data, participants' safety, and adherence to regulations and guidelines.

With various actors overseeing a trial, one may think the necessary checks and balances are in place to prevent any wrongdoings or unethical practices from occurring. Yet, the system has shown to be flawed. Institutional review boards are burdened with increasingly complex studies, time and budget limitations, lack of national guidelines, and inadequate standards. The Ministry of Health's database, which includes data on clinical trials for approval, is not transparent, as it is only available to employees of the Ministry, not the public. Therefore, journalists or civil society cannot access it. Sometimes, contract research organizations can have two roles: executing and overseeing the trial. This can raise questions about conflict of interest. They are hired by the trial sponsor – the pharmaceutical company – as 'independent' companies to monitor trials. But if they decide to stop a trial, they could compromise their future prospects with the 'employer' company.

Moreover, the company or contract research organization pays the researchers and doctors in clinical trials, for example for providing patients. This financial interest can compromise the independence of trial investigators. Negative trial results or unwanted course of events could compromise the relation between the investigator and the company or contract research organization, which means that trial data could be questionable. This also means that protection of participants' health could be put at risk.

CANCER IN EGYPT: CLINICAL TRIALS AND ETHICAL CONCERNS

In Egypt, the price of cancer drugs is exorbitantly high. Treatment can cost as high as EGP 50,000 (US\$5,600) per month. Clinical trials thus offer patients treatment they cannot afford. At the time of writing the original report (2016), over half of all trials in Egypt were cancer trials. *'Participating in clinical studies for the treatment of cancer patients ensures treatment with therapies not available in Egypt,'* says Raafat Ragae Abdul Malek, Assistant Professor of Oncology at Cairo University.



Yet, there is a fundamental inequality between Egyptian trial participants and those in more affluent countries. In the latter, cancer patients are given a proven treatment first; an experimental drug is usually administered if standard treatment does not work. In Egypt however, cancer patients may have no choice but to accept an experimental drug, as they cannot pay for standard proven cancer treatment due to unaffordable prices. This raises questions about whether this is ethical. The fact that Egyptian cancer patients have no other choice but to participate deems them vulnerable and unfit for a clinical trial according to ethical guidelines like the Declaration of Helsinki, as this means that their consent is not voluntary. Due to this vulnerable position of Egyptian cancer patients it is therefore all the more worrying that the trials that were included in this report raised alarm bells among experts. One of these trials is discussed below.

TRIAL CASE: A MULTI-CENTER STUDY OF BIOMARKER-DRIVEN THERAPY IN METASTATIC COLORECTAL CANCER (SPONSOR: ROCHE)¹

Sponsor: Roche

Investigational drug(s) of the sponsor:

bevacizumab (Brand name: Avastin), vemurafenib (Brandname: Zelboraf), capecitabine (Brand name: Xeloda), atezolizumab (No brand name yet)

Drug(s) of other companies:

cetuximab (Brand name: Erbitux, Imclone), oxaliplatin/fluorouracil/folinic acid (chemotherapy regimen named FOLFOX)

Original approval(s):

atezolizumab: None found (drug still in development), bevacizumab: 02/2004 (FDA), 01/2005 (EMA), 12/2004 (Swissmedic), capecitabine: 04/1998 (FDA), 02/2001 (EMA), 06/1998 (Swissmedic), vemurafenib: 08/2011 (FDA), 02/2012 (EMA), 10/2011 (Swissmedic)

Critical analysis: Phase II trial, active (recruiting). The design of this study is “completely chaotic” according to oncology experts, and results will be unclear given the large number of subgroups. This study is meant to benefit more the pharmaceutical company than patients and it is thought that it is being undertaken to get doctors to prescribe certain medicines such as bevacizumab. Using such a complex study design to test new medicines in such a large number of countries (24 in total, including many low- and middle-income countries) is extremely worrying given the high risk of study errors. Besides, the limited number of participants and the fact that the study uses two surrogate endpoints (or markers) – which are often poor predictors of actual clinical benefit and overall survival – considerably limits its power. Vemurafenib is being used off-label in this study as it has

¹ In: 'Industry-sponsored clinical drug trials in Egypt: ethical questions in a challenging context', p. 38.

been registered only for treatment against melanoma, not against colorectal cancer. There is a risk also of delayed effect of the initial therapy (bevacizumab + chemotherapy) into the maintenance phase, thus affecting the tumour response and increasing the risk of bias in the final results. The fact that atezolizumab is not yet approved in high-income countries contravenes Egyptian regulations that state that only medicines approved in their originating country can be used in foreign sponsored clinical trials in Egypt. Finally, all experimental combinations involved in this study are potentially very toxic and are expensive, which raises this issue of their future availability and affordability for Egyptian cancer patients. »

Comments of Roche (excerpts²):

'(...) Patients who did not receive prior therapy are initially treated with an approved regimen containing bevacizumab for the first four months; this portion of the trial is referred to as 'induction'. The second part of the treatment, which is referred to as 'maintenance', takes into consideration the molecular signature of a patient's tumors, and based on the tumor characteristics the treatment becomes more targeted. The innovative and highly adaptable trial design permits modification of current experimental arms and inclusion of additional treatment cohorts based on the latest scientific evidence. All experimental treatments are directly compared to the current standard-of-care.

"This study is designed to speed up detection of improved patient outcomes from the innovative treatment approaches when compared to the current standard-of-care. Emerging information from this study may guide further development of specific new medicines in this indication.

"The study is currently running in 24 countries, in more than 160 centers, and is looking to recruit more than 1,200 patients, 35 of which would be recruited in Egypt. A Steering Committee and an IDMC (Independent Data Monitoring Committee) are in place to monitor closely safety and efficacy of this study. (...)"

Roche did not comment on the controversial use of vemurafenib (off-label) and atezolizumab (not yet approved in high income countries) in Egypt, nor on their future availability and affordability for Egyptian cancer patients. Concerns over the design of this study being 'completely chaotic' with a 'high risk of study errors and misinterpretations' were left unanswered by Roche. This trial should remain under close scrutiny by the MOH REC and the relevant IRB. The question still remains as to why this trial has been authorised in the first place given that it contravenes Egyptian regulations.

² Email communication from Dr. Wolfgang Golisch, Regional Medical Director EEMEA, and Caroline Pecquet, Head Communications EEMEA, Hoffmann-La Roche Ltd, Basel, 10.6.2016.

TESTIMONIALS OF EGYPTIAN CANCER TRIAL PARTICIPANTS

Two testimonies of Egyptian cancer patients illustrate the vulnerability of those who participate in Egyptian clinical cancer trials. Because both women were uninsured and could not afford standard treatment, they were desperate and therefore easily recruited for the trials. And being desperate, they said they had not bothered to read the consent form, so their consent was not truly voluntary or informed. Their vulnerability is also illustrated by the fact that they both suffered severe symptoms during the trial, but one patient had been told by the researchers that her symptoms were not related to the trial drug.

Dania (name changed)

Dania's story – with legal repercussions – was introduced earlier (see Introduction). Dania participated in a clinical trial sponsored by the pharmaceutical company Roche in 2013. Three years earlier, she was diagnosed with breast cancer, but after the tumour was removed, it came back and had metastasized in her brain. Dania was not insured. The oncologist she consulted offered her the opportunity to participate in a clinical trial – with free treatment, tests and follow-up. Dania did not hesitate to agree: *'I had read the informed consent form quickly without paying much attention to detail because I was happy with the treatment team. Moreover, the trial was in the name of a well-known oncologist.'*

Since the beginning of the trial, however, Dania showed symptoms like skin burns, severe diarrhoea and nails falling out. Also, she suffered from cataract, but researchers told her that this symptom was not related to the trial drug, so she had to pay for the operations at her own expense. Her ophthalmologist told her that it was caused by a brain tumour. *'I used to inform the physician responsible for my follow up about the side effects and he used to photograph them and prescribe medicine. Many times the pain would be unbearable.'*



Walaa:

'I was so happy to have an opportunity for treatment after having lost hope. I signed the informed consent form immediately and did not care to read it in detail. I believe the pharmaceutical company was American.'

