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Industry-sponsored clinical drug trials in Egypt: ETHICAL QUESTIONS IN A CHALLENGING CONTEXT

CONTENTS

Executive summary	3
Abbreviations	5
Introduction	7
Methodology	9
1 Overview of industry-sponsored clinical drug trials in Egypt	11
2 The environment for clinical drug trials in Egypt	19
3 The conduct of trials in Egypt	23
4 Hepatitis C drug trials in Egypt	31
5 Cancer drug trials in Egypt	37
6 Affordability and accessibility of medicines tested in industry-sponsored clinical drug trials in Egypt	44
7 Upholding international ethical standards for clinical trials in Egypt	49
8 Recommendations	52
Appendix: List of experts interviewed for this research	55
References	57

A joint study by Public Eye (formerly Berne Declaration), Centre for Research on Multinational Corporations (SOMO), Wemos Foundation, Egyptian Initiative for Personal Rights and Shamseya for Innovative Community Healthcare Solutions

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EXECUTIVE SUMMARY

The past 20 years have seen a considerable shift in the location of clinical drug trials sponsored by transnational pharmaceutical companies (TNCs), with a significant expansion of such tests being conducted in low- and middle-income settings. This increased offshoring may result in serious ethical violations as highlighted by several recent field investigations and media reports.

An attractive research infrastructure, a fast-growing and largely treatment-naïve population, and lower costs make Egypt among the most popular places in the Middle East and Northern Africa (MENA) region for offshoring medicine testing. Egypt is second only to South Africa on the African continent in terms of the number of TNC-sponsored clinical trials it hosts.

At the same time, a large part of Egypt's population is struggling with daily access to essential medicines. Half of Egyptians have no health insurance and out-of-pocket payments represent nearly 72 per cent of total expenditure on health. The absence of comprehensive insurance coverage and the high cost of treatment to be borne by poor patients should be a red flag for a clinical trial environment: it leads to the unwanted and unethical situation that vulnerable people are joining a clinical trial just to have access to treatment, even though the results may be uncertain. This kind of environment exposes vulnerable people to being exploited as trial participants.

Of the 57 international drug trials that were active in Egypt in February 2016, over half were cancer trials. The two Swiss giants Novartis and Roche are responsible for almost 50 per cent of the international drug trials taking place in the country. The Arab spring events of early 2011 and the subsequent political unrest had no chilling effect on the number of active international drug trials – on the contrary.

The vast majority are late-stage clinical trials related to products already licensed in high-income countries, in accordance with Egypt's regulatory requirement that no foreign drug trial can be conducted in Egypt unless the product being tested has been granted market approval in the originating country. However, 16 per cent are Phase I and Phase II trials, raising ethical issues as to the relevance and benefit of these trials for the Egyptian population since tests on these medical products have already been completed elsewhere for marketing approval in a high-income country.

To protect clinical trial participants, and especially to protect vulnerable people, a robust legislative framework with functioning independent control systems is a prereq-

uisite, but this is clearly not present in Egypt. A fundamental flaw in the Egyptian system of clinical trials is the absence of comprehensive unified legislation. This means that there is no clear guidance to those bodies charged with overseeing clinical trials or to those stakeholders involved in executing clinical trials, leaving room for different interpretations and making it more difficult to identify violations and impose sanctions.

Egypt has the highest prevalence of viral hepatitis C in the world, and was the first low- or middle-income country in 2014 to negotiate preferential pricing for the new direct acting antiviral (DAA) treatment sofosbuvir (Sovaldi®) with manufacturer Gilead. However the deal (US\$

The absence of a comprehensive insurance coverage and the high cost of treatment lead to the unethical situation that vulnerable people are joining a clinical trial just to have access to treatment.

300 per month of treatment instead of US\$ 84,000 in the US) was criticised for its opacity. Egypt has a vibrant generic industry selling hepatitis C drugs at a fraction of the cost of DAAs produced by TNCs. The “Sovaldi deal” generated diverging opinions among Egyptian experts interviewed as to whether the state-subsidised free treatment programme is, in fact, a disguised clinical trial of national scale. Since hepatitis C is a public health priority and given that the state plays an important role in subsidising treatments, the issue of post-trial access and availability/affordability of treatments is probably less acute than, for example, those for cancer medicines. In quantitative terms, the number of active hepatitis C trials is much lower (about one-sixth) than the number of cancer trials.

This study interviewed more than 30 Egyptian experts as well as a dozen clinical trial participants and analysed several TNC-sponsored cancer drug trials that are or have been conducted in Egypt. Some of these cancer trials were deemed problematic from an ethical point of view, such as through depriving patients of best proven treatment, testing medicines that were not yet registered in

high-income countries, off-label use, unclear specific protection mechanism for vulnerable participants, no post-trial treatment access mechanisms. International experts raised doubts about the scientific validity of the designs of several cancer trials described in the report. Most of the

This study brings new evidence that unethical practices occur in Transnational pharmaceutical corporation sponsored clinical trials conducted in Egypt.

experimental cancer drugs were high-cost treatments, and it is unclear how these will be affordable for Egyptian patients if proven effective and safe.

This study brings new evidence that unethical practices occur in TNC-sponsored clinical trials conducted in Egypt, and that drugs tested in Egypt are not systematically available to and mostly unaffordable for the Egyptian population. This contravenes with the highest ethical standards such as the Declaration of Helsinki or the Council for International Organisations of Medical Sciences (CIOMS) Guidelines.

Both guidelines stress the importance of sharing the benefits of the research with the population where the clinical trials were carried out. This study shows that only a small amount of medicines tested in Egypt were approved for marketing in the country—contrary to higher-income countries. Even if the medicines are available on the Egyptian market, their cost often exceeds the financial capacity of most families. A monthly treatment with some of the medicines surveyed costs more than 20 times the official monthly public sector minimum wage. A large percentage of the medicines are also not dispensed by the Programme for Treatment at the Expense of the State, which often represents the last chance for uninsured people to get access to costly treatments.

Companies reviewed in this report were invited to comment before publication.

The authors of this report call on transnational pharmaceutical companies to fulfil their corporate responsibility to respect human rights as enshrined in the United Nations Guiding Principles on Business and Human Rights (UNGP) unanimously endorsed in 2011. When engaging in clinical trials in low- and middle-income countries with limited access to treatment, they should ascertain that the safety and rights of participants are properly protected and that their practices are in line with the highest ethical standards. They should also make sure that the medications tested in those countries are available at an affordable price.

Before granting a drug market authorisation, EU and Swiss regulatory authorities should demand a justification from the relevant pharmaceutical company as to why vulnerable populations were involved in a clinical trial and should ask which provisions the trial sponsor took to adequately protect these vulnerable participants. It is the responsibility of the European Medicines Agency and Swissmedic to ascertain that the same standards regarding clinical trials are complied with both within and outside their jurisdictions as data that serve for marketing authorisations in Europe are increasingly global. Furthermore, before granting market authorisation, European regulatory authorities should ascertain whether the trial sponsor has made adequate provisions for post-trial treatment access for participants in Egypt. Finally, this report's findings and conclusions justify an increase of inspections of clinical trials in Egypt by European Regulatory Authorities.

Egyptian authorities should develop a single, robust legislative framework with a functional independent control system that takes the Declaration of Helsinki and the CIOMS Guidelines as their reference point for ethical standards. Clinical research should be looked upon as a means to produce socially valuable knowledge that may or may not lead to new treatment plans. This change of mindset is key in a country where the state of the health-care system and costs make the pool of potential participants particularly vulnerable. This creates an increased likelihood of being wronged or of incurring additional harm, particularly in light of Egypt's deficient regulatory functions and lack of awareness and enforcement of patients' rights. Egyptian authorities should also create an online, regularly updated public registry of clinical trials conducted in Egypt. Ensuring access to information must be guaranteed as it is a fundamental prerequisite to enable civil society to play its role in signalling and unveiling unethical clinical trials practices.



With a population of 90 million, Egypt has a large pool of patients and a diverse range of diseases. These factors have driven the expansion of international clinical research into the country.

ABBREVIATIONS

ABS	Access and Benefit Sharing	IMF	International Monetary Fund
BD	Berne Declaration (CH), (Public Eye since Sep. 2016)	IRB	Institutional review board
CIOMS	Council for International Organizations of Medical Sciences	LI	Liver Institute
CRO	Contract research organisation	LMIC	Low- and middle-income countries
DAA	Direct acting antiviral	MAA	Marketing Authorisation Application
DOH	Declaration of Helsinki	MENA	Middle East and North Africa
EDA	Egyptian Drug Authority	MeSH	Medical Subject Headings
EGP	Egyptian pounds	MOH	Ministry of Health (EG)
EIPR	Egyptian Initiative for Personal Rights	MP	Member of Parliament
ENREC	Egyptian Network of Research Ethics Committees	NCCVH	National Committee for the Control of Viral Hepatitis (EG)
EMA	European Medicines Agency (EU)	NGO	Non-governmental organisation
EU	European Union	NRC	National Research Centre (EG)
FDA	Food and Drug Administration (US)	PCR	Polymerase Chain Reaction
GCP	Good clinical practice	PTA	Post-trial access to treatment
GDP	Gross Domestic Product	PTES	Program for Treatment at the Expense of State (EG)
GNI	Gross National Income	REC	Research Ethics Committee
HCV	Hepatitis C Virus	TNC	Transnational corporation
HIO	Health Insurance Organisation (EG)	SOMO	Centre for Research on Multinational Corporations (NL)
HIV	Human Immunodeficiency Virus	US NIH	United States National Institutes of Health
ICH	International Conference on Harmonisation	Wemos	Wemos Foundation (NL)
INN	International non-proprietary name	WHO	World Health Organization



Clinical drug trials are increasingly being carried out in low- and middle-income settings. Egypt is one of the most popular places for offshoring medicine testing in the Middle East and North Africa region.

