

# CLINICAL TRIALS REALITIES IN ZIMBABWE

Dealing with Possible Unethical Research

Investigator Study Site

Study Number: \_\_\_\_\_

Investigator name: \_\_\_\_\_

Investigator Address: \_\_\_\_\_

Lopinavir/Ritonavir 200 mg/50 mg  
120 Tablets

Lot #: **12-005754**

Subject #: \_\_\_\_\_

Subject Initials: \_\_\_\_\_

Store at 20 - 25°C (68 - 77°F). Excursions permitted as directed by your study protocol.

Take as directed by your study protocol.

Keep out of reach and sight of children.

**For Clinical Trial Use Only**



# Contents

Glossary of terms and definitions	3
Preface	5
Introduction	8
Methodology	6
Chapter one: Zimbabwe's health situation	10
Chapter two: Grace Mawere's story	16
Chapter three: Stakeholders' responses	21
Chapter four: Context	24
Chapter five: Conclusion and recommendations	32
References	35
Annex I: Letter to the MRC	41

# GLOSSARY OF TERMS AND DEFINITIONS

**AE** Adverse Event. According to the definition of the Food and Drug Administration (FDA) an adverse event is “any undesirable experience associated with the use of a medical product in a patient”<sup>1</sup>.

## **Antiretroviral drugs**

HIV is treated with antiretrovirals (ARVs), which work against the HIV infection by slowing down the spread of the virus in the body.

**Clinical trial** A clinical trial is any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes.

**CDC** Centre for Disease Control, a United States (US)-based publicly-funded institution.

## **Declaration of Helsinki**

The Declaration of Helsinki is a set of ethical principles regarding human experimentation developed for the medical community by the World Medical Association (WMA). It is widely regarded as the cornerstone document on human research ethics.

**CIOMS** The Council for International Organisations of Medical Sciences is an international non-governmental organisation (NGO) established jointly by WHO and UNESCO in 1949, based in Geneva, Switzerland.

## **EARNEST study**

Europe–Africa Research Network for Evaluation of Second Line Therapy.

**EDCTP** European and Developing Countries Clinical Trials Partnership, funder of the EARNEST study, based in The Hague, the Netherlands.

**EC** Ethics Committee, see definition IRB.

## **First-line treatment**

The first treatment given for a disease.

<sup>1</sup> FDA. 2014. MedWatch The FDA Safety Information and Adverse Event Reporting Program. Available at <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm053087.htm>

- HIV** The Human Immunodeficiency Virus (HIV) is a lentivirus that causes the Acquired Immunodeficiency Syndrome (AIDS), a condition in humans in which progressive failure of the immune system allows life-threatening opportunistic infections and cancers to thrive.
- IRB** Institutional Review Board also known as an independent ethics committee (IEC), or ethics committee, is an independent body constituting of medical scientific, and non-scientific members, whose responsibility it is to ensure the protection of the rights, safety, and well-being of human subjects involved in a trial by, among other things, reviewing, approving, and providing continuing review of trials, of protocols and amendments, and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects<sup>2</sup>.
- MRC** Medical Research Council is a publicly-funded institution based in the United Kingdom (UK).
- MRCZ** The Medical Research Council of Zimbabwe is the National Ethics Committee (NEC) that was established in 1974 in order to provide health researchers and institutions conducting health research with independent ethical advice on research conducted by those researchers or by/within those institutions.
- MCAZ** Medicines Control Authority of Zimbabwe, the regulator of medicines and health in Zimbabwe.
- NIH** National Institutes of Health, biomedical research facilities with headquarters in Bethesda, Maryland, US.

### **Opportunistic Infection**

An opportunistic infection is an infection caused by pathogens, (usually bacterial, viral, fungal or protozoan) that take advantage of a compromised immune system of the infected person and would normally not cause disease in a healthy host.

### **Randomisation**

In clinical trials, the participants are randomly assigned to either the experimental group or the control group, thereby avoiding any possibility of selection bias in a trial.

- RCZ** Research Council of Zimbabwe, a body that regulates and promotes research in Zimbabwe.
- SAE** Serious Adverse Event; “Any adverse event or adverse reaction that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.”<sup>3</sup>

<sup>2</sup> FDA. 1996. Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance. Available at: <http://www.fda.gov/downloads/Drugs/Guidances/ucm073122.pdf>

<sup>3</sup> National Institute for Health Research (NHS). Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR) Available at: <http://www.ct-toolkit.ac.uk/glossary/serious-adverse-event-sae-or-serious-adverse-reaction-sar>

**Second-line treatment**

Treatment that is given when initial treatment (first-line therapy) is no longer

**SOMO**

The Centre for Research on Multinational Corporations, SOMO, is an independent, not-for-profit research and network organisation working on social, ecological and economic issues related to sustainable development. SOMO is based in Amsterdam, the Netherlands.

**Sponsor**

The FDA defines the sponsor as the “person who initiates, but who does not actually conduct, the investigation, that is, the investigational device is administered, dispensed, or used under the immediate direction of another individual. A person other than an individual that uses one or more of its own employees to conduct an investigation that it has initiated is a sponsor, not a sponsor-investigator, and the employees are investigators.”<sup>4</sup>

**Parirenyatwa Hospital**

Zimbabwe’s biggest government-owned general hospital, located in Harare.

**PI**

A principal investigator is the lead scientist for a research project, such as a laboratory study or clinical trial.

<sup>4</sup> FDA. 2014. CFR - Code of Federal Regulations Title 21. Available at: <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=50.3>

## **PREFACE**

Early 2014, a Zimbabwean journalist, Terence Zimwara, brought to our attention the poignant story of a young Zimbabwean woman who became partially blind during a clinical trial in Zimbabwe. Although she and the above mentioned journalist repeatedly knocked on the doors of the actors responsible for the trial, calling for help, the doors remained shut. No one properly investigated the possible relation between the blindness and the trial drugs.

To date, limited information is publicly available about clinical trials on the African continent, while many trials are known to take place there. Wemos published two explorative reports on clinical trials in Africa, one on the clinical trial industry in South Africa in 2013 and one on medical research in Kenya in 2014. Our research shows that the combination of poverty, limited access to health care and weaknesses in clinical trial oversight in these countries leave room for possible violation of the rights of vulnerable test subjects. Awareness among policy makers and the broader public regarding the vulnerable position of trial subjects is vital. It is therefore paramount to continue vigilance and careful monitoring regarding drug testing in Africa.

In this light, Wemos welcomes this report that tells the story of a HIV-positive Zimbabwean woman attacked with blindness during her trial participation. A story unfolding against the backdrop of the Zimbabwean clinical trial landscape that faces different challenges and raises several concerns. This report provides a voice to one of those who are seldom heard, and sheds light on the worrying challenges in the ethical oversight and monitoring system in Zimbabwe.

The case described in the report highlights the importance of a well-organised, strong ethical review system in order to protect the rights of the trial participants. Wemos takes the position that the well-being and rights of the individual trial subject must always take precedence over other interests. We expect this report will incite action to structurally address and prevent unethical conduct in medical research. Moreover, the report will hopefully increase awareness in Zimbabwe about the potential risks faced by trial participants.

*Wemos, April 2015*

## INTRODUCTION

In 2005, 15-year old Grace Mawere<sup>5</sup> was diagnosed with HIV and started antiretroviral therapy. She was one of many hundreds of thousands in Zimbabwe living with the virus and seemed destined to carry her burden in anonymity. Fate decided otherwise. In late 2010, she participated in a drug trial. During the trial, partial blindness attacked her. It may well be that the loss of eyesight was caused by the trial drugs. However, hardly any effort was undertaken by the actors responsible for the trial to respond to her call for help. Eventually she came to meet Terence Zimwara, an investigative journalist and author of this report, with whom she shared her story.

Clinical trials to test new medications are increasingly carried out in low- and middle-income countries. India, China, Eastern Europe and Latin America have been popular living laboratories for some time now, for a number of reasons: it is easier to find trial subjects, less expensive to conduct clinical trials, and regulatory constraints are either less stringent or less actively monitored. More recently, the African continent has also started to become an interesting place for clinical research. This is partly due to the fact that the laws governing clinical trials in the aforementioned countries are becoming more stringent, whereas in African countries, those laws are still relatively lenient. Also, non-communicable diseases are on the rise in Africa, triggering strong interest of the pharmaceutical industry in the development and marketing of drugs to treat them.

This report on Zimbabwe sheds light on the clinical trial landscape of Zimbabwe. Unlike its neighbour South Africa, Zimbabwe has not yet sparked huge interest from the pharmaceutical industry. However, the countries' chilling HIV-incidence rates provide ample opportunity to test new treatments for this condition.

In this report the current health challenges faced by Zimbabwe are described. Against that background the case of Grace is extensively explored and compared to the current rules and regulations governing clinical trials in Zimbabwe. What emerges is a picture of vulnerable clinical trial participants and an equally vulnerable oversight system: the majority of Zimbabweans have no access to affordable health care or health insurance which may give them no other choice than to participate in clinical trials in order to receive treatment for their condition. Furthermore, the institutions charged with overseeing the clinical trials are seriously underfunded and non-compliance with Zimbabwean laws often goes unpunished. Zimbabwean law and regulations have provisions for compensation to trial subjects who suffer Serious Adverse Events (SAEs).

Zimbabwean journalist Terence Zimwara, who won the Health Reporter of the Year Award 2012/2013, is the main author of this report. He conducted the interviews as well as an extensive literature review. In 2013, Terence Zimwara came in contact with Grace Mawere, a young HIV-infected Zimbabwean mother, then 23, who had participated in a clinical trial, the EARNEST study: the Europe-Africa Research Network for Evaluation of Second Line Therapy<sup>6</sup>. Grace told him that she had become partially blind during the trial. Her precarious situation and the fact that her attempts to get treatment or compensation were not taken seriously by those responsible for the trial, were reasons for Terence Zimwara to investigate her case.

<sup>5</sup> To protect her privacy, her name has been altered in this report.

<sup>6</sup> More information on the EARNEST study can be found in the textbox 'EARNEST study' in chapter two.

As for the specific case of Grace, it cannot be proved beyond a reasonable doubt that her partial blindness was a result of the treatment she received during the trial. Neither the trial sponsor nor the principle investigator bothered to conduct a thorough physical examination of her eye condition. Although blindness has been documented to occur as a result of the clinical trial medication that Grace received, the sponsor of the trial denied this in communication with the investigative journalist. For Grace, the cause-effect relationship was clear. She therefore decided to drop out of the trial and defaulted on the second-line treatment, which she received during the trial. According to hospital records, stopping the treatment resulted in a deterioration of her health situation.

On 6 April 2014, Grace Mawere passed away, 24 years old, leaving behind her baby daughter. Her baby girl was taken to the baby's grandmother, who had little means to provide proper care. The girl died three months later, not even one year old.

### **Outline of the report**

The story of Grace runs as a common thread through the report. The first chapter provides some basic information about Zimbabwe's health situation and elaborates on the major health challenges Zimbabwe faces. In the second chapter, the story of Grace is told. It describes her participation in the clinical trial, her eyesight problems and the attempts to get help from the organisations responsible for the trial. The third chapter sets out the responses on Grace's case from the different organisations involved. The regulations and laws governing clinical trials in Zimbabwe are discussed in the fourth chapter. In addition, this chapter sheds light on the rules that were violated in the case of Grace, providing a good understanding of the worrying challenges in the Zimbabwean clinical trial regulatory and monitoring system. Finally, a brief conclusion is presented, summarising the main concerns. Further, it provides recommendations to the parties involved in the process of ensuring ethical research, containing some concrete steps that can be taken to reduce the incidents of un-ethical clinical trials.

## METHODOLOGY

The report was compiled on the basis of a combination of information sources: direct interviews, speeches made at health research conferences and desk research.

First of all, the report relies heavily on Grace's testimonies of what she experienced during the trial. In the period from October 2013 to March 2014, Grace provided Terence Zimwara with oral information concerning the EARNEST trial. She also gave him the clinical trial report. After she died, Grace's family provided him with the informed consent form and hand-written notes from the hospital. These documents provided the basis to investigate the case further. Unfortunately, the journalist has been unable to obtain other relevant documents, such as the report from the optometrist. Both Grace and her family repeatedly stressed the importance of making Grace's story public.

Furthermore, direct interviews were held with the Medical Research Council of Zimbabwe (MRCZ) and the Medicines Control Authority of Zimbabwe (MCAZ) (the primary organisations handling clinical trials in the Zimbabwe) and with Grace's close relatives.

No officials other than the director of MRCZ, Dr. Paul Ndebele, were willing to go on record. All questions were referred to either Dr. Paul Ndebele or the director general of MCAZ. One official of the MCAZ's pharmacovigilance department refused to speak with the investigative journalist on Grace's specific case, while two technical committee members of MRCZ referred the journalist to the organisation's director. The MRCZ director has been keen to have the media report more on medical research in Zimbabwe and to this end, he invites journalists to conferences organised by MRCZ. Prominent names in health research attend and make contributions at such medical research conferences. Therefore, this report also relies on information obtained from such conferences. The Research Council of Zimbabwe (RCZ), which approves applications by foreign researchers seeking to work in the country, has not responded to inquiries sent and its junior officials refused to comment.