Walaa

Lung cancer patient Walaa, also uninsured, was asked to join a clinical trial after initial removal of a tumour was unsuccessful, which affected the left side of her body. Follow-up surgery would have been an obstacle as applying for state-funded treatment was difficult. She took some treatment sessions at her own expense, until she got the offer to join the trial. *'I was so happy to have an opportunity for treatment after having lost hope. I signed the informed consent form immediately and did not care to read it in detail. I believe the pharmaceutical company was American. (...). The decision to continue the treatment was made by my family, due to the difficulty of securing EGP 120,000 (US\$ 13,500) annually. I was about to sell my last property.'*

According to Walaa, the trial drug caused painful and severe symptoms like stomach pains, hair loss and anaemia; for the latter, she underwent blood transfusion which she had to pay for herself. *'I heard they would follow up my case after the trial, which is good, because I've spent so much money since I started treatment. All I care for is receiving medication.'* After completing the trial, Walaa's condition still had not improved. Nonetheless she stated she would join a new trial again.

ARE CLINICAL TRIAL DRUGS AFFORDABLE FOR AND ACCESSIBLE TO THE EGYPTIAN POPULATION?

When it comes to access to medicines, two aspects are important to look into:

- **Post-trial access to treatment (PTA)** for the trial participants – and possibly additional benefits to the community – until the tested product is commercially available. If the trial is not conclusive, the standard of care should be provided.
- **Accessibility** of the tested medicine to the general population after marketing approval has been granted. Has a marketing approval been requested by the sponsor of the trials (availability)? If yes, are the medicines affordable for the population?

POST-TRIAL ACCESS TO TREATMENT: EXCEPTIONALLY RARE

The right to post-trial access to treatment (PTA) for trial participants is mentioned in leading international ethical guidelines like the Declaration of Helsinki and the CIOMS Guidelines. For example, Article 34 of the former states: *'In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.'*

In their policies, pharmaceutical companies state that they hold high the protection of trial participants, and therefore mention and adhere to PTA and leading guidelines. Roche, for example, mentions the following:

'As part of this commitment and in accordance with the Declaration of Helsinki, Roche offers patients who participate in Roche-sponsored clinical trials continued access to the investigational medicinal product that they received after trial completion, when appropriate.'

Another company, Novartis, says the following about PTA:

'Where applicable, e.g. in the case of life-saving therapies or serious consequences if the medication was withdrawn, research participants may, after trial completion, be offered participation in an extension study until marketing authorization.'

Although the companies both state they offer PTA, their policies are drafted in such a way – by using vague terms like 'when appropriate... where applicable' – that they can ultimately decide when and why they will provide PTA.

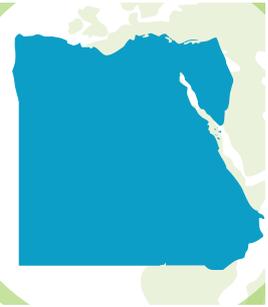
Our research found no clear evidence of PTA provisions in clinical trials in Egypt.

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AFFORDABILITY FOR GENERAL EGYPTIAN POPULATION AFTER MARKETING APPROVAL

Pharmaceutical companies state that if they have no plans to introduce a new drug in a specific country, they will not conduct trials for that drug in that country. For instance, Roche says: *'Where there are no plans to apply for market authorization of a particular medicinal product in a low- or middle-income country, Roche will not conduct clinical trials with that particular medicinal product in the concerned low- or middle-income country.'* And Novartis Oncology says: *'We commit to registering our new treatments in every country that has participated in the clinical trials and to making the treatments commercially available wherever feasible.'* Moreover, in a letter to the organization Berne Declaration, Novartis' chairman Jörg Reinhardt stressed that *'clinical trials will only be conducted in countries where marketing approval will be requested.'*

Still, we found availability and affordability of new drugs to be a problem in Egypt. In a sample of 24 drugs tested in Egypt during 2005-2015, 9 did not receive market approval, 15 were approved, but 75% of these were not state-subsidized (Program for Treatment at the Expense of the State, PTES) – making them unaffordable to most Egyptians. Two in three cost more than the Egyptian monthly minimum wage for a monthly treatment, and one in five even over 20 times the monthly minimum wage. ♦





LACK OF CAPACITY TO MONITOR CLINICAL TRIALS CAN LEAD TO HEALTH PROBLEMS OF CLINICAL TRIAL PARTICIPANTS REMAINING UNKNOWN TO TRIAL RESEARCHERS.

KENYA

Based on the report 'The Clinical Trials Industry in Kenya: Realities, Risks and Challenges' (Wemos, 2014)

Kenya has become a popular international business destination thanks to a large pool of foreign professionals, major infrastructure investments, high rates of computer literacy, and relative political stability. An expanding middle class, the discovery of natural resources (oil and gas), an abundance of wildlife and a tropical climate have further fuelled its international appeal and economic growth. And the capital city Nairobi is one of the region's most affluent and flourishing metropolises.

At the same time, Kenya is also one of the world's poorest countries, ranking 145 out of 187 countries on the 2013 UNDP Human Development Index. Food insecurity, drought and water scarcity exacerbate chronic poverty. Poverty and affluence co-exist side by side; slums are a common sight in Kenya. One of the world's biggest urban slums, Kibera, is located just five kilometres from the city center of Nairobi. Also, corruption hampers the development of key infrastructure and public services; Transparency International, the global corruption barometer, has ranked Kenya as the fourth most corrupt country globally.

The contrast between rich and poor is also reflected in Kenya's public health challenges, like affordable and equitable access to healthcare. The country is burdened with a high incidence of infectious diseases like malaria, tuberculosis (TB) and HIV/AIDS; it has the fifth highest TB burden in Africa, and the world's fourth largest HIV-positive population. Also, rapid economic growth and a growing, affluent middle class with a 'Westernized' lifestyle have contributed to the rise in non-communicable diseases (NCDs), like cardiovascular disease, asthma, cancer, and diabetes. At the same time, low-income classes too have adopted similar lifestyles consisting of poor diet, tobacco and alcohol consumption.

At the time of writing the original report (2014), there were over 5,000 health facilities in Kenya: the government oversees 41%, the private sector 43%, and NGOs 15%. WHO statistics show that just 2% of all physicians in Kenya work in the public sector. In the private sector, working and financial conditions are much more attractive. The contrast between public and private health facilities has led to a parallel health system, and obstructs government efforts to realize equitable access to health. Four factors restrict access to healthcare for the poor: public health facilities lack essential equipment, supplies and commodities; long travel distance to health facilities and expensive and/or scarce public transportation; expensive fees

for services and out-of-pocket payments; and low confidence in local public health facilities' services, resulting in the decision not to use them.

For those who are regularly employed or have consistent income, the National Hospital Insurance Fund (NHIF) provides health coverage. Yet, in the opinion of veteran Kenyan investigative journalist Douglas Okwach: *'It wouldn't cover the costs of consultations or medication. Many people also take out a private healthcare policy so everything is covered – you are in serious trouble if you only have the NHIF to rely on.'* Especially the poor in rural areas do not have geographical, physical or financial access to health facilities. To provide healthcare services for the poorest Kenyan households, the Household Insurance Subsidy Programme (HISP) has been initiated; its success remains to be seen. Nevertheless, poverty and inequality are dire issues in the country's health landscape – and it is this landscape that has facilitated the growing clinical trials industry in Kenya.



WHY IS KENYA ATTRACTIVE FOR PHARMACEUTICAL COMPANIES?

By 2014, when the original report was written, Kenya had become one of Africa's most popular destinations for clinical trials. One of the reasons for this was found in the growing presence of NCDs. While research organizations, universities and charities have been active in medical research due to Kenya's high burden of infectious diseases, international companies like Glaxo Smith Kline (GSK), Astra Zeneca, Pfizer, Novartis, Bayer, Ely Lilly, Sanofi Pasteur and Boehringer Ingelheim have joined the country's research landscape. The business-friendly government was keen to grasp this opportunity to become a player in clinical research. According to Minister of Public Health Beth Mugo, *'The government hopes to follow in the footsteps of other developing countries such as India that have managed to become pharmaceutical and health sectors of excellence. Through sustainable research, Kenya could leapfrog other nations and become a regional hub for East and Central Africa.'*

MOTIVATION TO JOIN A TRIAL AND INFORMED CONSENT

According to the leading ethical guidelines, informed consent is a pivotal aspect of ethics in clinical trials. Participants must be fully informed of what they are agreeing to join, and if they join, it must be voluntarily. So why would people join a trial in Kenya? An anonymous official of the Kenya Medical Research Institute (KEMRI) claimed that because the majority of trial participants are drawn from poor rural areas, they could be motivated by lack of access to better, affordable treatment, which makes them want to get treatment via a trial. Lack of literacy and education could undermine their full understanding of the consent form. This raises the question of whether consent is truly informed and voluntary. The same KEMRI official said: *'Many poor people are taking part in trials because it's the only way they can access healthcare and get a better chance for their kids'*. What is more, is that the 'Western' concept of informed – individual – consent might be different for rural, traditional Kenyan communities. In rural Kenya, it is in fact a communal process: potential trial participants ask advice from others, so by the time the form is signed, they will have spoken with and have been influenced by others. Moreover, trial sponsors are often under time pressure and want to acquire as many participants as possible, which could undermine the informed consent procedure.