INTRODUCTION

The past 20 years have seen a considerable shift in the location of industry-sponsored clinical drug trials. Until the 1990s the vast majority of testing of medicines on humans was carried out in high-income countries (the USA, western European countries, Japan). However, these tests are now increasingly being carried out in low- and middle-income settings.

As well as less stringent regulations for the conduct of clinical trials in these countries, strategic and economic factors – including the need for diverse patient populations for research, lower trial costs, a large pool of willing participants and access to new and potentially large markets – have driven the expansion of international clinical research into low- and middle-income settings.¹

The authors of this report are concerned about the increased offshoring and/or outsourcing of industry-sponsored clinical drug trials to low- and middle-income countries that result in serious ethical violations. Various field investigations gathering anecdotal evidence of unethical clinical trials have been published in recent years, highlighting the persistence of systemic regulatory loopholes and ethical oversight weaknesses that threaten the protection of vulnerable participants, i.e. in Russia,² Ukraine,³ Argentina,⁴ South Africa,⁵ Zimbabwe,⁶ Kenya⁷ and India.⁸

This report focuses on clinical drug trials since populations in countries hosting the trials are often faced with limited access to health care, and in particular, to medicines. Access to medicines as a human right is a core activity of all non-governmental organisations (NGOs) involved in this research. While there may be ethical issues and wrongdoings involved with academic trials too, this report focuses on industry-sponsored trials, since they represent the majority of drug trials (90 per cent according to sources).⁹ In addition, industry-sponsored clinical trials are often used for marketing authorisation purposes, thus introducing a commercial dimension of time pressure and additional risks of manipulation.

WHY FOCUS ON EGYPT?

We decided to focus on Egypt because it is the second biggest destination country for clinical trials in Africa (after South Africa). According to the United States National Institutes of Health (US NIH) Database, Egypt is also among the most popular places for offshoring medicine testing in the Middle East. Unlike other emerging countries such as Russia or China, Egypt does not make it compulsory to

have clinical trials conducted in-country on their population before marketing approval is granted.

Considering Egypt's recent history and current political situation (the Arab Spring, the ousting of President Hosni Mubarak and of his successor Mohamed Morsi), we might have expected the number of foreign drug trials to have fallen in recent years. However, international as well as national statistics tell a different story (see Chapter 1).

It could also be assumed that running complex international drug trials in such a context would be risky, not least because of the limited and fragmented legislative framework covering clinical research in Egypt. With a significant proportion of people living in poverty, and a public health insurance system that covers only half of the population, Egyptians face problems accessing medicines. Both these factors potentially expose vulnerable people to exploitation as trial participants because of insufficient public awareness and lack of monitoring by competent authorities.

New cancer and Hepatitis C treatments hitting the market over the last two or three years have sparked heated debates about their exorbitant prices. This, and the fact that Egypt faces the world's highest prevalence of Hepatitis C and an increasing burden of non-communicable diseases (particularly cancers) has led researchers to place a stronger focus on these two categories of diseases and related clinical trials.

The authors of this new study want to provide additional anecdotal evidence that increased ethical scrutiny is needed at the European level during the marketing authorisation processes, as clinical drug trials conducted in developing and emerging countries are often used to gain this authorisation. However, if clinical trials are conducted outside the EU and submitted as part of an application for marketing authorisation within the EU, they must follow the principles enshrined in European Union (EU) law and regulations¹⁰ in relation to the rights and safety of trial participants and the reliability of data generated in the trial.

The violation of these international ethical guidelines has been highlighted in earlier reports by the current authors (see endnotes 2 to 8). These reports made EU regulatory authorities realise and acknowledge that they have a duty to identify clinical trials that may have prompted special ethical concerns regarding the inclusion of vulnerable populations, and where necessary seek assurance that the inclusion of such populations was justified and that their rights and welfare were protected.¹¹

This report also intends to raise awareness and spark changes in Egypt to strengthen and clarify the regulatory and legislative frameworks that govern clinical trials con-



Patient's files at a clinical research facility in Cairo.

ducted in-country, in particular those sponsored by multinational corporations.

The authors of this report regard international ethical guidelines such as the Declaration of Helsinki (DOH) and the Council for International Organizations of Medical Sciences (CIOMS) Guidelines as the leading definitions of ethical practices in the conduct of clinical trials. A core ethical standard is the requirement that a trial should benefit the population where the trial is conducted.¹² Other core aspects concern: the right to continued treatment once a trial is over, also known as the right to post-trial access to treatment (PTA);¹³ the capability and opportunity of participants to give informed consent voluntarily;¹⁴ and the unacceptability of the use of placebos when proven interventions exist.¹⁵

CIOMS guidelines were developed specifically to guide the conduct of biomedical research in developing countries. This is reflected in the description of the general ethical principles, which include the statement that “the research project should leave low-resource countries or communities better off than previously or, at least, no worse off. It should be responsive to their health needs and priorities in that any product developed is made reasonably available to them, and as far as possible leave the population in a better position to obtain effective health care and protect its own health.”¹⁶

Another very relevant provision for low-resource countries is the section on research involving vulnerable persons, which states that “special justification is required for inviting vulnerable individuals to serve as research subjects and, if they are selected, the means of protecting their rights and welfare must be strictly applied.”¹⁷

However, pharmaceutical companies and regulatory authorities usually rely on the Good Clinical Practice Guidelines that were developed in 1996 by the International

Conference on Harmonisation (ICH GCP).¹⁸ These guidelines are currently being revised to “encourage implementation of improved and more efficient approaches to clinical trial design, conduct, oversight, recording and reporting while continuing to ensure human subject protection and data integrity”. They are also being enlarged to include Canada and Switzerland as far as adopting the same unified standards of mutual acceptance of clinical data by the regulatory authorities in these jurisdictions is concerned.¹⁹ While ICH GCP Guidelines are transposed into many national legislations – including in some low- and middle-income countries – the authors believe the ICH GCP Guidelines are less stringent than the Declaration of Helsinki and the CIOMS Guidelines as far as ethics of clinical trials in low- and middle income countries are concerned, in particular regarding the use of placebo and PTA obligations. In addition, the ICH GCP Guidelines have been heavily influenced by corporate interests and designed for wealthy environments as they were initially co-developed by the regulatory authorities and the pharmaceutical industry of Europe, Japan and the US.²⁰

In response to these concerns, the authors of this report aim to answer the following four research questions in this report:

1. Is Egypt attractive for industrial sponsors despite the unstable political context?
2. Do unethical practices occur in industry-sponsored clinical trials conducted in Egypt?
3. Are drugs tested in Egypt also available and affordable for the Egyptian population?
4. Is there a need for increased ethical scrutiny at the European level if pivotal clinical trials for an EU or Swiss marketing authorisation process were conducted in Egypt?

METHODOLOGY

This research builds on three main components:

- A field study carried out in Egypt to gather contextual elements and conduct interviews
- A desk study including the critical analysis of some clinical trials
- A review process involving pharmaceutical companies

1. THE FIELD STUDY

The field study is mainly based on the work of two Egyptian researchers: journalist Alyaa Abo Shahba and drug policy expert Heba Wanis. They also received support from two Egyptian NGOs – Shamseya for innovative community healthcare solutions and the Egyptian Initiative for Personal Rights (EIPR).

Shahba has vast experience of investigating Egypt's health system. She interviewed participants and other relevant actors countrywide, including researchers (principal investigators), academics, company representatives and members of ethics committees.

Wanis, an Egyptian public health expert and researcher with multiple advocacy groups, served as field study supervisor and contributed to the contextual elements of the research. She coordinated meetings with several experts and academics, and helped edit the field research findings.

The field study was coordinated by Public Eye (former Berne Declaration). A steering committee consisting of representatives of SOMO, Wemos and BD assisted with technical issues and monitored the field study's progress. The fieldwork took place between June 2015 and March 2016.

Interviewees were selected based on their knowledge and expertise in the field of clinical trials in Egypt. Finding these sources was not easy, since publicly available information on clinical trials is very sparse and many health professionals refused to talk about these trials. While the political situation made the research challenging, researchers were nevertheless able to talk to more than 30 Egyptian experts (listed in Appendix 1) and around 12 participants in clinical trials.

The researchers selected an environment in which interviewees felt safe. Most interviews were conducted at hospitals or private clinics, while some took place in private homes. In some cases interviewees wished to speak only if their names and/or job titles were not stated in the report. In those cases, anonymity was granted.

Non-profit Egyptian organisations – including EIPR and Shamseya – provided inputs, contributed additional

research and provided an expert review of the document. They are also supporting the dissemination of the study and will communicate its results to relevant stakeholders.

A survey of the status of marketing approval – and availability and affordability of selected, locally tested medications – was conducted in Egypt by Shamseya. The dates of marketing approvals were obtained via the online drug database tool provided by the Egyptian Drug Authority.²¹ Attempts to directly contact EDA and sponsor companies where clarifications were needed have been unsuccessful (no response). Prices were obtained on this by contacting two small pharmacies, one chain of pharmacies (Seif Pharmacies) and one online pharmacy.²²

2. THE DESK STUDY

SOMO, Wemos and BD undertook the desk study, which took place throughout the study period up to the finalisation of the report. The conclusions and recommendations are the sole responsibility of the organisations co-sponsoring this report.

The desk study comprised an inventory of industry-sponsored clinical trials in Egypt of all types of medicines active before the study started (August 2014), at the beginning of the study (March 2015) and towards the end of the study (February 2016), in order to capture the dynamics of international clinical trial activity in Egypt. In addition, a shortlist of completed Hepatitis C and cancer drug trials that took place recently in Egypt was discussed prior to the field study. The inventory of all active trials was used as a guiding tool for the field study.