The sponsor of the trial, the Medical Research Council (MRC), based in the UK, was also a key resource in creating this report. Spokesperson Cathy Beveridge was very helpful in providing clarification on some aspects of the EARNEST study. Also, the European & Developing Countries Clinical Trials Partnership (EDCTP) through its communications officer Gert Onne van de Klashorst, helped us understand the relationship between EDCTP and the study.

## CHAPTER ONE: Zimbabwe's health situation

Zimbabwe is a landlocked country endowed with a mix of natural resources yet it faces an on-going economic crisis. The economic situation inevitably affects the country's ability to meet some of its obligations towards its citizens. According to the authoritative media source, the Integrated Regional Information Networks (IRIN), "Zimbabwe's deepening economic crisis is severely affecting the government's ability to fund public health delivery and restricting poor people's access to health care."<sup>7</sup> Although the Zimbabwean health situation can be characterised as recovering after a decline during the first years of this century<sup>8</sup>, Zimbabwe still faces enormous health care challenges and equitable access to quality and affordable health care remains a critical challenge in the country. A high incidence of disease and a lack of access to affordable and quality health care are issues of alarming and often life-threatening concern for many Zimbabweans.

### Major health challenges in Zimbabwe

The heavy burden of disease Zimbabweans are facing is dominated by preventable diseases and treatable conditions such as HIV/AIDS, malaria, pregnancy-related and perinatal complications, malnutrition, and tuberculosis (TB). According to UNAIDS<sup>9</sup>, the top three health threats in the Sub-Saharan country are currently HIV/AIDS, malaria and TB. In 2013, roughly 1,400,000<sup>10</sup> of the 13.8 million Zimbabweans were living with the HIV virus. Put in terms of percentages, this means that 15 per cent of the adults in Zimbabwe, aged between 15 and 49 years, have been HIV infected. The second leading cause of severe illness and death is TB, which affects 603 per 100,000 Zimbabweans<sup>11</sup>. Almost three-quarters of the active TB cases are reported to be HIV co-infected. "This co-infection remains a major factor propelling the high death rate among TB patients in Zimbabwe," states USAID in their online information on the mitigation of TB in Zimbabwe<sup>12</sup>. In addition, the number of drug-resistant TB cases, in which the infection does not respond to the drugs administered, is increasing. This limits the possibilities for effective treatment of TB cases. Furthermore, according to international aid organisation Doctors Without Borders, severe funding gaps in the Zimbabwean TB programme, with less than 50 per cent of required funding available, have resulted in inadequate TB care and preventions programmes<sup>13</sup>. In addition to TB and HIV/AIDS, malaria also remains a major killer in Zimbabwe. Almost half of the population lives in malaria-prone areas<sup>14</sup>. As of December 2013, Zimbabwe's reported malaria-prevalence rate was 29 cases per 1,000 inhabitants<sup>15</sup>.

The above-mentioned diseases all contribute significantly to maternal deaths in Zimbabwe, which rose by 28 per cent between 1990 and 2010<sup>16</sup>. Zimbabwe is among the 40 countries with a maternal mortality rate of more than 960 maternal deaths per 100,000 live births.

<sup>7</sup> IRIN. 2014. Zimbabwe's health system in crisis. Available at: <http://www.irinnews.org/report/100474/zimbabwe-s-health-system-in-crisis>

<sup>8</sup> WHO. 2014. Country Cooperation Strategy Zimbabwe.

Available at: [http://www.who.int/countryfocus/cooperation\\_strategy/ccsbrief\\_zwe\\_en.pdf](http://www.who.int/countryfocus/cooperation_strategy/ccsbrief_zwe_en.pdf)

<sup>9</sup> USAID. Zimbabwe. Global Health. Available at: [http://photos.state.gov/libraries/zimbabwe/231771/PDFs/USAID\\_Global\\_Health\\_001.pdf](http://photos.state.gov/libraries/zimbabwe/231771/PDFs/USAID_Global_Health_001.pdf)

<sup>10</sup> UNAIDS. 2013 Hiv and AIDS estimates Zimbabwe. Available at: <http://www.unAids.org/en/regionscountries/countries/zimbabwe>

<sup>11</sup> WHO. 2014. Global tuberculosis report 2014. Available at: [http://www.who.int/tb/publications/global\\_report/en/](http://www.who.int/tb/publications/global_report/en/)

<sup>12</sup> USAID. Zimbabwe Mitigating Tuberculosis.

Available at: [http://photos.state.gov/libraries/zimbabwe/231771/PDFs/USAID\\_Zimbabwe\\_Mitigating\\_Tuberculosis.pdf](http://photos.state.gov/libraries/zimbabwe/231771/PDFs/USAID_Zimbabwe_Mitigating_Tuberculosis.pdf)

<sup>13</sup> MSF Access. 2014. Out of Step-Deadly implementation gaps in the TB response. A survey of TB diagnostic and treatment practices in eight countries- October 2014. Available at: [http://www.msfaaccess.org/sites/default/files/MSF\\_Out-of-Step\\_Final\\_for\\_printOct17\\_0.pdf](http://www.msfaaccess.org/sites/default/files/MSF_Out-of-Step_Final_for_printOct17_0.pdf)

<sup>14</sup> PMI. President's Malaria Initiative- Fighting Malaria and Saving lives.

Available at: [http://www.pmi.gov/docs/default-source/default-document-library/country-profiles/zimbabwe\\_profile.pdf?sfvrsn=16](http://www.pmi.gov/docs/default-source/default-document-library/country-profiles/zimbabwe_profile.pdf?sfvrsn=16)

<sup>15</sup> PMI. 2015. PRESIDENT'S MALARIA INITIATIVE Zimbabwe Malaria Operational Plan FY 2015. Available at: <http://www.pmi.gov/docs/default-source/default-document-library/malaria-operational-plans/fy-15/fy-2015-zimbabwe-malaria-operational-plan.pdf?sfvrsn=3>

<sup>16</sup> Gift Phiri, Aljazeera. 2014. Zimbabwe's maternal mortality crisis.

Available at: <http://www.aljazeera.com/indepth/features/2014/02/zimbabwe-maternal-mortality-crisis-20142561739198301.html>

Although hard to measure in the absence of a complete registration of deaths in Zimbabwe, estimates say that around 3,000 women died during delivery in 2010<sup>17</sup>. Also, Zimbabwe's child mortality is mainly caused by the high disease burden in the country and remains a major challenge in Zimbabwe. Every year, one out of every twelve Zimbabwean children dies before his or her fifth birthday. To put it differently, 35,500 children under the age of five die each year in Zimbabwe<sup>18</sup>.

The Zimbabwean public health system has so far not been able to effectively address the country's major health challenges. A lack of health financing, health personnel, medicines, leadership and governance and access to health care facilities are considerable factors in Zimbabwe's high morbidity and mortality rate<sup>19</sup>. According to the World Health Organisation (WHO)<sup>20</sup>, it is paramount to financially invest in the Zimbabwean health system in order to reverse its weaknesses. However, concerted actions to strengthen the health system remain constrained by national fiscal space that remains limited, resulting in insufficient health budget allocation.

## Health financing

Zimbabwe's health delivery system has suffered due to subsequent years of general economic decline that accelerated in 2000. The standoff between political rivals that began in 1999 plunged the country into deep economic and political turmoil<sup>21</sup>. On the economic front, things reached a crescendo in 2008, when the then hyperinflation rate reached a record level of 231 million per cent<sup>22</sup>. Although the creation of a coalition government<sup>23</sup> in 2009 helped in easing economic pressures, the recovery of the health sector was slow even during that term. Since 2013, the situation has been getting even worse<sup>24</sup>. Zimbabwe's Gross Domestic Product (GDP)<sup>25</sup> growth has slowed while inflation remained below one per cent for the most part of 2014. According to some economic commentators, the economy had slipped into deflation<sup>26</sup>. The precarious economic situation unfortunately affects the health delivery system as the government cannot readily meet all its obligations. For instance, the Community Working Group on Health (CWGH), a local NGO, concluded in its analysis of the country's 2015 national budget, that the health sector was seriously underfunded<sup>27</sup>. The country spends a skimpy six per cent of its \$4.1 billion budget on health, whereas the 2001 Abuja Declaration obliges African countries, including Zimbabwe, to pledge at least fifteen per cent of national budgets towards the health sector. In 2014, the Ministry of Health and Child Care received \$337 million of the annual budget, dropping to \$301 million in 2015, thereby falling short of its international pledge<sup>28</sup>. The difficult economic situation has culminated into the wholesale deterioration of the health sector as it has affected health workers as well.

<sup>17</sup> UN Zimbabwe. 2013. Maternal Mortality in Zimbabwe Evidence, Costs and Implications. Available at: [http://www.zw.one.un.org/sites/default/files/UN-ZW\\_IssuePaperSeries-1\\_MMR\\_June2013.pdf](http://www.zw.one.un.org/sites/default/files/UN-ZW_IssuePaperSeries-1_MMR_June2013.pdf)

<sup>18</sup> Unicef. National Child Survival Strategy for Zimbabwe 2010- 2015. Available at: [http://www.unicef.org/zimbabwe/Young\\_Child\\_Survival\\_Doc-Complete.pdf](http://www.unicef.org/zimbabwe/Young_Child_Survival_Doc-Complete.pdf)

<sup>19</sup> Ibidem 8.

<sup>20</sup> Ibidem 8.

<sup>21</sup> John Robertson, Zimbabwean Economist. ZIMBABWE – An Economy on the Edge, Since 1980. Available at: [http://www.economic.co.zw/index.php?option=com\\_content&view=article&id=1185:zimbabwe--an-economy-on-the-edge-since-1980&catid=111:zimbabwe-history&Itemid=557](http://www.economic.co.zw/index.php?option=com_content&view=article&id=1185:zimbabwe--an-economy-on-the-edge-since-1980&catid=111:zimbabwe-history&Itemid=557)

<sup>22</sup> Sebastian Berger, The Telegraph. 2008. Zimbabwe inflation hits 231 million percent. Available at: <http://www.telegraph.co.uk/news/worldnews/africaandindianocean/zimbabwe/3167379/Zimbabwe-inflation-hits-231-million-per-cent.html>

<sup>23</sup> Newsday. 2013. Zimbabwe Economy's life during the coalition government. Available at: <https://www.newsday.co.zw/2013/09/05/zimbabwes-economy-life-coalition-government/>

<sup>24</sup> IRIN. 2014. Zimbabwe's health system in crisis. Available at: <http://www.irinnews.org/printreport.aspx?reportid=100474>

<sup>25</sup> Trading Economics. Zimbabwe's GDP Annual Growth Rate between 1961-2015. Available at: <http://www.tradingeconomics.com/zimbabwe/gdp-growth-annual>

<sup>26</sup> Reserve Bank of Zimbabwe. Inflation trends. Available at: <http://www.rbz.co.zw/about/inflation.asp>

<sup>27</sup> CWGH. 2015. Post Budget Analysis for the health sector 2015 budget. Available at: <http://www.cwgh.co.zw/images/budget.pdf>

<sup>28</sup> WHO. 2011. The Abuja Declaration: Ten Years On. Available at: [http://www.who.int/healthsystems/publications/abuja\\_declaration/en/](http://www.who.int/healthsystems/publications/abuja_declaration/en/)

## Shortage of skilled workers and health facilities

Zimbabwe has recognised the need to increase the number of skilled health workers as this will lead to the provision of better quality health services. Zimbabwe ranks lowly when it comes to the number of physicians per capita: 0.1 per 1,000 persons<sup>29</sup>. This is in spite of the fact that training institutions like the University of Zimbabwe School of Health Science aim to produce more graduates every year.

In 2014, the problems in the health sector became manifested through a strike by junior doctors as they demanded better working conditions<sup>30</sup>. According to the Zimbabwe Hospital Doctors Association (ZHDA), the poor working conditions<sup>31</sup> were the main reasons the country's district hospitals were understaffed<sup>32</sup>. There are very few specialist doctors in the country with a population of 13.8 million. For instance, one media outlet reported in November 2013 that there was only one pathologist to serve the whole country and only seven specialist doctors in major referral hospitals<sup>33</sup>. Many doctors migrate to countries that offer better working conditions resulting in a high number of vacancies for doctors in most public hospitals. In 2014, a freeze on the recruitment of nurses, which had been in force for about three years, was finally lifted<sup>34</sup>. The freeze had exacerbated the shortage of nurses in public hospitals, which obviously affected the delivery of quality health care.