Another motivation that raises ethical questions is the financial incentive to join a trial. KEMRI officials and patients stated that the only compensation trial participants receive is a daily stipend for travel and time lost, and that they do not 'pay' participants to avoid having them join just for the money.

TESTIMONIAL OF A KENYAN CLINICAL TRIAL PARTICIPANT AND ETHICAL CONCERNS

**Edwin (name changed) – trial subject in TB study¹:
Pharmacokinetic and pharmacodynamics studies of efficacy, tolerability and safety of higher dosage Rifapentine for treatment of TB.**



For 47-year old Edwin, life has always been a struggle and the strain shows clearly on his face. Edwin has spent his entire life living in this area of the impoverished Manyatta estate, just outside Kisumu. His one-room mud hut opens out onto a muddy dirt path where chickens, pigs and goats drink from putrid pools of stagnant water. Malaria and water-borne diseases are rife here and it isn't hard to see why. Yet even amid the dirt and the squalor, it seems that small pockets of beauty can still prevail. Edwin has potted a few young banana plants and neatly lined them up in clean white plastic tubs at the entrance to his house. *'A small garden,'* he says with a smile.

Plastic is Edwin's trade. For the past twenty years, he has earned his living by patching up used water canisters and other plastic items, and re-selling them around the slum for a minimal profit. (...)

In 2012, Edwin started to feel unwell and lethargic. It was when he began coughing up blood that he was forced to use his mother's life savings for a doctor's consultation and then a chest x-ray in the local government hospital. Unsurprisingly, Edwin had contracted TB, a disease which still kills many in Kenya every year and spreads quickly in crowded places.

It was during a follow-up visit to the same local hospital a week later that Edwin was called out of the queue by a doctor and asked to come through to a separate room to meet a team medical researchers, whom he believes were from the CDC. *'They called me from the line and then they said that they knew I had TB and that I should think about trying a treatment. They said if I wanted to get better without paying anything, I should take the medication, so I just agreed. The other option was to pay five shillings for every hospital visit, and I couldn't afford it, so it was my only choice.'*

Edwin was asked to sign a consent form, written in the local language of Luo, which he did in the presence of a doctor. This doctor also signed as a witness. However, as our interview with Edwin unfolded, it became clear that, almost a year since the study had finished, Edwin was still not aware that he had taken part in a clinical trial. *'They just said it was a free treatment that would cure me and that some of my blood samples would go to Atlanta in America,'* he recounts, saying that even though he had been warned about the potential side effects, he just assumed the drug was free and safe for him to take. His mother Esther, listening intently, also appears to not fully understand that her son signed up for a clinical trial.

A copy of the consent form (for a copy of the form, see Annex I) revealed that Edwin

¹ In: 'The Clinical Trials Industry in Kenya: Realities, Risks and Challenges', p. 28.

had been enrolled on a test for CDC/KEMRI for the drug Rifapentine, which is made by the French MNC Sanofi Aventis. Approved in 2009, the 2012 trial in Kisumu entitled: 'Pharmacokinetic and pharmacodynamics studies of efficacy, tolerability and safety of higher dosage of Rifapentine for treatment of tuberculosis', was essentially testing the effect of higher dosages in a bid to cure TB more quickly.

'I was taking the drug for six months. They told me that I had to eat well to be strong, so every day, the researcher brought me a parcel of bread, boiled eggs, milk and ground nuts,' he recalls. 'The neighbours thought it was strange and accused me of being HIV positive, which I am not. They also gave me three hundred shillings for transport, but I preferred to keep the money and walk there, even though I felt quite weak.'

A few weeks after the trial had finished, Edwin started to notice some unusual symptoms, *'I started to sweat a lot at night, my joints were hurting and my eyes started watering,'* he remembers. *'Then slowly my eyesight started to get worse and now, six months later, I really have trouble seeing far away, which is affecting my work.'*

'I never had any kind of problems before, so I think it's the medication,' he says gaunt and with sunken cheeks. *'I am cured of the TB now and I signed the form, so I don't want to cause any trouble,'* he replies to our observation that problems with eyesight are listed as an adverse effect on the consent form. *'I haven't had any visits from the doctors in over ten months, so I couldn't tell anyone. At one point, they asked me to become a tracer and find other people in the slum with TB, but I said: "No". They have not cared about me, so why should I?'* We also point out to Edwin that, according to the consent form, the hospital should treat any symptoms relating to the trial. *'Please, I don't want to cause any trouble,'* he stresses. *'They will say my eyes are damaged because I go to smoky places,'* he says while his eyes are watering as he looks puzzled as we study the consent form, which seemingly means nothing to him.

Ethical concerns

Edwin's testimony showed that researchers of the trial gave him no other choice than to participate in the trial because he could not afford to pay for hospital visits. He also did not fully understand that he had joined a trial. Moreover, Edwin stated he did not want to cause trouble and was scared to go back to the researchers to pursue his case, as he was just glad he was cured of TB. This shows that Edwin's consent was not informed or voluntary. It also illustrates the fear of authority that is common in rural Kenyan communities. Moreover, during and after the trial, Edwin's health was not monitored by the researchers. The fact that he kept the money he received for transportation, and walked instead in his deteriorated health state, also shows that the researchers did not take their responsibility to protect their participants' health. This reimbursement fee and the prospect of free treatment probably added to Edwin's motivation to participate in the trial. But this does not justify the adverse health effects he endured afterwards, especially since he did not know he was a trial participant.

LACK OF POST-TRIAL ACCESS TO TREATMENT

In line with research and ethical standards, any trial study protocol in Kenya must include details regarding post-trial access to treatment. However experts quoted in our report expressed their

concern about the affordability and accessibility of drugs tested in Kenya. Ambrose Rachier (Head of the ethics committee at KEMRI): ‘What happens most often is that when the product comes into the country, it is unaffordable and therefore those who participated (in the study) do not get the benefit, despite taking the risk’. For example, in 2009, a vaccine manufacturer refused to subsidize the cost of a pneumonia vaccine, despite the research having been done on Kenyan children. But thanks to Public Health Minister Beth Mugo’s persistence, the PCv10 vaccine was eventually provided to children for free in all public health facilities in Kenya (before only available in private hospitals).



LONG-TERM BENEFIT TO KENYAN POPULATION

Another concern expressed by experts we interviewed for the original report was the long-term benefit of trials to the overall Kenyan population and healthcare service. David Makumi (Kenya Cancer Care): ‘I have heard of (pharma) companies coming to our public hospitals to do clinical trials and offering the staff laptops, modern registration cards and other fancy things, and then simply taking everything away once the study is finished’. ‘For every KES100 invested in a trial, only about 5 per cent comes back to Kenyans. This does not translate into benefit,’ said one anonymous KEMRI official.

“*What happens most often is that when the product comes into the country, it is unaffordable and therefore those who participated (in the study) do not get the benefit, despite taking the risk*”

Rachier:

REGULATORY FRAMEWORK AND FLAWS IN THE SYSTEM

Various Kenyan government agencies often appear to overlap and the extent of their authority remains unclear. Once a sponsor has decided Kenya is the most suitable destination for an upcoming trial, the organization has to firstly, by law, seek formal approval and a research permit from the NCST. This agency is responsible for coordinating all research work in Kenya and advising the government on research-related and scientific matters.

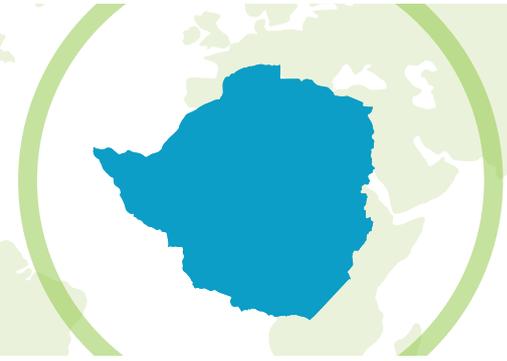
Yet, despite the stated official mandate and authority of the NCST, more detailed investigations and queries into the process revealed that a number of medical research institutions, all with ethics committees appointed by the NCST, actually are more active and influential when it comes to giving the final green light of the approval process.