In order to identify clinical trials in Egypt, the authors made use of the US NIH Database.²³ This database is probably not exhaustive but is considered by many experts as one of the most comprehensive web-based resources accessible to the public free of charge. Information on this database is provided and updated by the sponsors or principal investigators of the studies.

Since Egypt does not have a public registry of clinical trials, it was not possible to cross-check the information obtained. Nor were we able to cross-check the US NIH Database information with data appearing on individual corporate databases, as these do not form part of the clinical trials' primary registries recognised by the World Health Organization (WHO).²⁴ Some industry-sponsored international clinical trials conducted in Egypt may thus have been missed.

The various listings of clinical trials were established using the “advanced search” tool of the US NIH Database and selecting “Egypt” in the location field. Additional filters – such as study type (interventional), recruitment status (open studies + active, not recruiting) and funder type (industry) – were also used.

During the desk study, we asked independent experts to provide comments on some of the international trials taking place in Egypt. Their comments were based on analysis of the US NIH Database sheet only, and focused on the ethical aspects, scientific relevance and methodological designs of related trials. These experts included experienced oncologists, public health specialists or members of ethical review committees in Switzerland, the Netherlands, Canada and India. They are listed in Appendix 1.

3. REVIEW PROCESS INVOLVING PHARMACEUTICAL COMPANIES

The pharmaceutical companies Roche and Novartis were approached for an interview at headquarters level by the researchers, since they are responsible for conducting most industry-sponsored clinical trials in Egypt. An inter-

view with Roche took place in Cairo on 17 February 2016, while Novartis did not respond to the authors’ request. Other pharmaceutical companies, including contract research organisations (CROs), were approached at the national level during the field study. The companies quoted in this report (based on interviews) or whose trials were subject to a critical analysis by the authors of this report were given the opportunity to review a draft of the related sections and to provide comments and corrections of factual errors. Quotes of companies found in public sources such as newspapers or information originating from public clinical trial databases (US NIH) were not subject to review. The following companies were approached for review: Pfizer, Roche, AstraZeneca, Sanofi and AbbVie. Roche, AstraZeneca, AbbVie and Sanofi have made use of this opportunity and provided comments that have been incorporated in the final version of this report. As a result of the review process some parts were adjusted or have been removed. During the review process, Pfizer Egypt has distanced itself from their quotes in the report. We decided to remove them at their request, but kept the critical analysis of a Pfizer clinical trial which is based on information from public records. Pfizer did not comment on the latter issue, despite several requests.

Patrick Durisch (Public Eye, formerly Berne Declaration), Alyaa Abo Shaba and Irene Schipper (SOMO) interview Dr Magd Kotb from Abul-Rish Children’s Hospital (Cairo University) about clinical trials in Egypt.



1 OVERVIEW OF INDUSTRY-SPONSORED CLINICAL DRUG TRIALS IN EGYPT

A REGIONAL PERSPECTIVE

Egypt is part of the Middle East and North Africa (MENA) region, which comprises about 20 countries and extends from Morocco to Iran, and is home to 385 million people – 6 per cent of the world's population.²⁵

In 2011 the MENA region was considered to be one of the fastest growing economic blocs in the world.²⁶ However, today the World Bank paints the picture of a region where economic growth is stagnating because of low oil prices, conflict and the global economic slowdown.²⁷ Growth in MENA was expected to be about 2.9 per cent in 2015, slightly higher than 2014 but considerably below the 4–5 per cent enjoyed by the region between 2000–2010.²⁸

MENA's significant and rapid economic growth since the start of the new century has resulted in significant investments in health care, and modern hospitals using state-of-the-art equipment. In 2012 the MENA pharmaceutical market represented between 1.5–3 per cent of global pharmaceutical sales. The IMS Institute for Healthcare Informatics projected this market would continue to grow by 9–11 per cent over the next five years, in line with Asia and Latin America.²⁹ Several countries of the MENA region (Saudi Arabia, United Arab Emirates, Egypt, Algeria) are listed among the top 20 emerging pharmaceutical markets, the so-called “pharmerging countries”, according to the IMS Institute.³⁰

Clinical drug trials are on the rise in low- and middle-income countries, and the MENA region is no exception.³¹ Statistics show a 4 per cent rise in the total number of drug trials conducted in the region between 2006 and 2010 – the largest increase in any region of the world. In contrast, the number of drug trials in North America decreased by 11 per cent during the same period.³² A recent survey carried out on more than 1,500 consumers and nearly 600 physicians by the Memorial Sloan Kettering Cancer Center in the US shows that “65% of Americans would not enrol in clinical trials over concerns they would experience side effects, encounter higher costs, or receive a placebo instead of an actual medicine”.³³ The survey also found that even a majority of physicians (62 per cent) were unsure or indifferent about the extent to which participation in a clinical trial would benefit patients.

Clinical trials cost significantly less in MENA countries (about half) compared to the average cost of US\$ 300 million for a clinical trial in the US.³⁴

In recent years the MENA region has been projected to be one of the fastest growing markets for clinical research,

based on availability of the required infrastructure, access to necessary patients, faster timelines and lower costs compared to other markets.³⁵ Coupled with a fast-growing, largely treatment-naïve³⁶ population, this undoubtedly makes the MENA region an attractive place for clinical trials, although its potential has yet to be fully exploited and could increase by a factor 8–10 in the next decade.³⁷ The contract research organization (CRO) Quintiles even recently advertised Russia, Turkey and the MENA region as the “new darlings” in the world of biopharmaceutical sales.³⁸

In an interview aired in February 2010, contract research organisation ClinTec International's CEO, Dr Rabinder Buttar, said that patient recruitment was definitely easier to do in the region for oncology, cardiovascular diseases and diabetes. “Everybody is trying to find patients very quickly – especially treatment-naïve patients.”³⁹ This shows a clear trend – at least from CROs' point of view, for obvious commercial reasons – to attract more industry-sponsored trials to a region that is in turmoil and termed by the World Bank as a “puzzle”.⁴⁰

Hany Salim, Head of the Research Ethics Committee at the National Hepatology and Tropical Medicine Research Institute and President of the Egyptian Network of Research Ethics Committees, believes that the underlying causes for Egypt being such an attractive target for clinical trials lies not only in its dense population, but also in the abundance of researchers, universities and research centres, as well as being a significant market for drugs.

RECENT DYNAMICS IN INTERNATIONAL DRUG TRIALS IN EGYPT

According to the public register of the US National Institutes of Health (NIH),⁴¹ Egypt is second only to South Africa on the African continent in terms of the number of clinical trials it hosts. The number of trials nearly tripled between 2008 and 2011.⁴² In the aftermath of the Arab Spring of 2011, the number of interventional clinical drug trials sponsored by Swiss transnational pharmaceutical companies (TNCs) rose until 2013 and then stabilised or even declined between 2014–2016.

In an article published in March 2014 on Outsourcing-Pharma.com, Jamie Macdonald, CEO of a CRO called INC Research called the geopolitical strife in the region “a concern,” though he noted that INC Research ran studies throughout the Arab Spring. “As long as people are sensible about going to the site, the staff and patients are still

going – we’re careful about their transportation,” he says, adding: “The tension we look to avoid but it’s something people have grown up with there.” Overall he says: “That’s what we get paid for – to manage these situations and try to keep it inside the monitoring windows. We haven’t had any major problems yet and as it settles geopolitically, we’ll be able to benefit from that.”⁴³

The following statistics have been retrieved on a periodic basis from the US NIH Database by the authors of this report in order to get a sense of the actual industry-sponsored clinical drug trials business and dynamics in Egypt. For this section we focus only on active, interventional clinical drug trials that are sponsored by TNCs – in other words, those underway at the time of gathering the inventory. For ease of understanding, they will be described in this report as “active international drug trials”. The search methodology is described in the relevant section of the report.

ACTIVE INTERNATIONAL DRUG TRIALS IN EGYPT

In February 2016 there were 57 active international drug trials in Egypt. Compared to March 2015 (61) and August 2014 (63), based on the same source and using the same methodology, this appears to represent a slight decrease. Even though the aforementioned timespan is too short to be able to predict future trends, the number seems to have stabilised at around 60 in the past few years.

Even if substantially lower compared to other middle-income economies such as South Africa, China, India or some Latin American countries, the number of active international drug trials suggests that Egypt remains among the favourite destinations for TNCs to outsource some of their testing.

Looking in particular at the two TNCs that run most international drug trials in Egypt at the time of writing –

the Swiss companies Novartis and Roche – we can see that the Arab spring events of early 2011 and its subsequent political unrest did not have a chilling effect on the number of active international drug trials. On the contrary, the number of clinical trials actually increased for both companies between 2011 and 2016, reaching a peak in 2013 (see Figure 1).

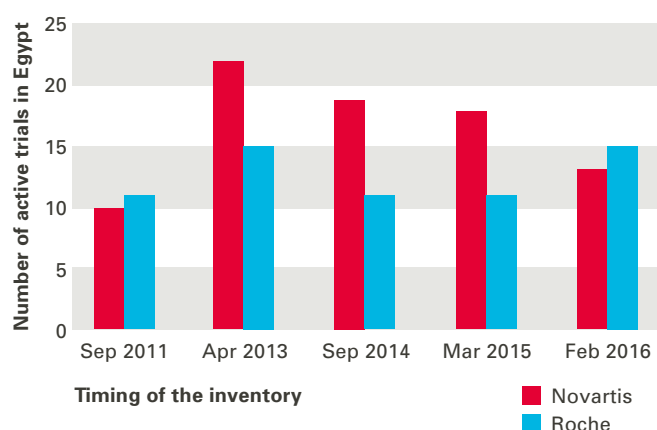
TRANSNATIONAL CORPORATIONS IN EGYPT

In February 2016, 21 international pharmaceutical and biotech companies were sponsoring active drug trials in Egypt. The two Swiss giants Novartis and Roche carry out the lion’s share of trials. As shown in Table 1, together these companies are responsible for almost half of the international drug trials taking place in the country (15 trials or 26 per cent for Novartis, and 13 trials or 23 per cent for Roche). These proportions have remained constant over the past two years (see Table 1).