Zimbabwe's health care challenges also include the need to increase the number of primary and secondary health facilities. There is an inequitable distribution of health facilities between the country's urban areas and rural areas, resulting in rural areas being seriously underserved. For instance, a study that collected data at community level in a rural province (Masvingo) and an urban province (Harare) of Zimbabwe, concluded that the maternal mortality rate lies at 85 and 168 per 100,000 live births in Harare and Masvingo respectively<sup>35</sup>. In addition, the shortage of essential medicines<sup>36</sup> in public hospitals further diminishes the ability of health staff to provide adequate health care to those who need it.

## Access to medicines

IRIN reports in a 2013 article<sup>37</sup> that "Chronic shortages of generic and antiretroviral drugs, stock-outs, high medication costs, and long distances to clinics are some of the hurdles people face in their quest to access essential medicines in Zimbabwe." In addition, irrational use, theft, improper storage, unaffordable prices, shortage of well-educated health workers, poor transport and a lacking infrastructure are important hindrances in ensuring universal access to medicines in Zimbabwe<sup>38</sup>. The available medicines are mainly externally funded. The national pharmaceutical industry is lacking resources and is therefore failing to meet the country's essential medicine requirements<sup>39</sup>.

<sup>29</sup> World Bank. 2015. Data Zimbabwe. Physicians per 1000 people. Available at: <http://data.worldbank.org/indicator/SH.MED.PHYS.ZS>

<sup>30</sup> Zimbabwe Independent. 2014. Doctors Strike; Holistic approach badly needed.

Available at: <http://www.theindependent.co.zw/2014/11/17/doctors-strike-holistic-approach-badly-needed/>

<sup>31</sup> Bulawayo. 2014. Doctors to go on strike. Available at: <http://bulawayo24.com/index-id-news-sc-health-byo-56050.html>

<sup>32</sup> Zimbabwe National Statistics Agency. 2011. Zimbabwe Statistical Agency link to Zimbabwe National Health Profile.

Available at: [http://www.zimstat.co.zw/dmdocuments/Health/ZNHHP\\_2011.pdf](http://www.zimstat.co.zw/dmdocuments/Health/ZNHHP_2011.pdf)

<sup>33</sup> The Financial Gazette. 2013. Specialist Shortage Hits Public.

Available at: <http://www.financialgazette.co.zw/specialist-shortage-hits-public-hospitals/>

<sup>34</sup> Patrick Chitumba, Chronical. 2014. PSC drags feet on nurse recruitment.

Available at: <http://www.chronicle.co.zw/psc-drags-feet-on-nurse-recruitment/>

<sup>35</sup> Mbizvo MT, Fawcus S, Lindmark G, Nystrom L. 1993. Maternal mortality in rural and urban Zimbabwe: social and reproductive factors in an incident case-referent study. *Soc Sci Med*; 36(9):1197-205.

<sup>36</sup> Phyllis Mbanje, Newsday. 2014. Shortage of essential drugs hits public hospitals.

Available at: <https://www.newsday.co.zw/2014/07/24/shortage-essential-drugs-hits-public-hospitals/>

<sup>37</sup> IRIN. 2013. Still struggling with drug shortages.

Available at: <http://www.irinnews.org/fr/report/97224/still-struggling-with-drug-shortages>

<sup>38</sup> CWGH. Consumer Action Forum Zimbabwe.

Available at: [http://www.cwgh.co.zw/index.php/en/?option=com\\_content&view=article&layout=edit&id=162](http://www.cwgh.co.zw/index.php/en/?option=com_content&view=article&layout=edit&id=162)

<sup>39</sup> IRIN. 2013. Still struggling with drug shortages.

Available at: <http://www.irinnews.org/fr/report/97224/still-struggling-with-drug-shortages>

Currently, most essential medicines are often only available at privately-owned hospitals, whose services are unaffordable to most Zimbabweans. A staggering seventy-two per cent of the low-income country's population lives below the poverty line, earning no more than \$1.25 a day<sup>40</sup>. Furthermore, the majority of the Zimbabweans do not have a health insurance<sup>41</sup>. According to some estimates, only ten per cent of the population has health insurance<sup>42</sup>. A vast majority of the population can therefore be classified as vulnerable as they cannot access health facilities<sup>43</sup>. In such circumstances, participation in a clinical trial becomes a luring perspective for patients like Grace. Studies in other countries have shown that access to treatment and transport allowances are important incentives for taking part in a clinical trial<sup>44</sup>.

## Emergence of clinical trials in Zimbabwe

Clinical trials by multinational sponsors such as pharmaceutical companies are increasingly carried out in low- and middle-income countries. India, China, South Africa and several Latin American countries have become important hubs for the pharmaceutical industry to test their new treatments. Reasons given for this trend are among others less stringent regulations, easier access to test subjects and access to new markets in these countries. When trying to gather data on the number and type of clinical trials carried out in Zimbabwe, the author of this report found out that this information is hardly available, let alone accessible. The Zimbabwean media has not been able to scrutinise clinical trials like media in other countries such as India have.

Terence Zimwara's inquiries with the MRCZ about the number of clinical trials did not produce any figures but just a few examples of trials completed. "There are numerous clinical trials that have been completed in Zimbabwe over the years on drugs and medical devices. In most of these clinical trials, Zimbabwean researchers have collaborated with foreign researchers," was the response from MRCZ. According to MRCZ, "the desire was to try as much as possible to ensure that clinical trials being conducted are relevant to the needs of Zimbabwe."

The most recent MRCZ Ethics guidelines state the following in relation to the emergence of trials: "The clinical trial industry in Zimbabwe reportedly increased in complexity and by size, growing by approximately 70 per cent between 2000 and 2007." However, there are no precise figures given to make comparisons. In the meantime, RCZ recently launched a database which will in the near future capture all clinical trials and medical research in general.

ClinicalTrials.gov, the world's largest clinical trials database, currently holding registrations of over 130,000 trials from more than 170 countries in the world, revealed 70 studies in Zimbabwe<sup>45</sup>.

Of these 70, 34 studies were already completed. At the time of the consultation, twenty studies were recruiting, nine ongoing, one not yet recruiting, two withdrawn, and one enrolling by invitation, while the status of three trials was unknown. Most of them were sponsored by universities and other non-commercial sponsors. 57 of the trials focused on treatments for HIV.

<sup>40</sup> The Independent. 2014. Rural poverty on the rise in Zimbabwe.

Available at: <http://www.theindependent.co.zw/2014/09/12/rural-poverty-rise-zim/>

<sup>41</sup> Zimbabwe National Statistics Agency. 2010-2011. Zimbabwe Demographic and Health Survey 2010-11. Available at: <http://dhsprogram.com/pubs/pdf/FR254/FR254.pdf>

<sup>42</sup> Daily News. 2014. Only 10% Zimbabweans on medical insurance.

Available at: <http://www.dailynews.co.zw/articles/2014/01/24/only-10pc-zimbabweans-on-medical-insurance>

<sup>43</sup> Vulnerable Subjects: Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate. Other vulnerable subjects include patients with incurable diseases, persons in nursing homes, unemployed or impoverished persons, and patients in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors, and those incapable of giving consent. GCP. Good Clinical Practice Terminology. Available at: <http://www.gcp-education.com/terminology.html>

<sup>44</sup> Wendler, D., Krohmal, B., Emanuel, E. J., & Grady, C. 2008. Why patients continue to participate in clinical research. *Archives of Internal Medicine*, 168(12), 1294-1299. Available at: <http://www.cphiv.dk/LinkClick.aspx?fileticket=HufTtug3jRM%3D&portalid=0>

<sup>45</sup> ClinicalTrials.gov was consulted on 12 March 2015.

When comparing these figures to the number of clinical trials in a neighbouring country like South Africa, a substantial difference was noticed. According to ClinicalTrials.gov, over 2,060 trials are listed in South Africa. Whereas trials in Zimbabwe are almost exclusively run by non-commercial sponsors, South Africa is an often-sought destination by pharmaceutical companies.

Reasons why companies seek to conduct clinical trials in countries like South Africa include the rapid recruitment, high prevalence of western-type diseases such as diabetes and a more developed research and health care infrastructure. Zimbabwe does not match South Africa in terms of the reasons mentioned above, which could explain the lower amount of trials. Nonetheless, Zimbabwe does have its own unique features that entice researchers to come, as noted by the MRCZ director.

The MRCZ director explained that researchers would like to conduct clinical trials in countries with a high burden of the diseases they are focussing on. For instance, Zimbabwe's HIV infections and death 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.

Besides the high incidence of certain types of diseases, foreign-sponsored research in Zimbabwe may be motivated by other reasons. In fact, experiences in countries like India<sup>46</sup>, have highlighted deficiencies in regulations to protect vulnerable people, this sparks the interest to carry out research in such countries. Such deficiencies include for instance, lower risks of litigation, less stringent ethical review and populations prepared to cooperate with almost any study that appears curative in nature. The *Stanford Journal of International Relations* states that “as regulations at home become more restrictive and funding for studies abroad increases, research in the developing world looks relatively attractive.”

The MRCZ director assured the investigative journalist that Zimbabwe's research oversight system had evolved over the past years to ensure adequate protection of trial participants. Significant efforts have been made to create an effective and professional clinical trial monitoring and approval process. However, as this research shows, there are also a number of concerns when it comes to the regulatory framework in Zimbabwe.

In 2010, a young Zimbabwean woman Grace Mawere joined a clinical trial that looked into one of Zimbabwe's killer disease — HIV/AIDS. Grace encountered problems during the study, which she associated with the clinical trial. The next chapter looks at Grace's experiences throughout her time in the study.

<sup>46</sup> Chemistry World. 2013. Supreme court ruling halts clinical trials in India. Available at: <http://www.rsc.org/chemistryworld/2013/10/supreme-court-ruling-clinical-trials-halt-india>

## **CHAPTER TWO:** **Grace Mawere's story**

### **Meeting Grace for the first time**

Zimbabwean journalists regularly make forays into the country's poorest suburbs like Mufakose and Epworth as they try to better understand how communities in these suburbs live. It was during one such foray in 2013, when the existence of clinical trials was brought to the attention of the journalist Terence Zimwara. During one of the discussions, the vulnerability of poverty-stricken people who participate in drug experiments was highlighted. In fact, it was the first time that Grace's case was mentioned and how she struggled as a result of the side effects she experienced during her participation in a clinical trial.

In September 2013, Terence met Grace Mawere for the first time. 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.

## EARNEST study

The EARNEST study, the clinical trial in which Grace was enrolled, is a multinational study that includes a European Commission-funded body, universities and drug companies. Its sponsor is the UK-based MRC<sup>48</sup>, and it received its funding from the EDCTP<sup>49</sup>. The aim of the trial is to identify the best antiretroviral therapy for HIV-positive individuals who need to switch antiretroviral therapy in a resource-limited setting since certain first-line treatments did not work for them. In doing so, the open-label, randomized-controlled EARNEST trial evaluated options for second-line therapy in patients failing certain first-line regimes in Africa. Trial participants were randomly assigned to one of the three different treatment groups in the trial: 1) Aluvia plus two non-nucleoside reverse transcriptase inhibitors (NRTIs) given continuously. 2) Aluvia plus Raltegravir, both given continuously. 3) Aluvia plus Raltegravir, with Raltegravir stopped after the first twelve weeks. Subjects of the trial had to attend clinics every four weeks for the first six months, then every six weeks until the end of the first year, and then every eight weeks until they had reached week 144 (almost three years after joining the trial). As of March 2010, 1,277 patients from five countries (Malawi, Uganda, Kenya, Zambia and Zimbabwe) enrolled in the clinical trial. The study was completed in January 2014.

### 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<sup>50</sup>.

<sup>48</sup> The MRC states that its mission is to improve human health through world-class medical research. To achieve this, it supports research across the biomedical spectrum, from fundamental lab-based science to clinical trials, and in all major disease areas like cancer and AIDS. It works closely with the National Health Service (NHS) in the UK and the UK Health Departments to deliver on its mission, as well as giving a high priority to research that is likely to make a real difference to clinical practice and the health of the population.

<sup>49</sup> The EDCTP aims to accelerate the development of new or improved drugs, vaccines, microbicides and diagnostics against HIV/AIDS, TB and malaria as well as other poverty-related and neglected infectious diseases in Sub-Saharan Africa, with a focus on phase II and III clinical trials. It has its head office in The Hague, Netherlands, while the European Commission provides part of the budget for this partnership.

<sup>50</sup> According to the informed consent form, “The commonest side effects experienced by people taking Aluvia are gastrointestinal (gut) disturbances such as diarrhoea. Very few people taking Raltegravir have experienced side effects, but gastrointestinal disturbances and dizziness occasionally happen. Although the NRTI medicines used in second-line therapy are usually well tolerated, there are a number of known possible side effects such as gastrointestinal disturbances (from didanosine), damage to kidneys and loss of bone mineral (from Tenofovir), and allergic reactions or possible cardiovascular (heart) disease risk (from Abacavir). If you are prescribed Abacavir you will be given a separate sheet of information about it. If you experience symptoms tell your clinic doctor at your next visit, or if you are worried, you should come to the clinic as soon as possible. It may be necessary to stop or change the medicine(s) after which the problem usually goes away.”