“Actually no single body has the final authority,” said KEMRI’s Ambrose Rachier. KEMRI is Kenya’s leading research institute, which, mandated by the Ministry of Health, is the authority to approve and authorize clinical trials in Kenya. “The NCST is the umbrella organization, which appoints and works with the ethics committees at institutions involved in research on human

subjects,” he clarified citing KEMRI, Kenyatta National Hospital, Aga Khan, MRNH and African Medical and Research Foundation (AMREF) as the key players in Kenya’s clinical trials. “KEMRI is the main gatekeeper for reviewing and approving clinical trials,” said Kizito Lubano (Head of Planning, Monitoring and Evaluation at KEMRI). “While researchers can seek final approval from the NCST, certain mandated institutions also have final approval power themselves.”

According to officials and experts interviewed in the original report, significant efforts are being made to create a professional, credible and effective clinical trial process. Several officials demonstrated expertise and commitment to protect the rights of clinical trial participants. However, the report also highlighted concerns about the Kenyan regulatory framework. One Kenyan official was concerned about the lack of capacity to monitor clinical trials, which could result in health problems of clinical trial participants remaining unknown to trial researchers. Another concern was the absence of concrete ethical guidance that leads to many ethics committees giving more attention to scientific review than to ethical aspects. This is particularly concerning knowing the vulnerable position of the clinical trial participant. Given the growing international interest in the Kenyan market, the caseload will likely increase, placing yet more pressure on approval bodies. This development renders the harmonization of ethical review and the verification that ethics committees have integrated ethical standards in their approval procedure essential. ♦





INSTITUTIONS INVOLVED IN CLINICAL TRIALS IN ZIMBABWE ARE UNDERFUNDED AND THERE IS NO PUBLIC SCRUTINY.

ZIMBABWE

Based on the report 'Clinical Trials Realities in Zimbabwe: Dealing with Possible Unethical Research' (Wemos, 2015)

Zimbabwe is a country with a mix of natural resources. Unfortunately, it has been struggling with major public health challenges for well over a decade after an economic crisis. This crisis has hampered the government's capacity to fund public health delivery and realize access to health care for the population. Zimbabwe's health challenges lie in the presence of diseases like HIV/AIDS, malaria, TB, which have also led to a high maternal mortality rate: it is one of 40 countries worldwide with over 960 maternal deaths per 100.000 live births.

Since 2013, the economic state of Zimbabwe has worsened, resulting in deterioration of the health sector and a negative effect on the health workforce. Due to poor working conditions for medical personnel, many have chosen to migrate to countries with better conditions (e.g. brain drain). This resulted in an increase in vacancies for doctors in most public hospitals, but these hospitals struggle with a shortage of essential medicines, hampering their ability to provide care. Access to medicines is also a problem in Zimbabwe. Drugs are mainly externally funded, as the country's own pharmaceutical industry lacks resources. A vast majority of the population can thus be described as vulnerable, as they do not have access to health facilities.

THE PHARMACEUTICAL INDUSTRY IN ZIMBABWE

Compared to neighbouring countries like South Africa, where trials are predominantly run by pharmaceutical companies, the number of trials in Zimbabwe is relatively low. Trials in Zimbabwe are almost exclusively run by non-commercial sponsors. There is very little information available or accessible about trials in the country, and media have hardly investigated this topic.

Rapid recruitment of participants, high prevalence of 'Western' diseases like diabetes, and a more developed research and health care infrastructure all make South Africa a highly-sought destination for pharmaceutical companies. Zimbabwe's features are in stark contrast with South Africa. Nonetheless, Zimbabwe does have its own unique features that attract trial researchers, as noted by Dr. Paul Ndebele (Director of MRCZ). He explained that researchers would like to conduct clinical trials in countries with a high burden of the diseases they are focusing on. For example, Zimbabwe's HIV infections and mortality rates are one of the highest in the world, making it an attractive study area for foreign researchers.

This also goes for malaria and TB, resulting in a number of clinical studies on these diseases, as evidenced by information on ClinicalTrials.gov.

REGULATORY FRAMEWORK AND FLAWS IN THE SYSTEM

Three bodies guide and regulate health research in Zimbabwe. The Medicines Control Authority of Zimbabwe (MCAZ) is a statutory body established by an act of Parliament. Its mandate is to protect public health and ensure that the available medicines and medical devices are safe, of good quality and effective by enforcing adherence to distributors' and manufacturers' standards. The MCAZ focuses on clinical trials in particular.

The second body, the National Ethics Committee – or the Medical Research Council of Zimbabwe (MRCZ) – is composed of medical experts, scientists, lawyers, ethicists and religious community representatives. The MRCZ promotes and coordinates the ethical conduct of health research in Zimbabwe. It provides ethical guidance and gives approval for clinical trials, thus playing a crucial role in ethical oversight.

The third body, the Research Council of Zimbabwe (RCZ), is a statutory body that promotes Zimbabwean research in all fields and coordinates and directs foreign research. Foreign researchers who want to conduct research in Zimbabwe must follow guidelines issued by and apply for research permits from the RCZ. Compared to the RCZ, MCAZ and MRCZ are more focused on clinical trial regulation.

For the original report, we also spoke with Dr. Paul Ndebele about challenges for the Zimbabwean regulatory system. In his opinion, the biggest impediment to the success of MRCZ in monitoring compliance to relevant laws and guidelines was the lack of financial resources, i.e. the fact that his organization was underfunded. The country's economic challenges have hampered the MRCZ in carrying out its mandate, and the organization was forced to seek financial assistance from 'other sources' (e.g. donor organizations and private funders). Other problems included researchers implementing unapproved studies, deviating from approved protocols, conducting studies without applying for approval, cases of unacceptable practices in research, and limited influence over research conducted in Zimbabwe. Ndebele said that MRCZ could tackle some of these practices, but has had limited success overall due to lack of financial resources and a strong mandate. This, and flaws in the approval and monitoring process, could lead to clinical trial participants being put in harmful positions. The case described in detail below is an example of this.

THE CASE OF A ZIMBABWEAN CLINICAL TRIAL PARTICIPANT: GRACE MAWERE

The Zimbabwean investigative journalist Terence Zimwara learned of clinical trials in September 2013, when he met Grace Mawere. Grace, an HIV-positive single mother, was unemployed, barely educated and had no health insurance. In 2005, she was diagnosed with HIV, whereupon she started antiretroviral therapy (ART). For six years, she was on first-line treatment when researchers from the trial study EARNEST asked if she wanted to join their trial. Her story - albeit an extremely unfortunate case and an outlier in the entire pool of trials in Zimbabwe - illustrates the vulnerability of the position in which clinical trial participants can find themselves.

In September 2013, Terence met Grace Mawere for the first time¹. Grace was an HIV-positive mother staying between either Mufakose or Goodhope, a suburb just outside Harare, at that time. When Terence met Grace, she looked relatively healthy, although she was suffering from eyesight problems. She had just given birth and because the father abandoned them, she was raising her baby alone. Just like many Zimbabweans, Grace was unemployed, she had limited education and no medical aid cover or insurance. She appeared eager to explain to Terence the chain of events leading up to the point where she started to experience vision problems, apparently as a result of the clinical trial in which she participated.

How it all began

Grace was diagnosed with the HIV virus in 2005 and was immediately placed on antiretroviral therapy. She started taking drugs called Stalanev and Co-trimoxazole (a first-line treatment) as part of her antiretroviral treatment regimen. After being on the first-line treatment for six years, Grace was approached by an organisation she did not know. They told her that there was a novel treatment regimen they wanted her to try, saying it could help her. *'In 2010, people from EARNEST suddenly came to my home and informed me that they were conducting clinical trials for people who had not responded well to regular antiretroviral therapy,'* she said. When Grace asked EARNEST how they knew of her and her illness, they told her they saw her file at the Rutsanana Clinic in the high-density township of Highfields in Harare. It was at the Rutsanana Clinic that Grace had been diagnosed with HIV and where she had been going to collect her drugs.