TABLE 1: Number of active drug trials by company in Egypt 2014–2016

Name of sponsoring company	August 2014	March 2015	February 2016
Novartis	19	18	15
Roche	11	11	13
Boehringer Ingelheim	5	5	5
Gilead	1	0	1
Astellas	3	2	1
Pfizer	2	2	1
Eli Lilly	4	4	2
AbbVie	1	1	2 ⁴⁵
Sanofi	3	1	1
AstraZeneca	1	1	2
Merck Sharp & Dohme	1	1	0
Janssen	2	4	3
Shire	1	1	0
Novo Nordisk	0	1	0
Other, smaller biotech companies	9	9	11
TOTAL NUMBER OF DRUG TRIALS	63	61	57

FIGURE 1: Evolution of trials of Roche and Novartis in Egypt 2011–2016



LOCATION OF DRUG TRIALS TAKING PLACE IN EGYPT

In February 2016, 57 active international drug trials were taking place at 131 sites spread over nine cities in Egypt. Unsurprisingly, the majority were in Cairo (75), followed by Alexandria (31) – together accounting for about 81 per cent of all sites.

It should be noted that several trials may take place in a same hospital or clinic, i.e. the number of sites does not equal the number of institutions. Furthermore, exact identification and locations of the hospitals/clinics where the drug trials are conducted is often not possible, based on the scarcity of information on the US NIH Database. Sometimes a number suggesting a postal (zip) code is indicated. Since there is no public register of clinical trials in Egypt, it is impossible to cross-check and it is often difficult to know with certainty in which institutions the trials actually take place. However, depending on the tested medicines and the required health infrastructure/expertise for such trials, the location of these trials can be assumed (e.g. viral hepatitis C treatments in liver institutes, cancer treatments in specialised oncology hospital units etc.).

The geographical spread of active international drug trials has not changed much between 2014 and 2016, as shown in Table 2.

TABLE 2: **Locations of active international drug trials in Egypt, 2014–201**

Locations	August 2014	March 2015	February 2016
Cairo	83	75	75
Alexandria	36	32	31
Mansoura	9	8	9
Dakahlia	3	6	6
Menoufiya	2	5	5
Giza	3	3	2
Tanta	3	3	2
Fayoum	1	1	0
Beni Swef	0	2	1
Ismailia	1	1	0
Zagazig	1	1	0
Al Minya	1	1	0
Assiut	0	1	0
TOTAL NUMBER OF DRUG TRIAL SITES	143	139	131

Source: US NIH Database (www.clinicaltrials.gov)

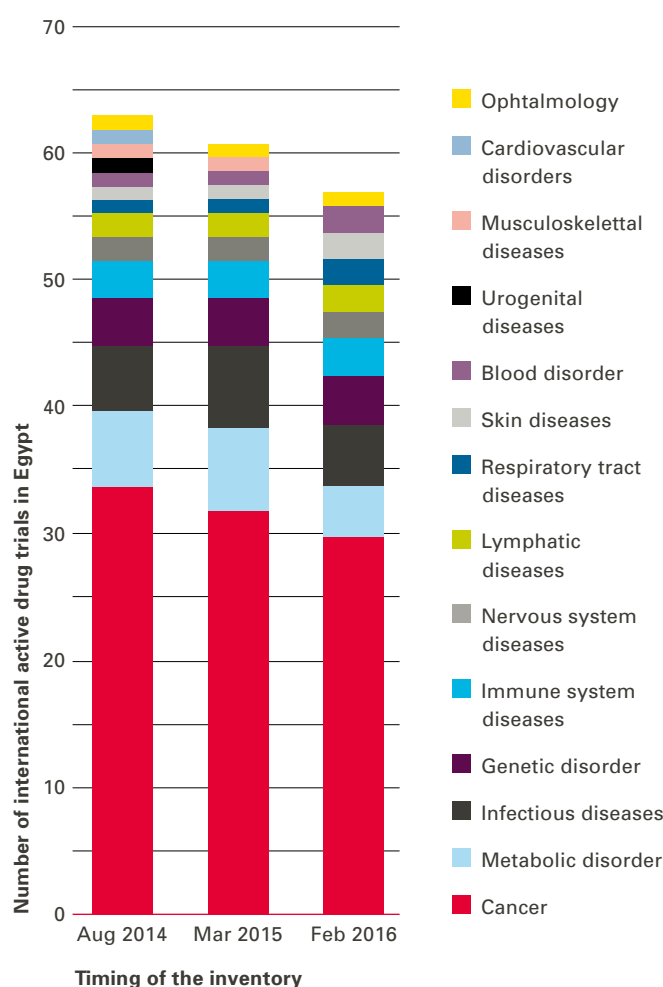
STATUS OF ACTIVE INTERNATIONAL DRUG TRIALS IN EGYPT

In February 2016, 51 per cent of active international drug trials in Egypt were either “not yet recruiting” or “recruiting” participants.⁴⁶ This indicates that new trials are regularly being launched, suggesting the ongoing attractiveness of Egypt as a destination country. About half of the other active international trials were “active, not recruiting”.

DISEASE CATEGORIES FOR INTERNATIONAL DRUG TRIALS IN EGYPT

Over half of all international active drug studies in Egypt are cancer trials, followed far behind by infectious diseases (10 per cent) and metabolic disorders (10 per cent).

FIGURE 2: **Active international drug trials by disease category, Egypt**



Source: US NIH Database (www.clinicaltrials.gov)

TABLE 3: Disease conditions against which TNC drugs are being tested, Egypt

Disease category	Conditions
Cancer	Lymphoma, Leukaemia, Gastrointestinal/Colorectal, Breast, Cushing's disease, Myelofibrosis, Melanoma, Ovarian, Lung, Head & Neck, Brain metastases, Mesothelioma, Liver
Metabolic disorder	Diabetes, Growth hormone deficiency, Amyloidosis
Infectious diseases	Hepatitis B, Hepatitis C, Fungal infections, Secondary infections in Cystic fibrosis patients
Genetic disorder	Fabry disease, Wolman disease, Gaucher disease
Immune system diseases	Rheumatoid arthritis, Lupus erythematosus, Transplantations, Autoimmune diseases
Nervous system diseases	Relapsing multiple sclerosis
Lymphatic diseases	Castleman's disease (lymphoproliferative disorder, Lymphoma-like)
Respiratory tract diseases	Chronic obstructive pulmonary disease (COPD)
Skin diseases	Psoriasis
Blood disorder	Sickle cell disease, Iron overload, Anaemia
Urogenital diseases	Overactive bladder, Urologic diseases
Musculoskeletal diseases	Arthritis
Cardiovascular disorders	Acute coronary syndrome
Ophthalmology	Age-related macular degeneration

Source: US NIH Database (www.clinicaltrials.gov)

The disease categories displayed in Figure 2 are taken from the Medical Subject Headings (MeSH) vocabulary and tree structure provided by the US National Library of Medicine.⁴⁷ Table 3 gives an idea of the different disease conditions within each disease category.

PHASES OF INTERNATIONAL DRUG TRIALS IN EGYPT

Clinical trials are conducted in a typical series of phases:⁴⁸

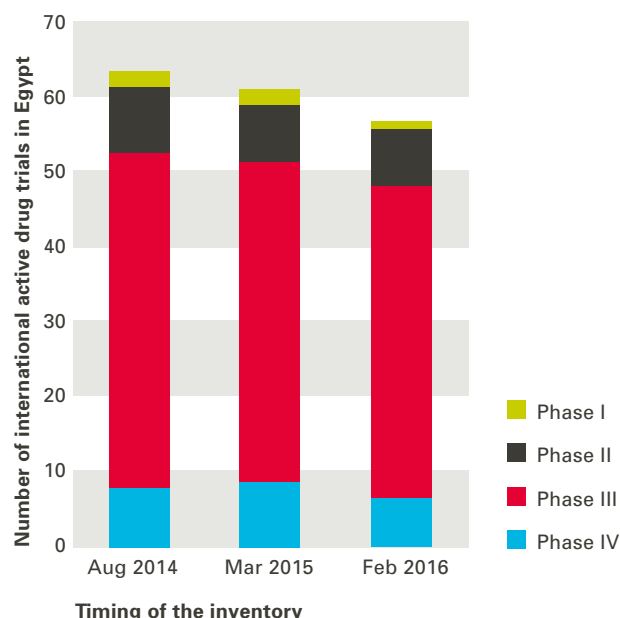
- **Phase I:** Initial trial of a new medicine, involving a small group of healthy volunteers or people with the disease/condition (usually 20-100), to evaluate the safety, determine a safe dosage range, and identify side effects.
- **Phase II:** The drug or treatment is given to a larger group of people with the disease/condition (up to several hundred people) to see if it is effective and to further evaluate its safety.
- **Phase III:** The drug or treatment is given to large groups of people with the disease/condition (usually 300-3,000) to confirm its effectiveness, monitor side effects, com-

pare it to standard treatments or placebo, and collect information that will allow the drug or treatment to be used safely. This phase is sometimes referred to as “pivotal trials” for the marketing approval process.

- **Phase IV (or post-marketing):** Studies that are done on a large number of people with the disease/condition (usually several thousands) after the drug or treatment has been marketed to gather information on the drug's effect in various populations and any side effects associated with long-term use.