“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 Clinical Research Centre<sup>51</sup> 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<sup>52-53</sup>. Grace’s clinical trial summary report does not mention anything about the eyesight problem<sup>54</sup>. 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<sup>55</sup>.

<sup>51</sup> The University of Zimbabwe Clinical Research Centre (UZCRC) in Harare, Zimbabwe, was founded in 2002. The Centre is located at the Parirenyatwa Hospital Annex, which is Zimbabwe’s premier referral hospital and one of the two teaching hospitals of the University of Zimbabwe, Harare. UZCRC is affiliated with the University of Zimbabwe and receives support from the government and competes for international research grants. There are currently 100 members of staff and volunteers working at the clinic. The clinic treats patients with HIV and related infectious diseases. As of the 1st of April 2010, there were approximately 2,000 HIV-positive patients on follow-up in this clinic, of whom approximately 1,700 patients are currently on first-line treatment, and approximately 300 patients have been started on second-line therapy. The site has a great deal of experience in clinical research and has participated in numerous trials. Available at: <http://earnest.cineca.org/harara.html> and the University of Zimbabwe Medicine Faculty webpage <http://www.uz.ac.zw/index.php/faculties/faculty-of-medicine>

<sup>52</sup> NHS. NHS drugs side effects.

Available at: <http://www.nhs.uk/medicine-guides/pages/MedicineSideEffects.aspx?condition=HIV%20infection&medicine=Lopinavir/Ritonavir&preparation=>

<sup>53</sup> Drugs.com. Information on other side effects of Kaletra side effects.

Available at: <http://www.drugs.com/sfx/lopinavir-ritonavir-side-effects.html>

<sup>54</sup> Her last clinical report, dated July 23, 2013, does not mention any problems with her eyesight. In fact, it only mentions a scar on her left upper eyelid from a time when she was hit by a car.

<sup>55</sup> The cut was reported to have occurred on April 27, 2012, and this occurrence or event was marked as resolved by May 17, 2012.

The next section of the report asks for any additional information on the patient, and it is blank and marked nil.

The sponsor of a clinical trial and investigators participating in a clinical trial are responsible for proper reporting of Serious Adverse Events (SAEs). The purpose of reporting SAEs is to better understand the toxicity and safety of investigational products. Reporting and monitoring of SAEs is required to alert the MCAZ, sponsor, and clinical investigators of real and potential volunteer safety issues. The MCAZ will carefully review the SAE Report and use this information to monitor the investigational product’s toxicity profile and volunteer safety, see page 31 of the ‘GCP Guidelines 2012 Zimbabwe MCAZ’.

## 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<sup>56</sup> 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.

<sup>56</sup> HIV-related stigma and discrimination refers to prejudice, negative attitudes and abuse directed at people living with HIV and AIDS. The consequences of stigma and discrimination are wide-ranging. Some people are shunned by family, peers and the wider community, while others face poor treatment in health care and education settings, erosion of their human rights, and psychological damage. These all limit access to HIV testing, treatment and other HIV services. See report titled ‘HIV & AIDS Stigma and Discrimination’ available at: <http://www.avert.org/hiv-Aids-stigma-and-discrimination.htm>

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 ZLHR.

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 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 dead.

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.

## CHAPTER THREE: Stakeholders' responses

### EDCTP: the funder

Terence asked the funder of the EARNEST study, EDCTP, about guidelines and standards of clinical research that the group endorses and finances. In response, the EDCTP said it requires all sponsors of EDCTP-funded clinical trials to abide by the principles of the International Conference on Harmonisation Guidelines for Good Clinical Practice. Gert Onne van de Klashorst, communications officer with the EDCTP, explained that his organisation only provides funding and does not conduct clinical trials.

“The sponsor of the clinical trial [MRC in this trial] has to undertake all legal obligations to make sure that all legal liabilities are covered. This usually includes the obligation to take insurance<sup>57</sup> to meet legal obligations,” Van de Klashorst said in a written response.

In the terminology of clinical trials and the good clinical practice guidelines, a sponsor has a specific duty to guarantee the quality of a trial, while the funding organisation [in this case, the EDCTP] provides the financial means. The sponsor of the EARNEST study, the MRC, confirmed that it carried out the EARNEST study and insisted that its clinical trials are conducted in accordance with the principles of the International Conference on Harmonisation Guidelines for Good Clinical Practice<sup>58</sup>. Zimbabwe has pledged to uphold these guidelines when approving and regulating clinical trials.

### The trial sponsor MRC's response

Responding to an inquiry about the case (to protect her identity, the inquiry did not mention Grace by name), Cathy Beveridge, senior press officer of the MRC, defended the drugs used in the trial. She also advised the victim to contact local authorities for a review of her case. “We are sorry to hear about the EARNEST trial participant and her experiences,” Beveridge responded. “The drugs used in the trial are in widespread use and there has been no previous evidence to demonstrate that they cause blindness. The trial only uses drugs that have been licensed for the treatment of HIV infection. These drugs have been tested extensively, are used worldwide and are not considered to be new or experimental drugs.”

“If the participant would like to pursue the matter further, then we recommend that she brings this to the attention of the Medical Research Council of Zimbabwe [MRCZ], the body responsible for oversight of clinical research in the country.” Meanwhile, when questioned further about Grace's particular case, Beveridge said the group could not discuss individual cases, citing patient confidentiality.

“If a patient has concerns, they should first discuss this issue with the hospital where they receive ongoing care,” she explained. “The medical history of all trial participants prior to their consent to participation in the trial, as well as during the study itself, including all adverse effects, are carefully documented,” Beveridge said, adding that trial protocol ensures that all patients receive regular

<sup>57</sup> According to MCAZ guidelines 7.12, “The sponsor should provide insurance or should indemnify the investigator/institution against claims arising from the trial except for claims that arise from malpractice and/or negligence.”

<sup>58</sup> Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve human subjects. Compliance with Good Clinical Practice guidelines assures that the rights, safety, and well-being of trial subjects are protected and that the clinical trial data are credible. This International Conference on Harmonisation (ICH) guidance provides a unified standard for the European Union, Japan, and the US to facilitate the mutual acceptance of clinical data by the regulatory authorities in those jurisdictions.

Available at: <http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/GuidanceInformationSheetsandNotices/ucm219488.htm>

follow-ups. When asked about the competence of staff and the capacity of its sites, the MRC spokeswoman only responded to the second part of the question. “The sites for the EARNEST trial were carefully chosen and monitored both before the start of the trial and during the course of the trial. This is to be sure that they have the appropriate levels of care and can deliver to the trial protocol effectively and safely,” Beveridge replied.

### The trial regulator MRCZ’s response

The executive director of MRCZ, Dr. Paul Ndebele, initially explained in a letter (written in July 2013) that his organisation requires researchers to report on drug reactions. “We also receive and conduct investigations on research participants’ complaints to ensure that corrective action is taken,” remarked the director. He also said the council takes participants’ complaints seriously and expressed his desire to get further information on Grace’s case so that action could be taken. However, when presenting Terence Zimwara’s findings in early January 2014, Dr. Paul Ndebele rejected the assertion that the second-line drugs were responsible for Grace’s loss of eyesight, suggesting instead that the blurred vision may have been brought about by her low CD4 count, not the clinical trial drugs.

“It is possible that her low CD4 count may have made her susceptible to opportunistic infections which likely could have attacked her optic nerve, resulting in her becoming partially blind,” Ndebele said. An opportunistic infection as a result of her low CD4 count could indeed have been the cause of the eyesight problems (see text box ‘The CMV virus’). At the same time, it cannot be ruled out that the partial loss of eyesight was induced by the trial drugs. Since the medical event of Grace was not reported to the MRC, no proper investigation of Grace’s case has been conducted, leaving the cause of the decay of Grace’s vision unclear and the request for assistance made by Grace unanswered. When asked why the clinical report did not mention this medical event, as is the requirement under the good clinical practices guideline, the MRCZ’s response was as follows:

#### The CMV virus

As mentioned earlier in the report, Grace’s CD4 count was very low at the start of the trial. If a patient’s CD4 count drops below 50, there is an increased risk of developing the viral infection CMV that can cause permanent vision loss and blindness. In Grace’s case, a possibility exists that she got infected with the CMV virus, which resulted in the partial loss of her eyesight. However, her eye problems could have also been caused by the trial drugs.

“This [the clinical report in the possession of the author of this report] is not the comprehensive report [to which only the MRCZ and MCAZ have access to], and [it is] likely [that] the acknowledgement of this medical event [the blindness] would be noted [only] in the comprehensive clinical report, which the media or patient would never have access to,” said MRCZ. To support this statement, the MCAZ SAE reporting manual states that MCAZ will maintain all SAE reports confidential on file and in a regulatory database.

Johari Veena, a lawyer, disputes this argument insisting that all the relevant information has to be captured on the clinical report that is issued to the patient. According to her: “The Principal Investigator (PI) is supposed to report all SAE[s] or AE[s]. Whether the SAE/AE is related to the trial drug would be the second step [to investigate]. But it should be reported that the participant has faced this problem [while] the treatment was given. And then how it was determined whether the AE/SAE was related to the trial drug or not, or whether it was due to [an]other reason, [which] needs to be stated in the papers of the participant. If the same is not done, then the PI is liable, and there could be a chance that he is manipulating the results of the drug.”

### **The principal investigator responds**

Shortly after the end of the MRCZ annual conference in November 2014, Terence Zimwara asked Professor James Hakim, the PI, if there had been reports of SAEs in the EARNEST study. Hakim said there had not been any and he went on to reveal that the study (EARNEST) had in fact been successful in supporting WHO guidelines.

Terence Zimwara discussed this matter with Dr. Amar Jesani. He expressed concern that Grace’s case might not have been recorded at all. As a result, this SAE will not be included in the list of possible SAEs of the drugs, thereby producing an incorrect image of the safety and side effects of the trial drugs.

## CHAPTER FOUR: Context

### Regulations and laws governing clinical trials in Zimbabwe

The Medicines and Allied Substance Control Act (MASCA) regulates clinical trials and general health research in Zimbabwe. The act, which was promulgated in 1991, has had a series of amendments to align it with changing international health research guidelines. In addition, Zimbabwe has specific guidelines to regulate various aspects of clinical trials.

Zimbabwean regulations are based on the Declaration of Helsinki (DoH)<sup>59</sup>, the Council of International Organisations of the Medical Sciences (CIOMS) Guidelines as well as the International Conference on Harmonisation for Good Clinical Practice guidelines.

The DoH was developed by the World Medical Association (WMA) 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. Consistent with the mandate of the WMA, the declaration is primarily intended for those directly involved in human research, but the WMA encourages all others involved in medical research with human subjects to also adopt these principles<sup>60</sup>. In the instance of an unexpected event during the course of the trial, the DoH states this needs to be reported immediately<sup>61</sup>.

CIOMS is an international, non-governmental, non-profit organisation established jointly by the WHO and UNESCO in 1949. Part of its mission is to facilitate and promote international activities in the field of biomedical sciences, especially when the participation of several international associations and national institutions is deemed necessary. For instance, CIOMS guidelines call on researchers to apply the principles for the respect of persons, beneficence, and justice when conducting research. If a research study has no benefit or deliberately harms trial subjects, such a study is deemed unethical and international institutions that may be interested in the results of such a study are bound by CIOMS guidelines not to use the research outcomes. Without acceptance, such clinical trial results are worthless, hence, guidelines like CIOMS force researchers to conduct trials in a manner that is acceptable.

Thirdly, there is the tripartite harmonised International Conference on Harmonisation for Good Clinical Practice guidelines that were finalised in May 1996<sup>62</sup>. This Good Clinical Practice document describes the responsibilities and expectations of all participants in the conduct of clinical trials, including investigators, monitors, sponsors and IRBs. Good Clinical Practice covers aspects of monitoring, reporting and archiving of clinical trials and incorporating addenda on the essential documents through the International Conference on Harmonisation process.

<sup>59</sup> WMA. WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. Available at: <http://www.wma.net/en/30publications/10policies/b3/>

<sup>60</sup> Ibidem 59.

<sup>61</sup> FDA. 1996. Guidance for Industry. E6 Good Clinical Practice: Consolidated Guidelines. Available at: <http://www.fda.gov/downloads/Drugs/Guidances/ucm073122.pdf> "4.11.1 All serious adverse events (SAEs) should be reported immediately to the sponsor except for those SAEs that the protocol or other document (e.g., Investigator's Brochure) identifies as not needing immediate reporting. The immediate reports should be followed promptly by detailed, written reports. The immediate and follow-up reports should identify subjects by unique code numbers assigned to the trial subjects rather than by the subjects' names, personal identification numbers, and/or addresses. The investigator should also comply with the applicable regulatory requirement(s) related to the reporting of unexpected serious adverse drug reactions to the regulatory authority(ies) and the IRB/IEC."