Randomisation

Grace told the journalist that at the start of her participation in the EARNEST trial, the *'people from EARNEST took me to Baines [an area just outside of Harare's central business district] to a specialist doctor, who then tested my CD4 [count] and told me my count had dropped to four.'* When the tests showed that Grace's CD4 count was four, EARNEST representatives explained to her that they had treatments they wanted to test to see if they could help people with a low CD4 count. According to her clinical trial report, Grace started participating in the trial on 4 November 2010. When she started, she used the medicines Aluvia (Lopinavir and Ritonavir) and Raltegravir. After a few months, on 27 January 2011, she stopped taking Raltegravir and changed to a boosted protease inhibitor (bPI) monotherapy. *'They told me the drugs were just like ordinary HIV drugs [antiretroviral] and that like all drugs, they could produce side effects,'* she explained. Grace said she was also told that the known side effects of these drugs were diarrhoea and a skin rash, which would only occur at the beginning of the course of treatment and eventually disappear.

'They told me that if these side effects started and persisted, I had to inform them as soon as possible or visit the nearest health centre,' Grace said. After agreeing to participate in the clinical trial, Grace was given an informed consent form to sign, which she did, and she was also given a copy of the form to keep for her records. *'Before I signed the informed consent form, I read the form with my own eyes and I signed with representatives of EARNEST witnessing this.'* To ensure that participants did not miss a dosage of these drugs, EARNEST would give each participant a transport allowance of \$30 each time they came to collect drugs. In Grace's case, this meant that she would go to the University of Zimbabwe

¹ In: Clinical Trials Realities in Zimbabwe: Dealing with Possible Unethical Research', p. 15.

Clinical Research Centre to pick up drugs once a month, as well as to get dosage instructions. Immediately after signing the consent form on 26 October 2010, Grace was placed on the treatment regimen.

Vision problems start

Just a few months after starting to take the new drugs, though, Grace started noticing that her vision was failing. *'I started to have problems with my eyes, I could not even walk to the centre [the University of Zimbabwe clinical research centre] because my eyesight was getting poor,'* she said. Grace complained that although her sight was poor during the day, she could still move around familiar places without much difficulty. After about 5 p.m., however, her mobility would be hampered by her poor eyesight. Although side effects like vision problems were not mentioned in the informed consent form, which is meant to inform the trial subject of potential side effects, problems with eyesight related to the drug that Grace took had been reported before by the NHS and other public sources. Grace's clinical trial summary report does not mention anything about the eyesight problem. The clinical report, which understates Grace's age by three years, was signed and endorsed by the physician who examined her health situation during the trial and it completely leaves out the visual impairment that Grace claimed to have suffered during the course of the clinical trial. However, hospital records that Terence Zimwara obtained after Grace's death in April 2014, clearly refer to her as being partially blind.

Getting help

Upon realising that she was going blind, Grace went back to the EARNEST site at the University of Zimbabwe Clinical Research Centre to seek assistance. She was advised to see an optometrist. When she told EARNEST staff that she did not have money to see such a specialist, they drafted a letter which she then used to get an appointment with an optometrist at Sekuru Kaguvi Eye Unit at the Parirenyatwa Group of Hospitals. It was during this consultation that she was given the most shocking news about the condition of her eyes.

'The optometrist who examined me told me there was nothing he could do anymore because the second-line treatment drugs that I was on had caused the wilting of a vein in my head. This resulted in my becoming partially blind. He told me that getting medication to treat the eyes at this stage was not going to help because the damage had already been done,' she said. The optometrist then referred Grace to the Dorothy Duncan Centre for the Blind, which assists the blind through training and offers Braille materials. Grace said she did not know who paid or made arrangements for her to be enlisted with this centre, but she was supposed to go there for three months as part of a training course for the visually impaired. However, Grace said that she only went to the centre for two weeks and she left the training when she was given a walking stick. Although she obviously struggled with her eyesight, Grace was unwilling to accept she was now disabled because of the extra stigmatisation burden it would bring. In the meantime, Grace was still taking the same drugs that she believed caused her partial blindness because she had been advised to continue doing so by the optometrist. *'The optometrist told me to continue with the drugs until I saw an HIV specialist who would then recommend new drugs that would not injure my eyes as had happened,'* she said.

Grace went back to EARNEST, hoping to get help in arranging an appointment with a



specialist. She said she would spend hours waiting for assistance, only to be told to return another day. Her only encounter with one of the study's coordinators ended with him advising her to get an eyeglass prescription that she could use to help her failing eyesight, she said. Grace explained to the study coordinator what had happened to her eyes, but the physician was always busy and out of the country most of the time and could not help her. She eventually gave up trying to get help from EARNEST.

Disappointment

Grace gave birth to an HIV-negative baby girl in July 2013, but to compound her woes, the father of the child refused to support her. Grace said he told her that he could not live with a visually-impaired mother who was also on antiretroviral treatment. When the father of her child left her, she was forced to support herself and her baby, but because of her disability, it was difficult to find work. *'People now exclude me from participating in many activities because they think my blindness means I am helpless,'* said Grace. She expressed her disappointment with EARNEST officials for failing to help her despite the value she offered to them by participating in the clinical trial. *'They acquired knowledge about the side effects of these drugs through me, and maybe now this drug has been withdrawn, yet I am struggling as a result of the side effects,'* she desperately said.

According to the clinical trial report of Grace Mawere, the last time her CD4 count was measured, in April 2013 during the trial, it was 202, a considerable increase compared to when she started the trial. However, Grace stopped using the trial drugs in the second half of 2013, because she was convinced the drugs were causing her eyesight problems. Grace experienced difficulties returning to the first-line treatment, which she took prior to her participation in the trial. The health clinics she approached, informed her they would need a letter from EARNEST to put her back on the first-line regimen. Eventually, she reverted to Co-trimoxazole, an antibiotic used to treat and prevent many different bacterial infections. On February 2014, Grace suddenly felt ill and was admitted to Parirenyatwa hospital in Harare. Her hospital records, which were written in early 2014, show that her CD4 count had dropped to 24 and suggested that the reason for Grace's deteriorating health was that the patient had defaulted on the second-line treatment.

Attempting to get compensation for Grace

In an attempt to assist Grace, the investigative journalist Terence approached a lawyer and two human rights organisations to assess the legal possibilities. The lawyer told Terence that Grace indeed had grounds to file a lawsuit for the injury. However, for the lawyers to execute this case, Grace needed all documents concerning the clinical trial, especially the signed informed consent form. Unfortunately, Grace could not find this document at that time. It was the failure to produce the consent form that limited Grace's chances even though the lawyer promised to work with the documents that were available at the time. Meanwhile, the journalist was pursuing the case with Zimbabwe Lawyers for Human Rights (ZLHR), a group of lawyers that specialises in assisting victims of abuse who cannot afford legal representation. After filling out the relevant documentation, Terence held a meeting with representatives of ZLHR. They explained that it was possible to launch legal proceedings on behalf of Grace. However, ZLHR wanted Grace to look for the consent form because it was the only legal document that could set the foundation of the case. In addition, ZLHR also wanted to speak with Grace before legal action was instituted. At the

time, Grace was bedridden at Parirenyatwa hospital and could not come to the offices of ZHLR. Lastly, Terence approached Zimbabwe Doctors for Human Rights (ZADHR) for assistance with Grace's case. They also expressed interest in the case and they suggested using Grace's experience as an example when advocating for better rights for trial subjects. » Again, the stumbling block was the unavailability of the informed consent form, as well as Grace's deteriorating health, which made it impossible for her to come for preliminary interviews with the ZADHR.

Grace Mawere's death

After Grace was hospitalised in the hospital Parirenyatwa, her health deteriorated further. Eventually the doctors recommended sending her to Mashambazhou Care Trust, a specialised centre that takes care of those affected with the HIV virus. On 6 April 2014, the 24-year old Grace passed away at this centre. The exact circumstances of her death are unknown, since the investigative journalist has not been able to get access to the latest hospital records relating to Grace's death. However, earlier hospital records mention that Grace had stopped her second-line treatment. It is likely that this aggravated her health situation. Grace's baby was taken to the baby's grandmother. However, it was very hard for the grandmother to take care of the baby as she had little means to give the baby proper care. In July 2014 the baby of Grace passed away as well. After Grace's death, there was no further communication with lawyers and the human rights organisations. The informed consent form was later found among some of Grace's belongings. Some of Grace's relatives now believe the case is dead². Following the passing of Grace and her baby, the investigative journalist consulted Amar Jesani, an independent researcher and teacher of Bioethics and Public Health in India, about the case of Grace. He was cautiously optimistic believing there was still some hope for getting compensation for Grace's case. He advised the family of Grace to get all the documentation concerning the case and launch a lawsuit. *'If there was trial insurance, then her relatives may apply for compensation with the insurer, or use the court of law. But unless good documentation is available, they may not succeed,'* said Jesani.