The vast majority (70 per cent) of active international drug trials in Egypt are Phase III trials, with the proportion remaining constant throughout the study period. This finding is not really surprising as the Phase III trials are the ones requiring a larger (statistically significant) number of participants demonstrating efficacy and safety of the treatment, which would thus facilitate obtaining marketing approval. Due to the large sample size they are also the most costly ones. Cost-savings are among the main motivations for TNCs to outsource clinical trials to low- and middle-income countries, including in the MENA region.⁴⁹

FIGURE 3: **Active international drug trials by phase, Egypt**



Source: US NIH Database (www.clinicaltrials.gov)

DISCUSSION OF FINDINGS

One fundamental question that needs to be addressed is whether all industry-sponsored international trials are relevant and whether they are of any value in the Egyptian context. This should be addressed from an ethical point of view but also from a medical standpoint, as clinical trials should remain scientific endeavours rather than just merely responding to regulatory requirements or used as marketing tools. In other words, the people on whom the medicines are tested, but also society as a whole, should clearly benefit from these clinical trials.

The ethical evaluation of clinical trials is a complex issue, as a single ethical principle is rarely absolute. Most situations involve multiple principles that might compete and ought to be balanced against each other. Ethical evaluation thus inevitably requires judgement.⁵⁰ This judgement call about whether trials are (or at least seem to be) problematic from an ethical point of view also depends on which guidelines are being used as a reference. The following analysis takes as a reference the Declaration of Helsinki (DOH) and Council for International Organizations of Medical Sciences (CIOMS) guidelines (see Introduction).

PREDOMINANCE OF LATE-STAGE TRIALS

At first glance, what is striking is that almost all international trials identified during this research are related to

drugs that already have a name – either the international non-proprietary name (INN),⁵¹ or even a brand name. This suggests that the vast majority of trials being conducted in Egypt are rather post-marketing ones – i.e. the products tested in Egypt had already been licensed in higher income countries (such as the US, Switzerland and EU countries).

This practice is in line with the current requirements of Egypt's regulatory authorities that no clinical trial sponsored by a TNC can be conducted in Egypt unless the product being tested has been granted market approval in the originating country. Several Egyptian experts interviewed during this research confirmed this prerequisite, presenting it as a shield against Egyptian patients being used as guinea pigs for testing totally new substances. The draft national law on clinical trials that was leaked to the media in 2014 tried to lift that safeguard – as was done some years ago in other low- and middle-income countries such as India – which sparked a heated public debate that led to the deferral of its endorsement (see Chapter 2).

According to several stakeholders interviewed, in comparison to other emerging countries such as Russia, there is no regulatory obligation to conduct clinical trials in-country before being able to request a licence for the drug in Egypt. Theoretically, medicines could thus be licensed in Egypt without further clinical trials being conducted in-country. The Egyptian drug authorities may, however, exert a discretionary right and ask that the medicines should first be tested on the Egyptian population before granting definitive market approval. This “conditional approval” may happen, for example, based on medical grounds such as genetic or disease specificities prevailing in Egypt.

INTRIGUING EARLY-STAGE INTERNATIONAL TRIALS

If medicines tested in Egypt by TNCs are supposed to be approved first in their originating countries, what is the value of conducting early-stage trials? Unless they are looking at a new indication or a new type of study population – e.g. people who are older or younger than the original study population, with different characteristics or varying disease stages – one might ask whether such early-stage trials are ethical in the Egyptian context since tests on these medical products have already been completed elsewhere for marketing approval in a high-income country.

Another important question is whether these early-stage international drug trials are legal. In a conference on research ethics held in December 2011 in Maryland (US), Tamer Hifnawy, Associate Professor of Public Health in Beni Suef University, clearly said that “regulations in Egypt do not allow phase 1 trials”.⁵² Imam Waked, Professor of Medicine and former Director of the National Liver Institute, Menoufiya, confirmed this fact, adding that it is also difficult to obtain approval for a Phase IIa trial in Egypt. Other Egyptian experts interviewed during this re-

search openly questioned the practice and relevance of early-stage international trials conducted in Egypt. We could not find any evidence in the legislative texts regarding a possible illegality of Phase I and Phase II international trials being conducted in Egypt. Hence we assume that they are legal.

We have identified nine Phase I and Phase II international trials that were active at some point during our research period (2014–2016) – meaning that on average one in six international trials conducted in Egypt is an early-stage one. According to the last inventory, six were still active and three had been completed by February 2016. These included trials for treatments against different types

Many Egyptian experts consulted mentioned that clinical trials are a good opportunity for patients to access free medicines that they could otherwise never afford.

of cancer (5), lymphatic diseases (2), genetic (1) or blood disorders (1). They were sponsored by major TNCs such as Roche (2), Novartis (1), Shire (1), AbbVie (1), Janssen (2), Pfizer (1) and AstraZeneca (1). Four of the trials were placebo-controlled.

In Chapter 5, which focuses on cancer trials, we discuss several Phase I and Phase II cancer trials, providing a short analysis of their design (methodology) and their possible value in the Egyptian context based on comments made by independent experts mentioned earlier in the report (see Methodology) as well as from our own reflections.

The partial information available on the US NIH Database does not allow us to draw a firm conclusion about whether clinical trials are ethical or not – especially since trial results are often missing even for “older” trials, i.e. trials that had been completed for over a year. In terms of the Egyptian trials discussed in this report, based on their sometimes questionable design and the fact that similar tests might well have already been completed elsewhere, we would argue that they should be considered unethical unless they are justified on medical and contextual grounds. The Egyptian authorities should take a closer look at these and future early-stage trials, at least until a clearer national legislation has been agreed upon.

Since they have been approved in high-income markets, we know their high price tags. Most of these medicines are clearly out of reach of the vast majority of Egyptians, and are not dispensed through the Program for Treatment at the Expense of the State (PTES), which often represents the last hope for non-insured patients (about 50 per cent of the population) to access such expensive treatments. For more details, see our research on the availability and affordability of medicines tested in Egypt (Chapter 6).

Many Egyptian experts consulted mentioned that clinical trials are a good opportunity for patients to access free medicines that they could otherwise never afford. However, there should be a clear difference between therapeutic programmes and clinical trials. Past research in the field of bioethics has shown that access to free medical treatment for economically disadvantaged populations represents a “decision-impaired inducement”, i.e. what is offered is so enticing that participants will sign up for the study no matter what, disregarding risks or giving risks insufficient weight in the decision-making process. This renders subjects relatively incapable of protecting their own interests, which is the very definition of vulnerability.⁵³

Another recently published paper emphasised that, “Research is, by definition, aimed at producing socially valuable knowledge, not at providing treatments for patients, and at a minimum there is a tension between the obligations researchers qua researchers and researchers in their fiduciary role as physicians. (...) Conceiving of clinical research as a mere vehicle for delivery of innovative or unproven treatments to participants thus risks subverting the importance of ensuring resources are used to produce socially valuable knowledge.”⁵⁴ Ethical standards such as the CIOMS Guidelines also emphasise the need for social value going beyond the group of participants in order for health-related research to be ethically justified. All stakeholders (sponsors, researchers, governments and research ethics committees) must therefore ensure that the benefits and burdens of research are equally distributed.⁵⁵

Is the local population benefitting from the 60 or so international trials that are taking place in Egypt? Are they well protected against any harm or abuse? We explore these questions in the next chapters.

WHO BENEFITS FROM INDUSTRY-SPONSORED TRIALS IN EGYPT?

There is a high proportion of studies on cancer medicines among the international trials identified (50 per cent).



Dania has breast cancer that has metastasised. When she was asked to participate in a clinical trial to test the efficacy of a new drug, she agreed readily. She does not have health insurance. With the trial, she was offered free treatment, medical tests and follow-up consultations.



Prior to joining the trial, Dania learned that the tumor had metastasised to her brain. "I didn't feel sad because this is the will of God," she said.

2 THE ENVIRONMENT FOR CLINICAL DRUG TRIALS IN EGYPT

PUBLIC HEALTH SYSTEM

According to the World Bank, Egypt is a lower-middle income economy.⁵⁶ It was ranked 110 out of 185 countries on the 2014 UN Development Programme's Human Development Index, which found that 14 per cent of people were living below the international poverty line of less than US\$ 2 per day.⁵⁷ With a population of 90 million, the country has a large pool of patients and a diverse range of diseases.

Ayman Sabae, a researcher at the Egyptian Initiative for Personal Rights (EIPR), states that the cost of medical treatment is beyond the budget of an average Egyptian family. To make matters worse, patient satisfaction with health services in Egypt is extremely low.

The Health Insurance Organisation (HIO), which manages the public health insurance system, is affiliated to the Ministry of Health (MOH) but maintains an independent budget. The HIO was established in 1964, providing compulsory health insurance to government employees, pensioners, widows, students and schoolchildren.⁵⁸ In 2008/2009, the HIO reported that it covered 42.8 million Egyptians, or just 57 per cent of the population. However, only an estimated 8 per cent use HIO facilities (due to the relatively poor quality of care provided through these facilities, the lack of trust in public service providers, the lack of social accountability mechanisms and the overwhelming preference for private health service providers). In short, people only resort to services provided, by the HIO if they can't afford private service providers and mostly for expensive inpatient care.⁵⁹ A complementary health-care system does exist, allowing for medical treatment at the expense of the state, which acts as a safety net for those who are not covered by public health insurance.

The public health system in Egypt is heavily fragmented. Service delivery is distributed between several ministries including the MOH, which provides only one third of health-care services. Services are provided variously by the private sector, charitable (NGO) hospitals and other public hospitals belonging to ministries other than the ministry of health (i.e. teaching hospitals follow the Ministry of Higher Education; army hospitals, policy hospitals, judge hospitals etc. each follow their respective ministries and the Ministry of Health has no authority over them). Egypt's government health expenditure is less than 1.5 per cent of Gross Domestic Product (GDP). The Egyptian constitution aims to increase this percentage to 3 per cent of GDP.