<sup>62</sup> ICH. International Conference on Harmonisation Guidelines for Good Clinical Practice guidelines website. Available at: <http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/good-clinical-practice.html>

## What Zimbabwean law says on serious adverse event reporting

The MCAZ has produced SAE reporting guidelines in addition to Good Clinical Practice guidelines. The SAE guidelines specifically state the need to report all events happening to patients during the course of the trial.

For instance, MCAZ SAE Guidelines part 7.15 states, “The sponsor should report to the MCAZ, institutions, all adverse events occurring during the course of the trial. The sponsor should expedite reporting all serious adverse events to the ethics committee and the MCAZ and the sponsor and the investigators should immediately undertake appropriate and necessary measures and treatment to protect the trial subjects.”

The SAE form must be completed and submitted to MCAZ as soon as possible (within 24-48 hours) after the site becomes aware of an event. MCAZ may need to contact the clinical site for additional information regarding the SAE.

When a SAE is determined to have occurred, the next step would be to compensate the victim. MCAZ Good Clinical Practice guidelines and national laws specifically call for compensation to trial subjects who experience harmful effects in clinical trials. In the next chapter, Zimbabwe’s compensation mechanisms and possibilities for compensation in Grace’s case are explored.

## What the Zimbabwean law says on compensation after trial injury

Zimbabwe’s national law, which does not discriminate between human and animals, demands that persons conducting trials must insure the human or animal subjects. The MASCA Statutory Instrument 150 of 1991, chapter 46 states that “for the purposes of paragraph (b) of section 21 of the Act, a person conducting a clinical trial shall insure the persons or animals participating in such trial for the sum of not less than one hundred thousand dollars in respect of each person or animal or such other amount as the Authority may direct.” The MCAZ Good Clinical Practice guidelines state that ethics committees should ascertain whether provisions have been made for compensation/treatment in case of injury or death if attributable to a clinical trial and indemnity to cover the liability of the investigator and sponsor. The guidelines also indicate that participants must have access to information about procedures for compensation.

In Zimbabwe, the technical committee of the MRCZ is responsible for assessing the reported cases of SAEs<sup>63</sup>. The committee is divided into two sub-committees, one that focuses on indigenous medicine and one that addresses AEs during trials. According to MRCZ, the latter is concerned with the safety of study participants in health research. It notes critical events and makes decisions depending on the severity of the reported AE. It also assesses the frequency of recurring SAEs and decides to either suspend the product or advise PIs to liaise with the sponsor on prevailing anomalies. Causality assessment of all submitted SAEs are also handled by this subcommittee. Only this committee determines whether a trial subject has suffered an SAE.

Grace felt her case made her a suitable candidate for compensation. However, based on the evidence that the investigative journalist found in this study it is unlikely that Grace’s health problems were reported to the MRCZ. It is therefore unlikely that the technical committee of the MRCZ ever assessed whether her partial blindness was in fact related to the treatment she received during the trial.

<sup>63</sup> MCAZ Good Clinical Practice guidelines define an SAE as follows, “A serious adverse event is an adverse experience occurring at any dose that results in the any of the following outcomes: death, a life-threatening adverse medicine experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, a congenital anomaly/birth defect, or an important medical event that, based upon appropriate medical judgment, may jeopardize the patient or subject and may require intervention to prevent one of the outcomes listed above.”

Furthermore, when Terence Zimwara presented his findings in early January 2014, when Grace Mawere no longer participated in the EARNEST trial, MRCZ simply dismissed the assertion that the second-line drugs were responsible for Grace's loss of eyesight, suggesting instead that the blurred vision may have been brought about by her low CD4 count, not the clinical trial drugs. As a result, Grace could not easily claim compensation from sponsors of the study. Ignorance of clinical trial regulations as well as lack of legal counsel, were some of the reasons why Grace did not immediately pursue other options open to her. According to Grace's testimonies, which are supported by her close relatives, the eyesight problems began a few months after the trial commenced.

## The functioning of the regulatory bodies involved in clinical research

Zimbabwe uses a number of laws and regulations to guide and regulate health research. Three bodies, the MCAZ, MRCZ and the Research Council of Zimbabwe (RCZ), work together to ensure the research meets the health needs of the country and that researchers operate within the confines of the law.

The first, the MCAZ, is a statutory body established by an act of Parliament, the Medicines and Allied Substances Control Act (MASCA) [Chapter 15:03]. The mandate of MCAZ is to protect public health ensuring that medicines and medical devices on the market are safe, effective and of good quality. MCAZ places particular emphasis on clinical trials and it regulates this through its Pharmacovigilance centre. This unit approves and monitors all clinical trials on medicines and devices that are conducted in Zimbabwe in terms of Part III of the MASCA Act of 1991 [Chapter 15:03]<sup>64</sup>. The Pharmacovigilance unit also carries out post-market surveillance of registered medicines; collecting and analysing adverse drug reports as well as drug information dissemination through publishing a quarterly drug information bulletin.

The second, the MRCZ, which is the National Ethics Committee (NEC)<sup>65</sup>, was established and supported by the Government of Zimbabwe through the Ministry of Health and Child Welfare. The MRCZ is composed of scientists, medical experts, lawyers, ethicists, and religious community representatives. Its mission is "to promote and coordinate the ethical conduct of health research that influences health policy and practice in Zimbabwe." The MRCZ has an important role in ethical oversight as it has to give its approval before a clinical trial may commence, it may suspend or terminate approval in case of unethical clinical trials and it has the power to form and give accreditation to IRBs.

The third, the RCZ, is a statutory body established to promote Zimbabwean research in all fields. It also provides for coordinating and directing of foreign research. To illustrate, foreign researchers wishing to conduct research in Zimbabwe on behalf of a foreign institution must follow the guidelines issued by RCZ<sup>67</sup> and are required to apply for research permits from the RCZ. These three organisations form the framework that governs health and medical research in the country and they collectively enforce the laws and regulations governing medical research.

<sup>64</sup> The MASCA legislation says: "To ensure adequate protection of the general public against any risks or SAEs from the clinical trial of any medicine authorized in terms of section eighteen, the Authority shall monitor such clinical trials from the beginning to the end so as to satisfy itself that all specific and general conditions subject to which the trial was authorized are being strictly observed by the person conducting the trial, and that to all intents and purposes the trial will achieve its aims and objectives."

<sup>65</sup> The NEC performs the following roles;

- To provide guidance, advice, and decision (in the form of 'approval /disapproval') of specific research protocols intended to be conducted in Zimbabwe by all researchers and health institutions.
- To provide ethical guidance and advice on research programmes undertaken within Zimbabwe.
- To provide ethical guidance and advice on specific ethical issues presented to it by the Institute Ethics Review Committees and any other interested parties.
- To develop and or review, as requested, ethical guidelines for Zimbabwe.

<sup>66</sup> MRCZ. About MRCZ. Available at: [http://www.mrcz.org.zw/index.php?option=com\\_content&view=article&id=5:aboutmrcz&Itemid=7](http://www.mrcz.org.zw/index.php?option=com_content&view=article&id=5:aboutmrcz&Itemid=7)

<sup>67</sup> RCZ. Approval procedures for foreign researchers in Zimbabwe.

Available at: <http://www.rcz.ac.zw/index.php/en/research-registrations/registration.html>

However, the MCAZ and MRCZ are more focused on clinical trial regulation than the RCZ, so in the efforts to understand clinical trials better, Terence Zimwara asked both to give their assessment of Zimbabwe's clinical trial landscape. In the next paragraph, the director of MRCZ, Dr. Paul Ndebele, who spoke to Terence Zimwara on behalf of MRCZ and MCAZ, explained the organisations' perception of the strengths and weaknesses of Zimbabwe's regulatory system.

## Strengths and weakness in the system according to the regulator

In written responses to questions sent, the MRCZ insisted there is a framework in place to ensure compliance with relevant laws and guidelines. Dr. Paul Ndebele said that the research oversight system is managed by MRCZ and MCAZ. According to Dr. Paul Ndebele, these two regulators ensure that clinical trials that are conducted in Zimbabwe are relevant to the health needs of Zimbabwe. They also ensure that the trials that are carried out in Zimbabwe uphold high ethical standards<sup>68</sup> as well as principles of respect for persons, beneficence, non-maleficence and justice, said Dr. Paul Ndebele. The MCAZ enforces the insurance requirement for clinical trial participants and ensures the quality of the investigational products<sup>69</sup>.

"MRCZ and MCAZ both review the same informed consent forms to ensure that unjust and unethical clauses are removed before potential trial participants can sign the informed consent documents," stated Dr. Paul Ndebele. However, to ensure that a trial does not deviate from some of these requirements, Zimbabwean authorities have extra requirements in place.

Dr. Paul Ndebele continues, stating that "regarding the review of research, the MRCZ has a system of review that utilises internal and external experts before proposals are deliberated by the MRCZ Technical Committee<sup>70</sup>. The MRCZ also works with health institutions in establishing Institutional Research Ethics Committees. The institutional committees are one other level in the research protection system and they review research before it is submitted to the MRCZ for final approval." MCAZ has additional measures to ensure total protection of participants, as the director of MRCZ expounded.

Ndebele explained that the regulators have several instruments to monitor on-going research on a continuous basis. For example regulators jointly conduct site inspections to verify whether a clinical trial is being carried out according to regulations.

When we look at the Zimbabwean regulations pertaining to clinical trials and the mandate and instruments that the regulators have, one could conclude that important requirements for adequate protection of the rights of clinical trial participants are in place. However, a public statement of Dr. Paul Ndebele highlights the challenges that the system currently faces.

<sup>68</sup> Part 3.1 of the Ethics Guidelines for health research involving human participants in Zimbabwe says "Respects and Dignity: Respect for the dignity, safety and well-being of participants should be the primary concern in health research involving human participants. Culture, language, beliefs, perceptions, and customs must all be considered."

<sup>69</sup> Statutory Instrument 150 of 1991, Chapter 46 states that "for the purposes of paragraph (b) of section 21 of the Act, a person conducting a clinical trial shall insure the persons or animals participating in such trial for the sum of not less than one hundred thousand dollars in respect of each person or animal or such other amount as the Authority may direct."

<sup>70</sup> MRCZ. Committees.

Available at: [http://www.mrcz.org.zw/index.php?option=com\\_content&view=article&id=4:committees&Itemid=12](http://www.mrcz.org.zw/index.php?option=com_content&view=article&id=4:committees&Itemid=12)

## Constraints regulators face

The biggest impediment to the success of MRCZ in monitoring compliance is the lack of resources. Speaking at the MRCZ annual conference in November 2014, director Dr. Paul Ndebele, explained that his organisation was underfunded. He said this problem started when the country began experiencing its current economic challenges. Zimbabwe struggles to meet some of its basic needs, hence the country's annual budget often has little money for MRCZ<sup>71</sup>. Consequently, MRCZ is forced to seek financial assistance from 'other sources' like donor organisations and supportive private funders.

In an earlier presentation, the MRCZ director outlined the problems which his organisation faced as it carried out its mandate, among which:

- An increasing number of cases of noncompliance with regulation;
- Researchers implementing unapproved studies;
- Researchers conducting their studies without applying [for approval];
- Researchers deviating from approved protocols;
- Cases of unacceptable practices in research;
- Non-cooperation/ refusal of access to sites for inspections;
- Limited influence over research that is conducted in Zimbabwe.

Ndebele said that the MRCZ was only able to stop some of these practices, but in reality it has had limited success in that effort due to lack of financial resources and a strong mandate<sup>72</sup>. MRCZ pins its hopes on the proposed National Health Research Act<sup>73</sup>, which would grant it more powers and resources.

## Which rules were violated in the case of Grace Mawere?

### Informed consent

According to the DoH: "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."

Similarly, the MRCZ Ethics guidelines state "Investigators must assure potential participants that participation is voluntary, and that refusal to participate, or a decision to discontinue participation, will not involve any form of penalty. The approximate number of participants should be disclosed.

<sup>71</sup> Zimbabwe announced \$4.1 billion budget for 2015. Of this budget, \$3.32 billion, which represents 81 per cent of total expenditures, will be on account of employment costs, leaving a balance of \$798 million for operations, debt service and capital development programmes. See the budget statement, available at: <http://www.zimtreasury.gov.zw/>

<sup>72</sup> MRCZ has not given examples.

<sup>73</sup> With respect to the Health Research Act, the MRCZ has submitted to the Ministry a draft of the MRCZ Notice as part of efforts to align all legislations with the New Constitution of Zimbabwe. In 2013, a new constitution replaced the Lancaster House Constitution and as consequence, all laws and acts must now reflect this new reality. The process has however been slow with many government departments still referring to the now defunct constitution. MRCZ has already started working on a draft Health Research Act, which it aims to finalise in 2015. MRCZ hopes that by mid-2015, the document will be ready for onward submission to the Ministry of Health and Child Care, according to director, Dr. Paul Ndebele.