² At the time of writing the original report (2015).

ETHICAL VIOLATIONS IN GRACE'S CASE

Several ethical concerns and violations arise from Grace's tragic story:

Informed consent

The MRCZ Ethics Guidelines state the same as the Declaration of Helsinki regarding informed consent: investigators must assure potential subjects that participation is voluntary, and that trial details and risks must be explained. Grace's consent form – which she had read and signed – did not mention loss of eyesight as a potential side effect, despite that it was already known.

Serious adverse event reporting (SAE)

The Guidelines for Good Clinical Practice in Zimbabwe 2012 state that loss of eyesight – a serious adverse event (SAE) – should be reported to MCAZ authorities within 48 hours. Grace experienced eyesight problems during the trial, but her trial report did not mention this. »

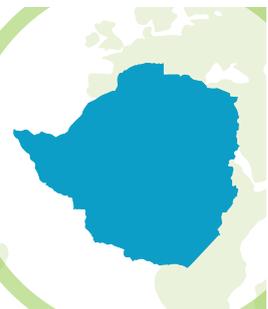
Moreover, the principal investigator of the EARNEST trial said there had been no SAE reports during the study. This is a serious violation of the Zimbabwean guidelines. Since Grace's eyesight problems were not reported, her participation was not terminated and she was not prescribed different drugs. Grace seemingly single-handedly dropped out of the trial and stopped taking her second-line ARV treatment drugs. This most likely led to her death. Also, as the technical committee did not examine her health problems, an important precondition for receiving (financial) compensation was not met. Lastly, by not reporting SAE like eyesight loss during a trial, an incorrect image of the drug's safety and side effects emerged.



*Grace Mawere:
'They acquired knowledge about the side effects of these drugs through me, and maybe now this drug has been withdrawn, yet I am struggling as a result of the side effects.'*

Compensation

Both the MRC in the UK, the sponsor of the trial, and the MRCZ in Zimbabwe failed to properly investigate whether the drugs Grace took during the trial caused her blindness. Therefore she never received compensation or treatment. The Guidelines for Good Clinical Practice in Zimbabwe 2012 – which state that in SAE, sponsors must take immediate proper action and measures to protect participants - were therefore violated on this point as well.



MEDIA, JOURNALIST AND CIVIL SOCIETY APATHY: NO PUBLIC SCRUTINY

In Zimbabwe, stories like that of Grace often go unreported. The average Zimbabwean journalist is not trained in investigative journalism, and national media attention often goes to politics instead of health research. In the past, it has been mostly international media and NGOs that have revealed problems related to clinical trials in the country.

Grace's story did not get any media coverage in Zimbabwe, apart from a publication by the NGO Rethinkaid. Publishing organizations that were approached found her story too long to publish. The lack of interest could in part be due to the absence of strong civil society organizations advocating for patients' rights in Zimbabwe. At the turn of the century, most civil society groups were more interested in politics, democracy, HIV/AIDS and human rights. The educative role of media and civil society should not be underestimated – it can contribute to more public scrutiny and awareness among the population about clinical trials and patients' rights in general. ♦



PLACEBO-CONTROLLED TRIALS ARE POPULAR BUT
COME WITH INCREASED RISK OF ETHICAL VIOLATIONS.

SOUTH AFRICA

Based on the report 'The Clinical Trials Industry in South Africa: Ethics, Rules and Realities' (Wemos, 2013)

South Africa's apartheid era policies left a legacy of sub-standard healthcare for most of the non-white population in South Africa and many people still find it difficult to access and afford the care they need. These inequalities persist and meaningful change has been slow.

Due to such visceral inequality, the most vulnerable do not have access to adequate or affordable health care. They see clinical trials as the only means to get access to health care and treatment. Drug companies are quick to exploit this opportunity.

'There are a lot more treatment naïve people in these [poor] countries and it's quicker to get them because they want to access medical care, which makes the trial shorter and cheaper. It's all about the money,' says Joel Lexchin, Professor of Public Health at York University in Canada.



*Professor Joel Lexchin:
'It's all about the money.'*

PHARMACEUTICAL COMPANIES IN SOUTH AFRICA

South Africa is unique for clinical trials for several reasons: a genetically diverse population, a high burden of 'traditional' and, due to a changing lifestyle, 'Western' lifestyle diseases, and limited access to health care for the majority of the people. The rise of 'Western' diseases like heart disease and hypertension makes South Africa appealing for companies that want to test drugs they hope will result in profits in Western markets. Also, the country has a well-established research infrastructure with a large pool of medical experts. Patient recruitment is easy, quicker and cheaper as compared to other countries. In addition, at the time of writing of the original report in 2013, South Africa had one of the world's highest rates of placebo-controlled trials, surpassing the UK, US, Germany, Israel, Italy, France, Canada and the Netherlands.

REGULATORY FRAMEWORK AND FLAWS IN THE SYSTEM

South Africa's constitution states that informed consent is required for clinical trials. The regulatory framework and standards for trials are included in the National Health Act 2003 and

the Good Clinical Practice (GCP) Guidelines. Moreover, all clinical trials in South Africa must be approved by the Medicines Control Council (MCC) and be registered in the South African National Trial Register. Pre-trial approval must also be given by at least one officially registered Research Ethics Committee (REC). Also, the MCC and the National Health Research Ethics Council (NHREC) state that clinical trials conducted in the country must adhere to the latest version of the Declaration of Helsinki (2008) (at the time of writing the original report; now the latest version is 2013).



At the time of writing the original report, the stringent regulatory system was however not flawless. An audit by the NHREC on 22 RECs in 2012 revealed that six of these approved 100 per cent of the submitted trial protocols, and of all trial protocols, just 1 per cent was not approved. The NRHEC also found that almost half of the RECs could not confirm that researchers adhered to research protocol conditions. Therefore the conclusion was that the chance of violation of rights of trial participants in approved trials where no active monitoring took place was high.

The South African National Clinical Trial Register, in which all clinical trials must be registered, should facilitate careful monitoring by independent researchers. Yet, in practice, the register is not user-friendly, non-transparent and has limited information. Also, companies and investigators can request non-disclosure of information when there are concerns about innovation or patient recruitment. The available public information is therefore often of little use to those who seek it for research purposes.

CONTRACT RESEARCH ORGANIZATIONS IN SOUTH AFRICA

Just like in aforementioned country reports, contract research organizations (CROs) play an increasingly important role in the South African clinical trial landscape too. South African ethics committees rely on clinical trial monitors employed by CROs for reports on ethical violations in trials. Yet, since CROs often manage trials themselves, such monitors could underreport violations or deliver misinformation so as not to undermine the trial study. Furthermore, it is uncertain whether pharmaceutical companies monitor CROs as stringently as they should. The Access to Medicine Index criticized the lack of oversight companies have over CROs, stating that most companies have no evidence of having influence over how CROs conduct trials.

PLACEBO-CONTROLLED TRIALS IN SOUTH AFRICA

With one of the world's highest rates of placebo-controlled trials in 2013, South Africa had a higher proportion than the UK, US, Germany, Israel, Italy, France, Canada and the Netherlands. Almost one in two of registered trials (see ClinicalTrials.gov) were placebo-controlled trials. Two advantages of such trials are: 1. Efficacy is demonstrated more easily when a new drug is tested against a placebo, and 2. Trials in which new and existing drugs are compared, require more patients, time and money.

The Declaration of Helsinki underlines the use of a placebo in a trial as acceptable if there is no proven intervention, or if its use is necessary for compelling and scientifically sound methodological reasons. However, regulatory authorities such as the US Food and Drug Administration (FDA) usually prefer these trials. In 2008, the FDA issued the controversial ruling that pharmaceutical companies do not need to comply with the Declaration of Helsinki in clinical trials conducted outside the US. Consequently, this meant that international companies overseas

only had to adhere to the Good Clinical Practice Guidelines of the International Conference on Harmonization (ICH GCP), which consists of industry representatives from high-income regions US, EU and Japan. These guidelines do not restrict the use of placebo-controlled trials. In Europe, the Declaration of Helsinki is enshrined in regulations. In principle, European regulatory authorities like the European Medicines Agency (EMA) require that companies conduct placebo-controlled trials. Yet, as European RECs are less likely to approve such trials due to concerns about ethical violations, companies are compelled to offshore placebo-controlled trials to locations outside Western Europe.