Out-of-pocket expenditure on health care is very high, on the other hand, comprising nearly 72 per cent of total

expenditure on health.⁶⁰ Spending on pharmaceuticals makes up more than 33 per cent of health-care spending.⁶¹ Private hospitals are very attractive for those who can afford to pay for their services. Some have a very good reputation and provide an alternative to public facilities. Monitoring of all non-governmental health facilities is mandated to a special division of the MOH, but generally there is limited oversight of private sector facilities.

The absence of a comprehensive insurance coverage and the high cost of treatment to be borne by poor patients should be a red flag for a clinical trial environment: it may lead to the unwanted and unethical situation that vulnerable people are joining a clinical trial just to have access to treatment, even though the results are uncertain. This kind of environment exposes vulnerable people to exploitation as trial participants.⁶²

Mohamed Hassan Khalil, Coordinator of the Commission for Defending the Right to Health, goes as far as to say that the informed consent of a volunteer is meaningless in Egypt, given the high rates of poverty. "We will always find people who would be willing to get paid for their blood, for their organs, or for taking part in experiments," he says.

Other professionals see clinical trials as beneficial to the health-care system – for exactly the same reason. "Trials provide free treatment for patients who cannot afford paying for it," says Hamdy Abdul Azim, Professor of Oncology and founder of the Oncology Clinical Trials Centre at Cairo University. "If it weren't for clinical trials, the government would have to bear the cost of their treatment."

INFRASTRUCTURE FOR TRIALS

Knowledge about research design and methodology is an important prerequisite for conducting clinical trials. However, these topics are usually not included in the formal curriculum of most MENA medical schools or in post-graduate training programmes.⁶³ Medical professionals in Egypt therefore tend to regard the involvement of TNCs in clinical trials as beneficial for their institutions' work.

According to Abdul Azim, the budget dedicated to research is very limited in Egypt and private funding allows for improvement of the scientific research system. "The Research Centre in the Oncology Department at Cairo University was established with private funding, it was not part of the university budget. A number of research facilities exist due to the fact that clinical trials are a good source for funding research bodies," he says.

Emad Hamada, Chair of the Oncology Department at Cairo University, agrees: “I receive an annual budget of EGP 4.5 million (US\$ 500,000), while treatment for our patients alone costs EGP 13 million (US\$ 1.5 million).” Dr Hamada says his department has to work with very limited resources, and depends on charity and donations. “We ask companies to help us establish research units,” he says.

Until 2008, trials could be conducted in private clinics applying the same standards as those in public university hospitals, after which the MOH banned them. Magdy El-Serafy, Director of the National Hepatology and Tropical Medicine Research Institute, does not approve of conducting clinical trials in private clinics, because of their limited patient flow compared to university hospitals and research institutions (which also enjoy more credibility). Since 2008 clinical trials are officially hosted only by public hospitals, and most are conducted at university hospitals.

There are 18 public universities in Egypt, 17 of which have a school of medicine. Cairo University’s Faculty of Medicine is one of the largest medical faculties in the Middle East, with 5,200 beds in nine hospitals; around 20,000 under- and postgraduate students; 3,000 staff; and 2 million patients per year.⁶⁴ Heba Khafagy, lecturer in the Oncology Department of the Cairo University Hospital (Kasr El-Aini), says that the high flow of patients and the diversity of medical conditions presented distinguish Kasr El-Aini as a clinical trial site.

As well as trained medical personnel, TNCs require a sound medical infrastructure to conduct clinical trials, including modern equipment for testing and treatment, up-to-date ethics training and the ability to maintain and store patient files.

One of the main challenges in clinical trials is getting tissue and blood specimens out of Egypt, because of security restrictions. Muhammad Ezz el-Arab, Professor and Director of the Cancer Treatment Unit in the Liver Institute at Cairo University, stated that delays arise from the obligation to obtain approvals from several agencies, including national security. Some trials conducted on an international scale require that all tests should be done at one central laboratory. Others require advanced laboratory equipment, which might not be available in Egypt. These are additional obstacles for running trials in Egypt.

LEGISLATIVE FRAMEWORK

No single national legislation exists in Egypt to regulate clinical trials. However, according to Doaa Abu Taleb, Professor at the Faculty of Law of Ain Shams University, in the absence of legislation on clinical trials there are nevertheless some legal regulations that address experimenting on humans:

- The Constitution of 2014 states in Article 60 that: “The human body is inviolable. Any assault, defilement or mu-

tilation thereof is a crime punishable by Law. Organ trafficking is forbidden, and no medical or scientific experiment may be performed thereon without a documented free consent of the subject according to established principles of the medical field as regulated by law.”⁶⁵ However, this clinical trial law that is referred to in the constitutional article has never seen the light of day.⁶⁶

- Law 71/2009 (Article 36) regulates the rights of psychiatric patients, while Articles 7 and 8 state the necessity to obtain prior approval from the Research Ethics Committee before exposing psychiatric patients to any clinical research. If approval is granted, full explanation of the trial must be provided to the patient. The law also forbids conducting trials on patients subject to mandatory admission and treatment.⁶⁷
- Law 127/1955 states in Articles 59 and 65 that no foreign pharmaceutical product may enter the country unless it is approved and registered by the Ministry of Health.⁶⁸

Some aspects of clinical trials are regulated in the following administrative decrees issued by the Ministry of Health:

- The Egyptian Medical Code of Conduct (or “Profession Ethics Regulation”) issued by Ministerial Decree 238/2003. In Part IV of this code, a set of instructions is issued to doctors assigned to clinical trials on humans. These obligations are, however, non-binding and they neither include detailed regulatory procedures nor mention the rights of persons participating in such trials.⁶⁹
- Ministerial Decree 95/2005 prohibits the conduct of clinical trial before obtaining approval of the MOH Research Ethics Committee. This is followed by a number of constitutive and regulatory decrees.⁷⁰
- Ministerial Decree 436/2006 on National Good Clinical Practice (GCP) Guidelines.⁷¹

In the absence of comprehensive, unified legislation, referring to the above regulations as well as to international standards is common. Experimenting on human subjects without their consent means that those in charge are potentially liable under both civil and criminal law. It is possible in such cases for people subject to experimentation to claim compensation for harm suffered. The law also criminalises concealing information from the patient or failing to obtain consent for a treatment, according to Magd Kotb, member of the IRB and Director of the Preventive Medicine Centre, Cairo University Paediatrics Hospital (Abul-Rish).

The enactment of comprehensive legislation would clearly establish the agencies permitted to conduct pharmacological research, research conditions and government regulatory bodies supervising this research, says Manal El-Tibi, member of the National Council for Human Rights. “All such measures are not currently provided for, despite their importance,” he says.

According to Magdy El-Serafy, Director of the National Hepatology and Tropical Medicine Research Institute and member of the National Committee for the Control of Viral

Hepatitis, current standards governing clinical trials applied by ethics committees at the MOH, research institutions or university hospitals are “inadequate, incomplete and need development”, and a law is needed.

Alaa Awad, Professor of Hepatic Diseases at the Theodor Bilharz Research Institute describes the central problem as being the lack of a legislative framework governing the execution of pharmacological experimentation by companies – that is to say establishing mandates, funding and control procedures for monitoring. There is no legislation compelling pharmaceutical companies to publish the results of trials, or make public the failure of such trials. Thus, the operations by drug companies in Egypt nowadays are untrustworthy. “I believe that the operation of such companies under such circumstances will never be acceptable – or trusted.”

THE DRAFT LAW

In 2002, Hossam Badrawy, Professor at the Faculty of Medicine, Cairo University, and Head of the Education and Scientific Parliamentary Committee at the time, proposed a draft law to govern the conducting of clinical trials of new pharmaceutical products in Egypt. Parliament deliberated the proposed law but did not pass it. In 2014, a new draft law on clinical trials was formulated in Egypt and the text was leaked to media. This draft caused much public concern because it contained an article allowing trials on children, pregnant women, drug addicts, detainees and psychiatric patients. According to critics, it would have paved the way to experimentation of medicines on vulnerable people.

Abdul Aziz, Chair of the Committee for Government-Employed Pharmacists, stated that the Pharmacists’ Syndicate rejected the draft law. MPs considering the draft law realised that it primarily served the interests of international pharmaceutical companies.

One objection to the draft law made by Magdy El-Serafy, was that it placed legal liability on the researcher – a liability that should instead be borne by the company sponsoring the trial. She is in favour of having the new law discussed first among researchers before it is made available for public debate.

Alaa Awad states that the enactment of relevant legislation is vital, adding that the draft law provided the sponsor, namely the pharmaceutical companies, with extensive privileges, without commensurate legal responsibility. “As for the vulnerable group, namely the subject or patient, the law failed to provide for sufficient safeguards for their protection,” says Awad. “However, this issue cannot be discussed [separately] from the socio-economic environment where poverty and illiteracy are rife.”

“The only mechanism available to protect participants are the Research Ethics Committee in the Ministry of Health, in the research centres and in university hospitals,” says Awad. “Despite the importance of these com-

No single national legislation exists in Egypt to regulate clinical trials.

mittees, it is still not sufficient to control all the procedures in a trial.”

According to Mohamed Hassan Khalil, Coordinator of the Commission for Defending the Right to Health, the draft law aimed to support investors at any expense. He maintains that the MOH should be protecting the health of the citizens – not considering giving permission to other countries to try out drugs in Egypt that are not tested in their own territories.

In debates that followed it was argued that testing of new medicines on Egyptians without testing them first in originators’ countries should not be allowed. Magd Kotb – Professor of Paediatrics, member of the Research Ethics Committee in the Faculty of Medicine, Cairo University, and Director of the Preventive Medicine Centre in Abul-Rish Children’s Hospital – is one of the staunch opponents of the former draft law. She even goes so far as to compare the injection of unknown substances to a type of biological warfare against Egyptians.