Details of treatment must be supplied and, where appropriate, the possibility of random assignment to various treatments or procedures must be made clear. The nature of experimental and control groups must be explained, as well as circumstances that might lead to the termination of participation. Unforeseeable risks obviously cannot be foreseen, but participants must be told the nature and extent of risks – including financial risks – attendant on participation. Participants must be made aware of their right to be informed of relevant new findings, and of the consequences of their withdrawal from research. They should know, too, whether the investigator might terminate participation.”

The informed consent form, read and signed by Grace, contains most of the information required by the DoH and the MRCZ Ethics guidelines, such as the aim and duration of the study, post-trial access to medicines, approximate number of participants, and the benefits for the trial participant. However, as the informed consent form does not mention loss of eyesight as a potential side effect, whilst this side effect was already known, it seems that the DOH and 2011 MRCZ Ethics guidelines were violated on this point.

### **Serious adverse event reporting**

Hospital records show that Grace experienced eyesight problems. According to the Guidelines for Good Clinical Practice in Zimbabwe (2012), a SAE such as loss of eyesight should be reported to the MCAZ authorities within 48 hours. However the clinical trial report does not mention any AEs nor SAEs and the principal investigator of the EARNEST trial said there had been no reports of SAEs in the EARNEST study. If this is indeed the case, this is a serious violation of Zimbabwean guidelines for three reasons. Because the health problems of Grace were apparently not reported there was most probably no investigation by the technical committee. As a result, the PI did not terminate her participation in the trial and did not prescribe different medicines to Grace. It seems that Grace single-handedly decided to drop out of the trial and started taking the antibiotic Co-trimoxazole instead of the second-line ARV treatment. A few months after defaulting on the treatment, her health condition deteriorated and her CD4 count dropped significantly. At the time of her death in April 2014, she had been admitted to Mashambazhou Care Trust, a specialised centre for HIV patients. Based on the information given in her hospital records, it can be considered very likely that quitting the drugs eventually led to her death. Moreover, because Grace’s health problems were not examined by the technical committee, an important precondition for receiving compensation was not met. Lastly, not reporting SAEs during a trial creates an incorrect image of the safety and side effects of a drug.

### **Compensation**

The informed consent form mentions that compensation will be provided in the event of injury if the claim for compensation is found to be justifiable. When the investigator of this report contacted the sponsor of the trial, the MRC, the representative of the sponsor said that there was no previous evidence of the medicines causing blindness and referred the matter to the MRCZ in Zimbabwe. Neither the MRC in the UK nor the MRCZ in Zimbabwe properly investigated whether there was a causal link between the tested drugs and Grace’s eyesight problems. As a result, Grace never received compensation or proper treatment. This is a clear violation of 2012 Guidelines for Good Clinical Practice in Zimbabwe, which states that in case of SAEs sponsors should immediately undertake appropriate and necessary measures and treatment to protect the trial subjects.

# Media monitoring of medical research in Zimbabwe

## Journalist apathy

Although the Zimbabwean medical research landscape is not without problems, these problems are difficult to uncover and often go unreported. Journalists are faced with the challenge of corroborating allegations before any account of misconduct or SAEs can be published. An average journalist in Zimbabwe is trained to report on news events and few get training in investigative journalism<sup>74</sup>. In addition to this, medical research in Zimbabwe is generally not transparent; officials always claim they are bound by non-disclosure agreements, even when it has become apparent that there are problems with a particular study.

Also, media attention is focused more on politics rather than on issues to do with health research or health in general. Zimbabwe has been experiencing turbulent politics since 2000 causing readers to want to know more about political events<sup>75</sup>. Scandals and sports news are other issues that get much more attention than the clinical trial industry in Zimbabwe. For instance, at the past two annual medical research conferences, only one journalist has attended, illustrating the lack of media interest in the clinical trial industry in Zimbabwe.

Nevertheless, there have been instances of adequate media coverage of health-related themes. For instance, in 2007 there was a cholera outbreak and thousands died. The story was a headline not only in Zimbabwe but internationally as well<sup>76</sup>. Other health issues that made headlines include the stocking of expired drugs by public hospitals in 2010<sup>77</sup> and the strike by health personnel in 2014<sup>78</sup>. And in the 1990s, there was extensive coverage of an illegal medical experiment conducted by a medical professional. The vast publicity motivated the authorities to take action. The accused was tried before court and was given a jail sentence.

## International media coverage

For the most part, it has been the foreign media or international organisations that have reported problems regarding clinical trials conducted in the country. For instance, Public Citizen, an advocacy organisation based in the US, along with international news outlets revealed the unethical issues surrounding the AZT trials in the 1990s<sup>79</sup>, conducted on HIV-positive African subjects by US physicians and the University of Zimbabwe. The trials were allegedly performed without proper informed consent. The US began testing AZT treatments in Africa in 1994, through projects funded by Centers for Disease Control (CDC) and the National Institutes of Health (NIH). Public Citizen found out that the subjects did not fully understand the testing methods, the effectiveness, possible dangers, or the nature of a placebo in testing situations.

<sup>74</sup> Journalism certificates and diploma courses require candidates to have passed a minimum of five secondary education subjects or two passed high school subjects. Universities also offer journalism and media studies degrees where the minimum requirement is two passed subjects at high school level. Journalists can enhance themselves by enrolling for further courses in financial reporting or health reporting. See <http://www.zimbabwe.cc/html/education-in-zimbabwe.html>

<sup>75</sup> Zimbabwe Today. Available at: <http://www.zimbabwetoday.org/>

<sup>76</sup> Petra Thonycraft, The Telegraph. 2008. Cholera epidemic hits 10000. Available at: <http://www.telegraph.co.uk/news/worldnews/africa-andindianocean/zimbabwe/3536824/Zimbabwes-cholera-epidemic-hits-10000.html>

<sup>77</sup> The Zimbabwean. 2010. Gweru hospital overstocked with expired drugs. Available at: <http://www.thezimbabwean.co/news/31025/gweru-hospital-overstocked-with-expired-drugs.html> <http://zimbabweonlinenews.com/%EF%BB%BFmps-uneath-expired-drugs-at-byo-hospitals/>

<sup>78</sup> Herald Daily Newspaper. 2014. Doctors end strike. Available at: <http://www.herald.co.zw/doctors-end-strike/>

<sup>79</sup> Public Citizen. 1997. Letter Concerning Funding of Unethical Trials Which Administers Placebos to HIV-infected Pregnant Women. Available at: <http://www.citizen.org/Page.aspx?pid=2329>

The Zimbabwe Depo Provera drug trial is another example of an illegal drug trial conducted in the 1970s. The drug was eventually banned after publication of the case by international media<sup>80</sup>. A SOMO and Wemos briefing paper on ethics in clinical trials dated February 2008 provided a list of unethical trials that have been conducted worldwide. The report questioned the ART treatment interruption trials as a possible unethical aspect of the Development of Anti-Retroviral Therapy in Africa (DART) study. The DART study was conducted in Zimbabwe, Uganda and Ivory Coast<sup>81</sup>.

### Civil society and media apathy

In the case of the EARNEST study there are no known reports of SAEs besides that of Grace, a case which did not get any media coverage, apart from a publication by the NGO Rethinkaid. Local publishing organisations that were approached reacted that the story was too long to publish. It could not be used by conventional tabloids as it required a lot of space. Perhaps the absence of strong civil society organisations advocating for better patients' rights contributes to this lack of interest. Most civil society groups that have emerged since the year 2000, were more focused on politics, democracy, HIV/AIDS and human rights violations in general. With the political situation now having somewhat calmed, some influential people are now urging civil society to change their approach, especially when dealing with the government. In June 2014, the former European Union ambassador to Zimbabwe, Aldo Dell'Araccia, said that Zimbabwean civil society groups were 'living in the past' and they had to change their attitude towards the government<sup>82</sup>. Also, Pedzisai Ruhanya, a prominent human activist and director of the Zimbabwe Democracy Institute, urged NGOs to abandon the so-called regime change agenda. Zimbabwe Democracy Institute has since produced a policy document titled 'Priorities for civil society-donors engagement in Zimbabwe', which should guide civil society organisations' activities<sup>83</sup>. Without a media and civil society that educates, the vast majority of the population will remain ignorant of clinical trials in general and the violation of patients' rights in particular.

<sup>80</sup> The Multinational Monitor. 1981. Zimbabwe Bans Dangerous Contraceptive, Depo-Provera. Available at: <http://www.multinationalmonitor.org/hyper/issues/1981/09/zimbabwe.html>

<sup>81</sup> SOMO & Wemos. 2006. SOMO briefing paper on ethics in clinical trials. Available at: [http://somo.nl/html/paginas/pdf/Examples\\_of\\_unethical\\_trials\\_nov\\_2006\\_NL.pdf](http://somo.nl/html/paginas/pdf/Examples_of_unethical_trials_nov_2006_NL.pdf)

<sup>82</sup> Innocent Ruwende and Nyemudzai Kakore, The Herald. 2015. EU chides Zim NGOs. Available at: <http://www.herald.co.zw/eu-chides-zim-ngos-critics/>

<sup>83</sup> New Zimbabwe. 2015. Drop "regime change agenda" NGOs urged. Available at: <http://www.newzimbabwe.com/news-19777-Drop+%E2%80%9Cregime+change+agenda%E2%80%9D,+NGOs+urged/news.aspx>

## **CHAPTER FIVE:**

# **Conclusion and recommendations**

With fifteen per cent of the adults being HIV infected, a doctor to patient ratio of 0.1 per 1,000 people, limited access to health services, medicines and health insurance, Zimbabwe faces a huge challenge to meet its population's health demands.

Clinical trials are needed to develop new and better treatments for the countries' most common diseases. It is encouraging that the clinical trials that were found in the US registry, ClinicalTrials.gov address the public health priorities of Zimbabwe: HIV, TB and Malaria.

However, the investigation of the case of Grace Mawere, the interviews with the director of MRCZ, Dr. Paul Ndebele, and public statements of senior Zimbabwean officials raise concerns about the flaws in the current system of clinical trials oversight in Zimbabwe. This may result in lack of protection of the rights of clinical trial participants due to undescribed side effects of clinical trials as is demonstrated by the case of Grace.

### **Systemic flaws**

Although Zimbabwe's laws and guidelines concerning clinical trials are based on international ethical and Good Clinical Practice guidelines, the director of MRCZ stated that the Zimbabwean authorities responsible for monitoring clinical trials are seriously underfunded. Furthermore, in a public speech the director of MRCZ, the most authoritative clinical trial oversight body, listed a number of worrying challenges such as researchers implementing unapproved studies, refusal to access sites for inspections and limited influence over research that is conducted in Zimbabwe. The flaws in the approval and monitoring process could potentially lead to violations of the rights of the trial participants. This concern emerges in the case of Grace.

## **What went wrong in the case of Grace?**

### **Several aspects of the case of Grace raise concerns**

First of all, her informed consent form did not list eyesight problems as a possible side effect even though eyesight problems are known to occur as a result of the treatment that Grace received. Secondly, the eyesight problems of Grace were apparently not reported to the MRCZ which is a violation of Zimbabwean guidelines, which says that SAEs should be reported within 48 hours. Because the health problems of Grace were apparently not reported there seems to have been no investigation by the technical committee. As a result, Grace's chances for receiving proper care and compensation were seriously compromised. Finally, not reporting SAEs during a trial may lead to incorrect reporting of the side effects of a drug.

### **The legal and moral responsibility of the sponsor**

When the Zimbabwean investigator approached the sponsor of the trial (MRC) in the UK, the representative of the sponsor said that there was no previous evidence of the medicines causing blindness. They referred the matter to the MRCZ in Zimbabwe, knowing that MRCZ had also not investigated the SAE. In the above, it has already been substantiated that the MRC could have known that the medicines used may cause blindness.

The sponsor is legally responsible for compliance of the clinical trial with Good Clinical Practice and ethical guidelines. Therefore, the MRC should have started an investigation immediately. The MRC only indicated it would start investigating after SOMO, the European Center for Constitutional and Human Rights (ECCHR) and Wemos sent a letter supporting the case of Grace. The letter was sent on Tuesday 18 November 2014. Despite several requests for response, no results of the promised investigation have been received<sup>84</sup>.

Next to the legal responsibility as a sponsor, Wemos feels that the MRC has a moral responsibility to protect the rights of vulnerable trial participants, especially because it was carrying out research in a weak health system and a flawed clinical trial oversight system. Dismissing serious health problems the way MRC did, knowing that the person making the claims most likely has limited access to health care, shows a lack of commitment to the well-being of the individual trial participant.

Neither the MRC in the UK nor the MRCZ in Zimbabwe properly investigated whether there was a causal link between the tested drugs and Grace's eyesight problems. As a result, Grace never received compensation or proper treatment. This is a clear violation of the 2012 Guidelines for Good Clinical Practice in Zimbabwe, which states that in case of adverse events sponsors should immediately undertake appropriate and necessary measures and provide treatment to protect the trial subjects.