One of the placebo-controlled trials we looked into for our research in South Africa is described in detail below.



TRIAL CASE: ASTRAZENECA CHASE 1 STUDY ON ASTHMATIC CHILDREN¹

Asthma is increasingly common in South Africa, affecting almost 10 per cent of children nationally. Many asthma drugs are off patent meaning effective medicines for asthma are cheap and widely available. According to ClinicalTrials.gov, there are 44 asthma clinical trials registered across South Africa – 31 of which involve a placebo arm. One of them is from the British-Swedish company AstraZeneca that conducted a placebo-controlled clinical trial named CHASE 1 on asthmatic children, using a widely used drug called budesonide, one of the drugs for preventing asthma attacks.

For the CHASE 1 study, AstraZeneca recruited asthmatics between 6 and 12 years old in the US, South Africa, Latvia, Hungary, Bulgaria, Slovakia and Poland who used daily preventive asthma medicines. One group of the children were randomized into a placebo group and received a dummy inhaler for six weeks. The other group received 160 micrograms (μg) of budesonide, an inhaled corticosteroid (ICS), twice a day.

AstraZeneca says the FDA required a further clinical trial before it would consider approving AstraZeneca's combination inhaler Symbicort pMDI (pressurized Metered Dose Inhaler) – which contains budesonide and another drug, formoterol – for use in children between 6 and 12 with moderate/severe asthma in the US. *'The CHASE 1 study is part of the plan agreed with the FDA for investigating our asthma medicine Symbicort pMDI (a combination of budesonide and formoterol) in children. As part of that plan the FDA asked that we look at the dose of the mono-components in a pMDI formulation. CHASE 1 is to confirm the efficacy of the budesonide dose (160 μg bid), while a similar study called CHASE 2 is evaluating the formoterol mono-component,'* says the company.

Ethical and safety concerns

Denying or withdrawing a proven treatment for the sake of a placebo-controlled trial has raised the alarm amongst a number of health professionals. A nurse from an asthma charity in the UK says: *'The key to managing your asthma is to be aware of your asthma triggers, do what you can to avoid these, and most importantly to ensure that you take your medicines as prescribed.'* *'We would be very concerned about any situations where children or adults were not taking asthma treatments, and what affect this may have on their health. Stopping someone's medicine can lead to a deterioration of their symptoms and ultimately an asthma attack which can be a terrifying experience and can prove to be fatal; tragically three people [mainly adults] die every day because of their asthma in the UK.'*

¹ In: 'The Clinical Trials Industry in South Africa: Ethics, Rules and Realities', p. 15.

A spokesperson from the same charity also has concerns about the potential for serious asthma attacks during placebo-controlled studies. *'If children or adults prescribed daily medication to prevent inflammation in their airways stop their medication, then the inflammation and symptoms like wheezing and coughing will come back, maybe they'll be okay for two weeks, but then they will get worse and we know in the most serious cases people will die. There will be warning signs so that they can use a reliever inhaler and if that doesn't work call an ambulance, but it is a terrifying experience.'*

When asked about the potential health risks posed to children taking part in the trial, AstraZeneca gave assurances that the children enrolled in the study had relatively mild asthma, that the study design used the shortest placebo-controlled period likely to show clinical response (6 weeks) and that rescue treatments were provided. Furthermore, AstraZeneca stated that it had included safeguards to minimize the risks for the placebo group such as regular clinic visits, lung function assessments and an asthma safety plan.

'We as well as the FDA believe that the current study designs are ethical, otherwise we would not be conducting them. ... Again, these trials are being performed according to a study plan agreed with the FDA. Study approvals have also been granted by ethics committees in the countries where the study is conducted, and by the relevant regulatory agencies. In South Africa specifically, approval was granted by the South African Medicines Control Council,' says the company.

However, it is difficult to verify how adequately the aforementioned safeguards were enforced as AstraZeneca outsourced the trial to a CRO. Furthermore, asthma attacks are not easy to predict. The risk of a serious attack among children with mild and moderate asthma is lower than for children with severe asthma, but there is still a risk, according to emergency room doctor and Professor Joel Lexchin. *'Personally if my children had asthma I would not enrol them in this trial.'* AstraZeneca says it always complied with the laws and regulations of the trial countries and had adhered to strict policy and standards in line with ICH GCP.

According to AstraZeneca, the FDA formally agreed to a placebo trial for the combination budesonide/formoterol inhaler in writing: *'This trial is being conducted in response to a formal written request from the FDA and is performed according to a study plan agreed with the FDA aiming at an approval of the medicine in children aged 6-12 years in the US,'* explains the company. It also says: *'The best way to determine the true magnitude of effect is to compare it to a placebo baseline. To perform a comparator study would take many more patients and could potentially expose more children than necessary to an ineffective therapy. We would surely perform the comparator study if a placebo controlled study was not ethical to perform; however, this is not the situation in this case.'*

For Dr Amar Jesani, editor of the Indian Journal of Medical Ethics, the use of placebo-controlled trials undertaken when proven treatment is available is a serious breach of ethics standards: *'The Helsinki Declaration, the Council for International Organizations of Medical Sciences (CIOMS) guidelines are very clear that placebo controlled trials can be conducted only in those conditions where there is no proven treatment/prophylaxis/prevention method available.... By admitting that the international pharmaceutical companies are doing*



placebo trials just for regulatory reasons, they are admitting the large scale violation of ethical guidelines of the medical profession and the World Health Organization.'

Benefits for South Africa and other countries where the trial took place

Aside from the concerns about the safety of asthmatic children taking part in placebo-controlled trials, other questions concerning the relevance and benefit of such trials in South Africa have been raised by a number of experts. Budesonide was first licensed in 1981 and has since been studied and marketed by AstraZeneca and generic companies in different doses around the globe. It is hard to see what new and relevant medical evidence the CHASE 1 study could yield which could benefit countries such as South Africa.

'This trial is hard to justify and it has been very hard to recruit,' says private Paediatrician Dr. Ahmed Ismail Manjr who has been involved in recruiting asthmatics for the CHASE 1 trial. *'I think it is of dubious scientific value, I know the FDA wants it but we have no problems with it in South Africa where it [budesonide] has been licensed for use in children aged 6 and up for more than 20 years – the MCC is not asking for any more information... it is an old molecule.'* Symbicort pMDI has not yet been approved for use in children aged between 6 and 12 in South Africa.

Benefits for the company

Symbicort is one of AstraZeneca's leading, most lucrative brands, with global sales of almost 3.2 billion US dollar in 2012.²⁵ In the US, the patent on Symbicort (combination) will expire in 2014, whilst the patent on the pMDI device will expire in 2026.

Getting approval for Symbicort pMDI for children between 6 and 12 in the US can be seen as an example of a common strategy by pharmaceutical companies, namely to expand the use of a drug to as many age groups as possible to maximize the benefit of the patent protection period. However, the question is whether there is a clinical need for and added value of Symbicort pMDI compared to already existing drug/device combinations for children in the US.

Professor Lainie Ross (paediatrician at University of Chicago) says: *'We have heard this same excuse for 15 years, it is time to get beyond this. The FDA needs to rethink how it can use well-done international data. The pharmaceutical companies need to acknowledge their moral responsibility. It is not justifiable to do a placebo-controlled trial when similar trials have been done in many other countries such that the safety and efficacy data are already known.'*

'Hidden business model'

According to experts we interviewed, placebo-controlled trials discussed in the (original) report are in fact merely intended to protect the market share of the pharmaceutical company. They are not meant for the development of new drugs: by slightly altering 'blockbuster' drugs, companies want to introduce 'new' drugs to the market when the old drug's patent expires. These trials – which have little to no true benefit for patients – are highly ethically questionable. This problem is key to what experts we interviewed call the 'hidden business model', as a result of which only one in ten newly approved medicines substantially benefits patients. According to experts cited in the original report, drug regulators such as EMA and



FDA play an important role in sustaining this model as they do not require new drugs to be significantly better than drugs that are already on the market; neither do they evaluate whether there is a public health need for such a drug. Instead they treat drugs as if they were common commodities.