In response to the criticism, Adel Adawy, Egyptian Minister of Health at the time, issued a decree ordering the deferral of the draft law and reopening its articles for deliberation among clinical, academic and civil society circles before submitting it to parliament for endorsement. Recently, in an Egyptian media report, the present Minister of Health Ahmed Emad El-Din Rady was said to have announced the imminent completion of a new law on clinical trials.⁷²

PATIENTS’ RIGHTS CHARTER

There are no civil society organisations (CSOs) that specifically focus on clinical trials in Egypt. However, the Egyptian Initiative for Personal Rights (EIPR) has a strong right-to-health programme, which also covers access to medicines. It is considered to be one of the most important human rights organisations in Egypt.

For the past year, EIPR researcher Ayman Sabae and his team have worked on a Patients’ Rights Charter. Around 10,000 patients were interviewed nationwide in order to develop the charter and it is hoped that this will develop into legislation to be presented to parliament.

Increasingly, patients in Egypt are also demanding access to their medical records, as well as full knowledge of their health conditions – requests that are usually ignored by doctors. Sabae added that consent of patients in clinical trials was very limited, with some of the companies exaggerating the trials’ impact on patients. Some patients also agree to be part of these trials because they cannot afford the cost of treatment.



Medicine storage in a clinical research centre in Cairo. The access to research drugs is regulated by the Egyptian Ministry of Health.

Sabae highlighted the lack of informed consent in trials and the absence of responsibility on the part of research facilities for the side-effects suffered by patients, and confirmed that current standards followed by the Research Ethics Committees were not sufficient. “The issue of informed consent is a major concern in terms of patients’ rights in Egypt,” he says. “In the limited cases where a written consent is to be signed by the patients before any intervention, we often see this taking place right before surgeries on the operating table. These practices directly affect the faculty of the patient in the consent process, nullifying its value as an actual, reliable informed consent. This is especially true in clinical trials.”

INTERNATIONAL REGULATORY FRAMEWORK

Because Egypt does not yet have comprehensive, unified legislation governing clinical trials, stakeholders that engage in clinical trials in Egypt are bound by international guidelines. The Declaration of Helsinki (DOH) and the CIOMS Guidelines are the most authoritative international ethical standards for human research. The DOH describes, among others things, requirements pertaining to informed consent and ethics committee approval.

Several sections of the DOH make it particularly relevant for those engaging in clinical trials in low- and middle-income countries, such as the following section: “Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.”

The US Food and Drug Administration (FDA) has eliminated reference to the DOH in its regulations pertaining to clinical trials outside the US and replaced it with a reference to the less rigorous ICH GCP guidelines.⁷³ EU legisla-

tion pertaining to approval of clinical trials and market authorisation of new drugs, however, refers to the DOH.⁷⁴ As the US and the EU are the largest markets for medicines in the world, their regulations have an impact on the behaviour of the pharmaceutical industry in terms of outsourcing their testing.

On paper, the European Medicines Agency (EMA) takes this responsibility seriously by endorsing a non-binding *Reflection paper on ethical and GCP aspects of clinical trials in medicinal products for human use conducted outside the EU/EEA and submitted in marketing authorisation applications to the EU regulatory authorities*.⁷⁵ The paper states that, “EU Regulatory Authorities should identify those studies that may give rise to special ethical concern regarding the inclusion of vulnerable populations and where applicable to seek additional assurance that the inclusion of such populations was justified and their rights and welfare protected”.

Regarding post-trial access to treatment, the paper states the following: “The applicant for an MAA [Marketing Authorisation Application] should provide EU Regulatory Authorities with a description of the situation of trial participants with regard to post-trial access to treatment and medical care depending on their localization and the national or regional healthcare system. The applicant should describe the provisions made for post-trial access to treatment and medical care for study participants depending on their localization and the treatment and medical care otherwise available. This information can form part of the clinical study report section on ethical considerations in accordance with ICH E3.”

If consistently implemented by regulatory authorities at the time of market authorisation in high-income countries, these provisions could provide substantial incentives to the pharmaceutical industry to comply with ethical guidelines that are crucial to protecting the rights of trial participants in low- and middle-income countries.

3 THE CONDUCT OF TRIALS IN EGYPT

THE APPROVAL OF CLINICAL TRIALS

The Research Ethics Committee (REC) of the Ministry of Health is the official body primarily responsible for granting clinical trial approvals in Egypt. It was established in 2005 by Ministerial Decree 95/2005, which forbids the conducting of research before obtaining the approval of the Central Administration for Research and Health Development at the Ministry of Health (MOH).

The MOH REC includes 20 eminent experts from different medical fields with training in research ethics. It is registered internationally and its structure is designed to ensure confidentiality and eliminate conflicts of interest.⁷⁶

In practice, to start a clinical trial, a sponsor company submits an application to the MOH REC, and to the institutional review board (IRB) at the relevant research institutions where the trial would be conducted, usually a university hospital. The sponsor of the trial bears the expenses of drugs, tests and transport for participants, as well as covering the cost of all examinations conducted prior to, during and after the trial. The costs of patient follow-ups after the trial ends are also borne by the sponsor, with no limit on the duration.

All clinical trials in Egypt must be registered before the start of the trial. Nevertheless, the clinical trials database at the Egyptian MOH is not an actual registry system. It includes data on clinical trials submitted to the MOH for scientific and ethical approval (mostly trials sponsored by pharmaceutical companies). However, it does not include clinical trials conducted in universities under the Ministry of Higher Education or trials conducted in some MOH research centres. Furthermore, the database is not publicly available as it contains confidential data. Access to and control of the database resides solely with the MOH,⁷⁷ and there is no access for journalists or any other member of civil society.

The MOH Central Administration for Research and Health Development examines proposed research projects within 60 days of submission, and then communicates its decision to applicants. The overall approval time of 60-90 days in the MENA region is similar to mature markets such as Australia.⁷⁸

Raafat Ragae Abdul Malek, Assistant Professor of Oncology at the Faculty of Medicine, Cairo University, points out that approvals and procedures can sometimes take up to a year. According to him, this is one of the key problems faced when conducting clinical trials in Egypt. Abdul Malek also remarks that the REC does not usually indicate

all the comments in one report but rather in several reports sent over months, which wastes additional time.

When asked about what they consider one of the major problems in conducting clinical trials in Egypt, Roche representatives also spontaneously mentioned the lengthy duration for getting initial trial approval.⁷⁹

Another reason for the lengthy duration of the process is that access to research drugs is also regulated by the MOH. Approval for the importation of medicines to be tested is provided only after documents are presented that prove the completion of previous stages of trials of the drug.

INSTITUTIONAL REVIEW BOARDS

University teaching hospitals have their own in-house institutional review boards (IRB), which provide training to medical doctors and researchers participating in clinical trials. They are also responsible for approving the conducting of trials as well as monitoring them, says Magdy El-Serafy, Director of the National Hepatology and Tropical Medicine Research Institute.

Before IRBs were established at clinical trial sites, a trial participant was treated just like any other patient. "Each physician had a cupboard where she or he kept the research files. Research drugs were dispensed through the hospital pharmacy, just like any other drugs. Staff were not sufficiently controlled or supervised," recalls Nadia Zaki, Director of the Clinical Research Centre at the Faculty of Medicine, Alexandria University, which did not have an IRB until 2005.

In 2008, the Egyptian Network for Research Ethics (ENREC) was established as a civil society entity operating under the auspices of the Egyptian Society for Healthcare Development, a non-governmental organisation (NGO). The main aim of the ENREC is to facilitate information and knowledge-sharing between the different IRBs in universities and academic institutions in order to enhance ethical review processes and ensure fulfilment of the highest ethical standards. By the end of March 2016, ENREC listed 39 IRBs operating in Egypt.⁸⁰

A recent search on the website of the Office for Human Research Protections from the United States Department of Health and Human Services listed 56 Egyptian IRBs. Of these, 24 were "active" and 32 were considered "deactivated", meaning that registration has not been renewed within three years from the date of the last entry or change made to the registration information.⁸¹

There is no law in Egypt that regulates the selection of members of IRBs. International standards applied by IRBs are derived from the Helsinki Declaration (1964, 1975 and 2000 versions), the Nuremberg Code (1947) and the Islamic Code of Medical Ethics (1982).

Anecdotal evidence shows that the lack of such legislation leads to a random array of membership compositions in different IRBs in Egypt. A member of the IRB at the National Research Centre in Cairo states: “The IRB has members from heads of science departments. They are selected for a term of three years.” He adds that “members also should include a media reporter and a professor in Islamic religion”.

Yasser Abdul Qader, Professor of Oncology and Director of the Clinical Research Unit at the Department of Oncology, Kasr el-Aini, criticises the fact that IRBs mainly consist of elderly people. “It is impossible to have among the members [of the IRB] the professor who supervised my masters and doctoral theses – and I am now in my 60s.”

Reports of IRBs are not publicly available, as they are considered to be internal documents, and there is little academic research in Egypt on their work. The Library of the Scientific Research Academy, which keeps copies of scientific studies conducted at Egyptian universities, does not contain any studies on the functioning of IRBs in Egypt.

The IRB at the National Research Centre in Cairo meets on a monthly basis to discuss research proposals (study protocols) and to follow up on approved projects, accord-

ing to member Aida Abdul Mohsen, Professor of Public Health and Director of Clinics, National Research Centre. She also explained that any research is refereed by three experts, one of which is external. The IRB pays members a very small incentive for each meeting and there are no fees charged for protocol review.