Although this report focuses on the case of Grace, the above mentioned flaws in the system lead us to suspect that this is not an isolated incident.

## **The role of the media and civil society**

The lack of media and civil society organisations that focus on the rights of clinical trial patients means a majority of patients will remain ignorant of their rights and the violation thereof. This clearly emerges in Grace's case.

## **Recommendations**

This report wishes to provide the actors involved in drug testing in Zimbabwe, such as the MRCZ, MCAZ, RCZ, as well as civil society organisations and the media, with recommendations to reduce the number of incidents of clinical trials. In the first place, the capacity of the MRCZ should be strengthened to enable them to carry out their mandate more effectively. Secondly, the monitoring and oversight of SAE reporting should be made more robust to ensure that SAEs are properly reported and investigated. Thirdly, there has to be transparency, meaning regulators should disseminate relevant and accurate information to the public. This will also enable media to better perform its task of monitoring the regulators and write about the flaws in the system of medical research in order to raise awareness of the general population. Fourthly, civil society organisations are recommended to give more attention to clinical trials. Also, the establishment of a civil society organisation that primarily deals with the education of the general public about clinical trials, pressing for rights of trial subjects and working with media to drive this agenda, will be very important and one step along the road to protect participant's rights.

<sup>84</sup> The letter and MRC's response can be found in annex I. Wemos also shared the paragraphs in which MRC is mentioned with them before making the report public. However, MRC did not respond to this within the time given and Wemos had to proceed to publishing the report.

Finally, it is highly recommendable that the trial sponsor MRC monitors trials in vulnerable settings more closely. As a sponsor, MRC is legally responsible for assuring that SAEs are reported in a timely manner. Therefore, it is highly recommended that MRC strengthens its systems of monitoring SAE reporting. Furthermore, looking at the testimony of Grace Mawere, the fact that she stopped her second-line treatment could have been prevented if the EARNEST doctors that she interacted with had taken her complaints more seriously. Therefore, in its capacity of trial sponsor MRC should always emphasise, when interacting with those who are closely involved in the trial, that the well-being of individual trial participants must always take precedence over all other interests. The importance of clinical research cannot be overemphasised. The emergence of diseases like Ebola means clinical trials are more important than ever before. However, the rights of those participating in clinical trials are equally sacrosanct. Researchers must abide by all regulations at all times as unethical conduct in all medical research is unacceptable. The well-being and rights of individual trial participants must always take precedence over other interests.

## References

### Reports

Food and Drug Administration (FDA). 1996. Guidance for Industry. Available at <http://www.fda.gov/downloads/Drugs/Guidances/ucm073122.pdf>

Médecins Sans Frontières (MSF) Access. 2014. Out of Step-Deadly implementation gaps in the TB response. A survey of TB diagnostic and treatment practices in eight countries. Available at [http://www.msfacecess.org/sites/default/files/MSF\\_Out-of-Step\\_Final\\_for\\_printOct17\\_0.pdf](http://www.msfacecess.org/sites/default/files/MSF_Out-of-Step_Final_for_printOct17_0.pdf)

National AIDS Council. 2014. Global AIDS Response Country Progress Report. Available at [http://www.nac.org.zw/sites/default/files/Zimbabwe%20Country%20report2014\\_0.pdf](http://www.nac.org.zw/sites/default/files/Zimbabwe%20Country%20report2014_0.pdf)

PMI. 2015. Malaria Operational Plan FY 2015. Available at <http://www.pmi.gov/docs/default-source/default-document-library/malaria-operational-plans/fy-15/fy-2015-zimbabwe-malaria-operational-plan.pdf?sfvrsn=3>

SOMO & Wemos. 2006. Examples of unethical trials. Available at [http://somo.nl/html/paginas/pdf/Examples\\_of\\_unethical\\_trials\\_nov\\_2006\\_NL.pdf](http://somo.nl/html/paginas/pdf/Examples_of_unethical_trials_nov_2006_NL.pdf)

UNICEF. 2007. ZMPMS report. Available at [http://www.unicef.org/zimbabwe/ZMPMS\\_report.pdf](http://www.unicef.org/zimbabwe/ZMPMS_report.pdf)

UNICEF. National Child Survival Strategy for Zimbabwe 2010-2015. Available at [http://www.unicef.org/zimbabwe/Young\\_Child\\_Survival\\_Doc-Complete.pdf](http://www.unicef.org/zimbabwe/Young_Child_Survival_Doc-Complete.pdf)

UN Zimbabwe. 2013. Maternal Mortality in Zimbabwe Evidence, Costs and Implications. Available at [http://www.zw.one.un.org/sites/default/files/UN-ZW\\_IssuePaperSeries-1\\_MMR\\_June2013.pdf](http://www.zw.one.un.org/sites/default/files/UN-ZW_IssuePaperSeries-1_MMR_June2013.pdf)

UZ-UCSF. 2014. Twenty years of innovative research on HIV and AIDS prevention, care and treatment in Zimbabwe and globally. Available at <http://www.uz-ucsf.co.zw/wp-content/uploads/2014/03/UZ-UCSF-38.pdf>

WHO. 2014. Global tuberculosis report 2014. Available at [http://www.who.int/tb/publications/global\\_report/en/](http://www.who.int/tb/publications/global_report/en/)

## Organisations and web links

AVERT. HIV & AIDS Stigma and Discrimination.

Available at <http://www.avert.org/hiv-Aids-stigma-and-discrimination.htm>

Central Intelligence Agency (CIA). The World Factbook- Zimbabwe.

Available at <https://www.cia.gov/library/publications/the-world-factbook/geos/zi.html>

ClinicalTrials.gov. Zimbabwean Clinical Trials.

Available at <https://clinicaltrials.gov/ct2/results?term=Zimbabwe+clinical+trials&Search=Search>

Community Working Group on Health (CWGH). Post Budget Analysis for the health sector 2015 budget. Available at <http://www.cwgh.co.zw/images/budget.pdf>

Community Working Group on Health (CWGH). Consumer Action Forum Zimbabwe.

Available at [http://www.cwgh.co.zw/index.php/en/?option=com\\_content&view=article&layout=edit&id=162](http://www.cwgh.co.zw/index.php/en/?option=com_content&view=article&layout=edit&id=162)

Drugs.com. Side effects of Lopinavir Ritonavir.

Available at <http://www.drugs.com/sfx/lopinavir-ritonavir-side-effects.html>

EARNEST Study. Available at <http://earnest.cineca.org/harara.html>

Food and Drug Administration (FDA). ICH Guidance Documents.

Available at <http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/GuidancesInformationSheetsandNotices/ucm219488.htm>

Food and Drug Administration (FDA). 2014. CFR - Code of Federal Regulations Title 21.

Available at <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=50.3>

Food and Drug Administration (FDA). 2014. MedWatch The FDA Safety Information and Adverse Event Reporting Program.

Available at <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm053087.htm>

Good Clinical Practice (GCP) Education.

Available at <http://www.gcp-education.com/terminology.html>

ICH. Guidelines.

Available at <http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/good-clinical-practice.html>

MCAZ. Good Clinical Practice guidelines 2012.

Available at <http://www.mcaz.co.zw/index.php/downloads/category/14-guidelines>

Medical Research Council (MRC). 2014. EARNEST trial results.

Available at [http://www.ctu.mrc.ac.uk/news/2014/EARNEST\\_trial\\_results\\_18\\_Jul\\_2014](http://www.ctu.mrc.ac.uk/news/2014/EARNEST_trial_results_18_Jul_2014)

Medical Research Council of Zimbabwe (MRCZ). Available at <http://www.mrcz.org.zw/>

Medical Research Council of Zimbabwe (MRCZ). 2011. Ethics Guidelines for Health Research Involving Human Participants in Zimbabwe. Available at [http://www.mrcz.org.zw/index.php?option=com\\_phocadownload&view=category&download=50:ethics-guidelines](http://www.mrcz.org.zw/index.php?option=com_phocadownload&view=category&download=50:ethics-guidelines)

Multinational Monitor. Zimbabwe Bans Dangerous Contraceptive, Depo-Provera. Available at <http://www.multinationalmonitor.org/hyper/issues/1981/09/zimbabwe.html>

National Institute for Health Research (NHS). Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR). Available at <http://www.ct-toolkit.ac.uk/glossary/serious-adverse-event-sae-or-serious-adverse-reaction-sar>

PMI. President's Malaria Initiative- Fighting Malaria and Saving lives. Available at [http://www.pmi.gov/docs/default-source/default-document-library/country-profiles/zimbabwe\\_profile.pdf?sfvrsn=16](http://www.pmi.gov/docs/default-source/default-document-library/country-profiles/zimbabwe_profile.pdf?sfvrsn=16)

Public Citizen. 1997. A USA based advocacy group. Available at <http://www.citizen.org/Page.aspx?pid=2329>

Research Council of Zimbabwe (RCZ). National Research Database. Available at <http://researchdatabase.ac.zw/>

Research Council of Zimbabwe (RCZ). Registration. Available at <http://www.rcz.ac.zw/index.php/en/research-registrations/registration.html>

Reserve Bank of Zimbabwe. Inflation. Available at <http://www.rbz.co.zw/about/inflation.asp>

Robertson. Zimbabwe – An Economy on the Edge, Since 1980. Available at [http://www.economic.co.zw/index.php?option=com\\_content&view=article&id=1185:zimbabwe--an-economy-on-the-edge-since-1980&catid=111:zimbabwe-history&Itemid=557](http://www.economic.co.zw/index.php?option=com_content&view=article&id=1185:zimbabwe--an-economy-on-the-edge-since-1980&catid=111:zimbabwe-history&Itemid=557)

D. Sachan (Chemistry World). 2015. Supreme court ruling brings clinical trials to a halt in India. Available at <http://www.rsc.org/chemistryworld/2013/10/supreme-court-ruling-clinical-trials-halt-india>

Trading Economics. Zimbabwe GDP Annual Growth Rate. Available at <http://www.tradingeconomics.com/zimbabwe/gdp-growth-annual>

UNAIDS. HIV and AIDS estimates Zimbabwe. Available at <http://www.unAids.org/en/regionscountries/countries/zimbabwe>

UNDP. Available at <http://www.undp.org/mdg/>

University of Zimbabwe. Faculty of Medicine. Available at <http://www.uz.ac.zw/index.php/faculties/faculty-of-medicine>

USAID. Zimbabwe Mitigating Tuberculosis. Available at [http://photos.state.gov/libraries/zimbabwe/231771/PDFs/USAID\\_Zimbabwe\\_Mitigating\\_Tuberculosis.pdf](http://photos.state.gov/libraries/zimbabwe/231771/PDFs/USAID_Zimbabwe_Mitigating_Tuberculosis.pdf)

World Health Organisation (WHO). Abuja Declaration.  
Available at [http://www.who.int/healthsystems/publications/abuja\\_declaration/en/](http://www.who.int/healthsystems/publications/abuja_declaration/en/)

World Health Organisation (WHO). 2014. Country Cooperation Strategy Zimbabwe. Available at [http://www.who.int/countryfocus/cooperation\\_strategy/ccsbrief\\_zwe\\_en.pdf](http://www.who.int/countryfocus/cooperation_strategy/ccsbrief_zwe_en.pdf)

The World Bank. Physicians (per 1,000 people).  
Available at <http://data.worldbank.org/indicator/SH.MED.PHYS.ZS>

World Medical Association (WMA). Available at <http://www.wma.net>

World Medical Association (WMA). WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects.  
Available at <http://www.wma.net/en/30publications/10policies/b3/>

Zimbabwe Doctors for Human Rights. Available at <http://www.zadhr.org/>

Zimbabwe. Education. Available at <http://www.zimbabwe.cc/html/education-in-zimbabwe.html>

Zimbabwe Lawyers for Human Rights. Available at <http://www.zlhr.org.zw/>

Zimbabwe Ministry of Finance and Economic Development. 2015 National Budget. Available at <http://www.zimtreasury.gov.zw/>

Zimbabwe Today. Available at <http://www.zimbabwetoday.org/>

Zimstat. 2011. Zimbabwe National Health Profile 2011.  
Available at [http://www.zimstat.co.zw/dmdocuments/Health/ZNHP\\_2011.pdf](http://www.zimstat.co.zw/dmdocuments/Health/ZNHP_2011.pdf)

## **Media Sources**

Aljazeera. 2014. Zimbabwe's maternal mortality crisis. Available at <http://www.aljazeera.com/indepth/features/2014/02/zimbabwe-maternal-mortality-crisis-20142561739198301.html>

Bulawayo. 2014. Doctors go on strike.  
Available at <http://bulawayo24.com/index-id-news-sc-health-byo-56050.html>

Chronicle. 2014. PSC drags feet on nurse recruitment.  
Available at <http://www.chronicle.co.zw/psc-drags-feet-on-nurse-recruitment/>

Daily News. 2014. 10% Zimbabweans on medical insurance. Available at <http://www.dailynews.co.zw/articles/2014/01/24/only-10pc-zimbabweans-on-medical-insurance>

Financial Gazette. 2013. Specialist Shortage Hits Public Hospitals.