*Professor Lainie Ross:
‘It is not justifiable to do a placebo-controlled trial when similar trials have been done in many other countries such that the safety and efficacy data are already known.’*



EUROPEAN AND AMERICAN REGULATORS ON PLACEBO-CONTROLLED TRIALS

According to the EMA and its scientific Committee for Medicinal Products for Human Use (CHMP), placebo-controlled trials are important but should only be conducted if they are ethical, regardless of therapeutic or scientific value. This means that trials must be conducted in a highly controlled setting, and that those in the placebo group who relapse get active treatment.

The FDA's view is as follows: *‘You cannot put people at risk of harm by denying them a known effective treatment in order to do a placebo-controlled trial (ICH E-10). [...] We would not require one where use of a placebo would endanger the patient. Thus, in trials in serious infections, cancer (where there is an effective treatment), and other settings in which lack of the standard treatment would put a patient at risk, you cannot use a placebo, and the trials done are always active control trials. An active control trial where the new drug is more effective is always an acceptable option. This is very clearly set forth in ICH E-10.’* ♦



CONCLUDING REMARKS: WHO BENEFITS FROM CLINICAL TRIALS?



Clinical trial participants have the right to participate in trials that are ethically sound. However, over recent years, we have seen that the ethical conduct of trials by the global clinical trials industry is not a systematic *modus operandi*. This is also true for the four African countries presented in our reports, which have shown that ethical violations in clinical trials in these countries are imminent.

Although Egypt, Kenya, Zimbabwe and South Africa differ in terms of infrastructure, legislation and societal aspects - like weak civil society and lack of media interest (Zimbabwe) or lack of unified clinical research legislation (Egypt) - we found similarities in systemic flaws in all countries that can thwart the ethical conduct of clinical trials. We found that institutions charged with overseeing clinical trials often lack resources (whether human or financial) to carefully monitor clinical trials. Oversight and approval of trials was also found to be problematic due to the involvement of multiple bodies. Another aspect undermining the protection of clinical trial participants are conflicts of interest such as medical doctors being paid substantial sums to recruit their patients for trials and trial researchers being members of ethics committees.

Our reports clearly describe why such systemic flaws are worrying: clinical trial participants find themselves in a vulnerable and dire position. Clinical trial participants in the four countries under study share a weak socio-economic position. Participants are often uninsured and often do not have access to healthcare. This forces them to participate in clinical trials and take experimental drugs – of which safety has not been definitely determined - instead of safe, proven treatments. One could argue that for patients living in resource-poor settings, having an experimental treatment is better than no treatment at all. Nevertheless, when given the choice, patients usually prefer to have safe, proven treatment first. Like in affluent countries, clinical trial participants should have the freedom to choose between an existing and experimental treatment. Also, we found that trial participants are often not aware that they participate in a clinical trial, nor do they always understand the risk participation entails. Due to the fact that lack of access to healthcare pushes them to participate in a clinical trial, and the fact that full understanding of a clinical trial is not always evident, one could argue that their consent is therefore not always voluntary or informed.

Other factors also contribute to systemic flaws that hinder ethical clinical trials. An involved media and civil society, and access to information constitute the pillars of public scrutiny, which is an important instrument in protecting the rights of clinical trial participants. Public scrutiny can act as a check-and-balance. Our reports show how access to information in the four countries is often hampered by the fact that trial registers are incomplete or not up to date, and that inspection reports are not publicly accessible. The case of the Egyptian cancer

patient Dania (see Introduction) shows that public scrutiny can be undermined by legal steps taken by trial sponsors, such as the court case against Public Eye, one of our partner organizations in the Egypt report.

Worryingly, we found that vulnerable trial participants were subjected to placebo-controlled trials without proper justification as required in the Declaration of Helsinki. We are deeply concerned about placebo-controlled trials in countries with fragile health systems and weak oversight, because when a trial participant experiences physical harm during a trial, medical follow-up, let alone compensation, have shown to be extremely difficult to receive.

Leading international ethical guidelines like the Declaration of Helsinki and the CIOMS Guidelines include the right to post-trial-access to medicine (PTA) for participants in clinical trials. While companies' policies ensure that PTA is given to trial participants, reality has revealed that this is rather the exception than the rule. Additionally, when trial participants experience physical harm during a trial, trial sponsors (usually the company) often deny that there is a relation between the physical harm and the experimental drug. This also makes receiving financial compensation extremely difficult for trial participants.

Development of new medicines – and conducting clinical trials – should benefit public health. This right is enshrined in the Declaration of Helsinki and the CIOMS Guidelines. But our research revealed that several of the trials included in this report were not meant to develop new drugs benefiting public health, but rather to protect the market share of the pharmaceutical company. Companies add minor variations to their blockbuster drugs to introduce a 'new' product on the market when the patent of the old drug has expired, thereby preserving their revenue stream. Such clinical trials - which have little or no benefits for patients - are ethically questionable, according to Wemos.

According to experts we interviewed, drug regulators such as the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) play an important role in sustaining the current way in which clinical trials are conducted to develop drugs that have little to no true added therapeutic value, as they do not require new drugs to be therapeutically more effective than existing drugs. They only evaluate the drug's efficacy and safety, while not considering its added therapeutic value.



RECOMMENDATIONS TO THE EUROPEAN MEDICINES AGENCY

The European Medicines Agency (EMA) has formulated several regulatory actions that give the European regulatory authorities ample opportunity to ascertain that medicines tested outside the European Union comply with the same ethical standards as those tested within the EU. Directive 2003/63/EC states that drugs tested in low- and middle-income countries can only be considered for EU marketing authorization if they have been tested according to guidelines, like the Good Clinical Practice (GCP) or Declaration of Helsinki Guidelines.

While EMA has promised to perform extra checks on clinical trials conducted outside the EU before medicines tested in those trials are authorized for the European market, it remains unclear how the agency guarantees that trials are conducted ethically. On April 27 2017, the European Parliament voted in favour of a report on the EMA discharge. The report states

that EMA must annually report its actions to ensure that drugs intended for the European market are tested ethically in lower- and middle-income countries. We find it an enormous step forward that from now on, the European Parliament can hold EMA accountable for its role in ensuring that medicines entering the European market are tested according to ethical standards. We believe that as a result of this decision, EMA will need to assume more responsibility for the rights of clinical trial participants.



Next to this important decision taken by the European Parliament, other measures should be taken by EMA. We find that the systemic weaknesses and ethical violations described in our report justify **an increase of inspections of clinical trials in low- and middle-income countries by EMA**. The agency does not provide specific information regarding GCP inspections. **Therefore we recommend that GCP inspection reports be made public**. This would be an important step towards facilitating the public scrutiny needed to hold the pharmaceutical industry accountable. European and national regulatory institutions like EMA should attach more importance to the **evaluation of the added therapeutic value** of new medicines on the EU market. Not only the safety and efficacy of medicines should be evaluated: a new medicine should have added therapeutic value over existing treatments.

Finally, we want to remind EMA of its promises formulated in the reflection paper on ethical and GCP aspects of clinical trials of medicinal products for human use conducted outside of the EU/EEA and submitted in marketing authorization applications to the EU regulatory authorities. Furthermore, before granting a drug market authorization, EMA should:

- **Demand a justification from the pharmaceutical company** as to why vulnerable populations were involved in a clinical trial, and ask which provisions the trial sponsor has taken to adequately protect these vulnerable participants.
- **Demand a justification for the use of a placebo drug in placebo-controlled trials** and seek assurance that the trial design was appropriate and ethically applicable.
- **Demand a description of how informed consent was taken**. Even if proper procedures were apparently followed in obtaining informed consent, EU regulatory authorities should be aware of the fact that many patients who participated in these trials may not have had other adequate medical treatment options.
- **Ascertain whether the trial sponsor has made adequate provisions for post-trial treatment** access for participants in low- and middle-income countries.
- **Ascertain whether the trial sponsor has made adequate provisions** for compensation for trial participants who have experienced trial-related injury.

APPENDIX

World Medical Association (WMA) – Declaration of Helsinki - Ethical principles for medical research involving human subjects¹

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient’s best interest when providing medical care.”
4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician’s knowledge and conscience are dedicated to the fulfilment of this duty.
5. Medical progress is based on research that ultimately must include studies involving human subjects.
6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.
7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.
8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.
9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.
10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international

¹ Declaration of Helsinki (2013). On: <https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/>

norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.
12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.
13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.
14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.
22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.
26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding,

any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.
28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.
29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.
30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.
31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.
32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations

where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.
36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.



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