Available at <http://www.financialgazette.co.zw/specialist-shortage-hits-public-hospitals/>

The Guardian. 2012. Bad Pharma review.

Available at <http://www.theguardian.com/books/2012/oct/17/bad-pharma-ben-goldacre-review>

Herald. 2014. Doctors end strike. Available at <http://www.herald.co.zw/doctors-end-strike/>

Herald. 2014. EU chides Zim NGOs, critics, authors Innocent Ruwende and Nyemudzai Kakore.

Available at <http://www.herald.co.zw/eu-chides-zim-ngos-critics/>

Herald. 2014. Health Budget falls short of Abuja target.

Available at <http://www.herald.co.zw/health-budget-falls-short-of-abuja-target/>

The Independent. 2014. Doctors Strike; Holistic approach badly needed.

Available at <http://www.theindependent.co.zw/2014/11/17/doctors-strike-holistic-approach-badly-needed/>

The Independent. 2014. Workers Still Earning below PDL.

Available at <http://www.theindependent.co.zw/2014/08/29/workers-still-earning-pdl/>

IRIN. 2014. Zimbabwe's health system in crisis.

Available at <http://www.irinnews.org/printreport.aspx?reportid=100474>

News. 1999. Doctor sentenced for culpable homicide. Available at <http://www.ipsnews.net/1999/03/health-zimbabwe-doctor-sentenced-for-culpable-homicide/>

Newsday. 2013. Zimbabwe's economy during the life of the coalition government.

Available at <https://www.newsday.co.zw/2013/09/05/zimbabwes-economy-life-coalition-government/>

Newsday. 2014. Shortage of essential drugs hits public hospitals.

Available at <https://www.newsday.co.zw/2014/07/24/shortage-essential-drugs-hits-public-hospitals/>

New Zimbabwe. 2015. Drop "regime change agenda", NGOs urged.

Available at <http://www.newzimbabwe.com/news-19777-Drop+%E2%80%9Cregime+change+agenda%E2%80%9D,+NGOs+urged/news.aspx>

Telegraph. 2008. Zimbabwe's cholera epidemic hits 10,000.

Available at <http://www.telegraph.co.uk/news/worldnews/africaandindianocean/zimbabwe/3536824/Zimbabwes-cholera-epidemic-hits-10000.html>

Telegraph. 2008. Zimbabwe inflation hits 231 million per cent.

Available at <http://www.telegraph.co.uk/news/worldnews/africaandindianocean/zimbabwe/3167379/Zimbabwe-inflation-hits-231-million-per-cent.html>

Zimeye. 2013. HIV cure not illegal.

Available at <http://www.zimeye.org/breakthrough-hiv-herbal-cure-not-illegal-in-zimbabwe/>

The Zimbabwean. 2010. Gweru hospital overstocked with expired drugs.

Available at <http://www.thezimbabwean.co/news/31025/gweru-hospital-overstocked-with-expired-drugs.html>

Zimbabwe Online. 2014. MPs Unearth Expired Drugs At Byo Hospitals.

Available at <http://zimbabweonlinenews.com/%EF%BB%BFmps-unearth-expired-drugs-at-byo-hospitals/>

### **Scholarly articles**

Mbizvo, M.T., Fawcus, S., Lindmark, G., & Nystrom, L. 1993. Maternal mortality in rural and urban Zimbabwe: social and reproductive factors in an incident case-referent study. *SocSci Med* 36(9). 1197- 1205

Silverio, A. HIV Research in Africa. *The Stanford Journal of International Relations*.

Available at [http://web.stanford.edu/group/sjir/3.2.05\\_silverio.html](http://web.stanford.edu/group/sjir/3.2.05_silverio.html)

Wendler, D., Krohmal, B., Emanuel, E. J., & Grady, C. 2008. Why patients continue to participate in clinical research. *Archives of Internal Medicine*, 168 (12), 1294-1299.

Available at <http://www.cphiv.dk/LinkClick.aspx?fileticket=HufTtug3jRM%3D&portalid=0>

## Annex I

# Letter to the MRC



Medical Research Council



Date  
18 November 2014

Page  
1/3

Email address  
diana.hoefake@wemos.nl

Subject  
EARNEST trial Zimbabwe

Dear [REDACTED],

We, the European Center for Constitutional and Human Rights (ECCHR), SOMO and Wemos, advocate the protection of the rights of vulnerable clinical trials participants.<sup>1</sup> As such we were approached by the Zimbabwean investigative journalist Mr. Terence Zimwara, who brought to our attention a case of a participant who became partially blind during her participation in the EARNEST trial in Zimbabwe. We are concerned about the lack of response and appropriate action on this case by the responsible actors of the EARNEST trial.

As we find the case both well documented and the alleged violations serious, we now turn to you as Medical Research Council (MRC), the sponsor of this trial. In the following letter we have outlined our main concerns. We hope you will give this consideration and take consecutive steps to address the case.

According to the investigation of Mr. Terence Zimwara, one of the participants, [REDACTED], who participated in the trial from October 2010 until August 2013, allegedly became partially blind during the course of the EARNEST trial. According to the investigation<sup>2</sup> of Mr. Zimwara, hospital records indicate that [REDACTED] had eyesight problems. Disturbingly, these problems were not mentioned in the clinical report, which was signed by [REDACTED]. While [REDACTED] was not informed of such risks, the NHS mentions eye and eyesight problems as side effects of Lopinavir/Ritonavir.<sup>3</sup> These drugs were part of the treatment administered to [REDACTED] by EARNEST at the University of Zimbabwe Clinical Research

<sup>1</sup> Wemos is a global health advocacy organization that has been advocating the protection of vulnerable clinical trial participants for the last 10 years. The European Center for Constitutional and Human Rights (ECCHR) is an independent, non-profit legal organization dedicated to protecting civil and human rights. SOMO is an independent, non-profit research organization that has published several reports on the ethics of drug testing in low- and middle-income countries.

<sup>2</sup> The report of the investigation of Mr. Zimwara can be found in the annex.

<sup>3</sup> <http://www.nhs.uk/medicine-guides/pages/MedicineSideEffects.aspx?condition=HIV%20infection&medicine=Lopinavir/Ritonavir&preparation=>

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Center. However, at the start of the trial, ██████ was not aware of this risk, since eye problems were not mentioned as one of the potential side effects in the informed consent form.

When Mr. Zimwara contacted the MRC, the senior press officer ██████ said that there is no previous evidence of the medicines causing blindness. Furthermore, she advised the participant to bring the matter to the attention of the Medical Research Council of Zimbabwe. At the same time, according to ██████, the EARNEST trial operates within the bounds of the International Conference (ICH) on harmonization Guidelines for Good Clinical Practice.

Even though the trial is conducted in Zimbabwe, the MRC, as the sponsor of the EARNEST trial, maintains its legal obligations in accordance with the ICH Good Clinical Practice Guidelines.<sup>4</sup> The delegation of certain tasks does not release the sponsor from its responsibilities.<sup>5</sup> This includes the obligation to ensure that adverse events are properly reviewed and timely notified to the relevant authorities.<sup>6</sup> A similar obligation is codified in the Serious Adverse Events Reporting manual for clinical trials in Zimbabwe. Notably, permanent disabilities have to be reported even if a relationship with the investigational product is not established.<sup>7</sup>

According to the Guidelines for Good Clinical Practice in Zimbabwe (2012), a serious adverse event, such as the loss of eyesight, has to be reported to the MCAZ authorities within 48 hours after the site becomes aware of the event. However, according to the investigation by Mr. Zimwara this has not been the case, which means that this trial violated Zimbabwean regulations.

**We find that in order to ascertain that Good Clinical Practice and ethical guidelines were properly implemented MRC should have investigated the allegations or should have seen to it that MRC Zimbabwe investigated the allegations. These steps are essential to establish side effects of the administered treatment and to ascertain whether the participant is eligible to receive compensation.**

The informed consent form mentions that compensation will be provided in the event of injury if the claim for compensation is found to be justifiable. Despite repeated requests for assistance by ██████ to the EARNEST staff, including the study coordinator ██████ and even though an optometrist at the Sekuru Kaguvi Eye Unit at the Parirenyatwa Group of Hospitals indicated a causal link between the clinical trial and the loss of eyesight<sup>8</sup>, the case of ██████ has not been properly examined by MRC. As a result, ██████ never received compensation or proper treatment. This violates the Guidelines for Good Clinical Trial Practice in Zimbabwe (2012), according to which in the case of adverse events sponsors should immediately undertake appropriate and necessary measures and treatment to protect the trial subjects.<sup>9</sup> Moreover, sponsors should ensure the availability of

<sup>4</sup> Section 5.2

<sup>5</sup> Guidelines for Good Clinical Trial Practice in Zimbabwe (2012), section 7.3.

<sup>6</sup> Section 5.1

<sup>7</sup> Page 4 of the Manual.

<sup>8</sup> According to ██████ testimony.

<sup>9</sup> Section 7.15

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healthcare services that are essential to the safe conduct of the research and treatment of subjects who suffer injury as a consequence of research intervention.<sup>10</sup>

MRC failed to establish whether the injury was trial related or not, even though visual impairment was more recently listed by the manufacturer as an adverse reaction in earlier clinical trials.<sup>11</sup> In addition, it is assumed that in concordance with the ICH Good Clinical Practice<sup>12</sup> and the relevant legislation in Zimbabwe,<sup>13</sup> MRC has ensured the relevant insurance in the case of injuries sustained during the trial. The information provided in the consent form – that compensation would be provided in the event of injury – thus turned out to be an empty promise, as it was never investigated if the claim was justifiable.

On 6 April 2014, the 24-year old ██████ passed away leaving a one-year old child to the care of her grandmother. Based on our description of the case of ██████, we kindly request you to investigate the case and consider ways to compensate the relatives. In addition, we find that further evaluations are needed to improve the current system of adverse event reporting and providing compensation. We would like to urge the MRC to take action to prevent similar failures in the future. The protection of the rights, safety and wellbeing of the trial participant is paramount and should in all cases guide the decisions taken in the process of conducting, reviewing and monitoring future clinical trials.

Thank you for your attention to this important clinical trial issue. Please contact us if you have any questions or need additional information. We further request to be informed of the steps that you take to address this case.

Sincerely,

MSc. Annelies den Boer  
*Wemos*

MSc. Diana Hoeflake  
*Wemos*

Dr. Carolijn Terwindt  
*European Center for Constitutional and Human Rights*

MSc. Irene Schipper  
*Centre for Research on Multinational Corporations (SOMO)*

<sup>10</sup> Guidelines for Good Clinical Trial Practice in Zimbabwe (2012), section 7.18 which refer to Guideline 21 of the International Ethical Guidelines for Biomedical Research involving Human Subjects (CIOMS 2002).

<sup>11</sup> See table 4, Adverse Reaction of Moderate or Severe Intensity Occurring in at Least 0.1% of Adult Patients Receiving KALETRA in Combined Phase II/IV Studies (N=2,612) in: highlights of Prescribing Information Kaletra, November 2013, <http://www.rxabbvie.com/pdf/kaletratabpi.pdf> [Accessed 22 Oct. 14].

<sup>12</sup> ICH Good Clinical Practice, section 5.8.1

<sup>13</sup> The Medicines and allied substances control act, Chapter 15, section 21(1)b. In addition, section 7.13 of the Guidelines for Good Clinical Trial Practice in Zimbabwe (2012) specifies that the sponsor policies and procedures should address the costs of

## MRC's e-mail response to the letter sent to them by Wemos, ECCHR, and SOMO

- 13 April 2015:

*"I am afraid there has been a fire near our London Office and we have not been able to access the building since before Easter. A reply should be with you later this week."*

- 2 March 2015:

*"I am sorry this is taking a lot longer than I expected. We decided to have an independent corroboration of the report we received from the trial site, and expect to have this later this week."*

- 24 December 2014:

*"As you know, [...] asked me to look into the points raised in your letter.*

*I am writing to let you know that I am indeed doing so. Now that we have the participant's name we are in a position to investigate what happened, but this is taking longer than anticipated.*

*I hope that [...] will be able to reply more fully in January."*

- 5 December 2014:

*"Thank you for your email of the 3rd December – although the email you planned to send on the 18th November seems to have been correctly addressed, we cannot find it in our inbox so please accept my apologies, but the first I knew of your enquiry was on December 3rd.*

*I have passed the material to MRC's Corporate Affairs Group so that we can consider the issues you raise and respond accordingly. With thanks."*

## COLOPHON

This publication, written by the independent investigative journalist Terence Zimwara, is supported by the Medicines project of Wemos. The research has been conducted by Terence Zimwara. Wemos verified the results of the research, described in this report, to the extent possible. We trust the journalist's competence for interpreting the information derived from the interviews. Wemos is not responsible for any misinterpretations that may have been made in this report.

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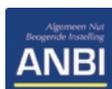
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