IRBs face numerous obstacles to achieving their goal of improving protection for research participants. Since its formation, the IRB of the National Research Centre has faced problems because of budget constraints, its inability to monitor approved protocols and a lack of national guidelines and accreditation mechanisms for IRBs in Egypt.⁸²

The number of protocols revised by IRBs has increased significantly during the last few years. Those submitted to the Cairo University IRB, for example, have increased from 21 in 2008 to 104 in 2011, of which 67 per cent were unconditionally approved.⁸³ The complexity of health research studies being performed in Egypt has also increased. This burden on IRBs results in wide variability of their reviews – a lack of uniformity that creates an uneven protection of trial participants.

The quality and consistency of ethical review remains unclear, admits Hany Sleem of ENREC.⁸⁴ According to Ayman Sabae, researcher at the EIPR, current standards followed by IRBs in Egypt are not adequate. “One proof of this is the approved trial to test the device to treat and cure viral hepatitis C and HIV developed by the military [see

BOX 1: EXAMPLE OF A TRIAL THAT SHOULD NEVER HAVE BEEN APPROVED: THE “KOF TA” DEVICE

In 2014, there were vocal public debates after the Egyptian military announced the development of a device for treating viral hepatitis C and HIV, claiming that the device was proven to be effective. “I defeated AIDS with the grace of my God at the rate of 100 per cent – and I defeated hepatitis C,” said Major General Ibrahim Abdel-Atti, Head of the Cancer Treatment and Screening Center in an announcement in February 2014.

There was scathing criticism straight away, with medical researchers expressing concern that the announcement would damage the nation’s image. “I want to be clear and explicit, what has been said and published about the invention of the armed forces hurts the image of scientists and science in Egypt,” said Essam Heggy, the scientific adviser to the President in the private *Al-Watan* newspaper. He called the declaration a “scientific scandal” for the nation.⁸⁵

The so-called “Complete Cure Device” was supposed to draw blood from a patient, break down the virus and return the purified blood back to the body. The “C-Fast” looked like an antenna affixed to the handle of a blender.⁸⁶ “I will take the AIDS from the patient and I will nourish the patient

on the AIDS treatment. I will give it to him like a skewer of Kofta to nourish him,” said Abdel-Atti, referring to a dish made of ground meat.

Then military chief Abdel Fattah El-Sisi, current President of Egypt, attended the unveiling of the device registered under the armed forces and approved by the country’s Ministry of Health. Dr Gamal Shiha, a leading liver specialist and member of a team evaluating a controversial device developed by Egypt’s military for detecting hepatitis C without drawing blood from a patient, said the announcement shocked him and his colleagues. “What has been said is not scientifically disciplined. There is nothing published, and there is nothing in medical conferences, and there is no single eminent professor around the project,” Shiha told CNN. In fact, a patent application for the device can be found on the internet.⁸⁷

Nonetheless, at a later news conference, with only selected Egyptian news outlets allowed to attend, officials again said that it had successfully treated patients and that the device would be used on 160 more patients for testing purposes over the following six months.⁸⁸

BOX 2: THE PATIENT BROKER

A patient broker is a person well known to medical students and professors at different colleges in Egypt. The broker or middleman is someone who provides medical students with patients so they can run tests on them for their studies. The middleman receives a certain sum of money from the students and shares it with the patients after persuading them to consent to a trial.

Despite it being an illegal profession, the law does not pursue patient brokers. Journalist Gehad Abbas wrote an investigative report on the practice that was published in *Al-Watan* newspaper in 2015. Although she reported on the practice in more than one hospital, there was no response at all by the government to the investigation.

The field study team decided to contact one of the most famous patient brokers in the old Manial area where Kasr El-Aini Educational Hospital is based. Omar⁸⁹ described his work as being “humanitarian charity” as he helps

patients who have lost their means of financial support because of illness. “The patients do not have enough money for their treatment and medication, also the government does not provide them with any social help nor does it give them real treatment,” he told us.

Omar himself suffers from muscular dystrophy and has to use an electric wheelchair. He has been a regular visitor to hospitals since he was a child. “I memorised by heart the names of drugs and diseases in English, and because I work in this profession for 20 years now I know most of the professors since the time they were students, and they also know me.”

By the age of 15 Omar had started to act as a middleman, providing medical students with patients. Asked about how he chooses the patients, Omar said that he recognises poor patients by the way they look. He convinces the patient that he will provide him or her with treatment and reimbursement, and the patient often agrees.

Box 1]. This trial turned out to be non-scientific and ultimately a failure which should never have been approved by any ethics committee.”

RECRUITMENT OF PATIENTS

Once approval for a clinical trial is obtained, researchers have to find suitable patients for the trial. Raafat Ragae Abdul Malek explains the process. “We inform our colleagues in the Department of Oncology. The physician would propose the matter to the patient. We inform the patient: ‘you’ll be part of a trial; and you have the choice of either receiving traditional treatment or another which could be potentially better’.”

Heba Khafagy at the Oncology Department, Cairo University, noted that criteria are set by the trial sponsors, as is the required number of patients. Usually, cancer trials do not enrol large numbers of patients because of the high cost of treatment. She points out that, in cancer trials, patients who have not started any treatment (so-called “treatment-naïve patients”) are preferred (see Chapter 5). The selection of patients stringently follows the prerequisites of the sponsor.

On the criteria of patient selection for trials, an executive at the National Hepatology and Tropical Medicine Research Institute explained that there is a preference for moderate cases and those who are relatively young in age. The executive also confirmed the general preference for treatment-naïve patients.

On a less formal level, Egyptian health professionals are familiar with a cruder form of recruiting patients for medical research. Many hospitals are flanked by an illegal system whereby ‘patient brokers’ supply needy patients to medical students (see Box 2). Although there is no proof that this kind of recruitment applies to industry-sponsored trials, it is a widespread practice in the informal health sector in Egypt.

INFORMED CONSENT

All medical professionals interviewed for this report agreed that the signing of an informed consent form is an important part of enrolment to a clinical trial. The form is supposed to state the duration of the research, the number of patients, the number of samples, potential risks and the liability of the researchers to treat any side-effects, expected benefits and contact information for officers in charge of receiving reports on any abuses. Ezz el-Arab claims that members of the department are entitled to intervene to stop the trial in case of any breach.

However, a substantial number of patients in the MENA region are unable to read and understand the consent forms. Another challenge common in the MENA region is the difficulty of drawing a clear distinction between “voluntary participation” and “free treatment opportunity”.⁹⁰

Emad Hamada, Chair of the Oncology Department at Cairo University, says that its IRB issued clear terms and conditions concerning the design of the informed consent

form. If the patient fails to understand the potential side-effects, he or she would not be included in the trial. "It is impossible that a patient joins a clinical trial without knowing it," says Heba Khafagy, Professor of Oncology, Cairo University Hospital (Kasr El-Aini).

Many of the professionals interviewed claim that the signing of the informed consent form is based on knowledge: if the patient is illiterate, one of their relatives has to bear witness to their signature showing consent. They also say that the information is presented in simple language for patients from modest educational backgrounds. Apparently, some trial protocols even stipulate that participating patients should be educated, or that a patient's participation should be at the discretion of the physician.

Noha Abdel Raziq, pharmacist at the Clinical Trials Centre of the Oncology Department, Cairo University Hospital (Kasr El-Aini), highlights some of the patient rights in the consent form: "We allow the patient the time to think before signing the consent form, from 15 to 28 days before the trial starts. We explain all possible side effects. The form has the trial title in Arabic and explains the patient's right to withdraw and to continue to receive treatment in case of withdrawal. It also explains the nature of required specimen and travel costs in case the patient lives outside Cairo."

When compiling the testimonies for this report, another issue became clear. The need for free treatment in Egypt in some cases is so urgent that participants do not take the trouble to understand the consent form. The lack of access to treatment makes them vulnerable and unfit for a careful informed consent process.

Dr Ayman Sabae, researcher for the Right to Health Programme at EIPR says that consent of patients in clinical trials is very limited. Some patients agree because they cannot otherwise afford the cost of treatment. Thus, they consider participating in the trial as a means to receiving treatment, and consequently they accept it even if the side-effects are uncertain. He also points to the absence of responsibility on the part of research facilities for any side-effects suffered by patients. To make matters worse, there are no laws protecting patients who take part in these trials or any mechanisms in place to ensure their rights.

INSURANCE DURING A CLINICAL TRIAL

Magd Kotb, Professor of Paediatrics and a member of the IRB at the Faculty of Medicine, and Director of Preventive Medicine Centre in Abul-Rish Children's Hospital, says that any research should fulfil three prerequisites: to have a stated scientific goal; to inform the patient that he or she is the subject of a trial; and to follow the governing ethical provisions based on the Declaration of Helsinki.

In addition, the patient must be insured against any complications of the drug. This insurance is obligatory because the patient is not paid for being part of the trial, as he

or she has agreed freely to have the drug tested on them. However, the impact of the trial should be borne by the pharmaceutical company, which at times disappears after side-effects are observed – leaving the patient to deal with the insurance company.

"The MOH will not approve a study without the supporting insurance policy covering the entire duration of the trials," says a former employee of the CRO Quintiles, who spoke on the condition of anonymity.

However, compulsory insurance is no guarantee that participants will receive compensation should adverse events arise. This has been best shown in Russia, where a survey made by CROs on more than 70,000 insured clinical trial participants (spread over hundreds of clinical trials) showed that not one single insurance claim had been filed by a participant over a three-year period (2007-2009).⁹¹ For the insurance to be activated, the causal link between the tested product and the side-effects must be established. This is very often denied by the principal investigator, who is paid by the sponsor. There is nothing resembling an independent evaluation to establish (or dismiss) this causal link. The onus of proof of any causal link thus relies on participants themselves. In addition, insurance claims can be very bureaucratic and complex, which may deter participants – particularly vulnerable patients – from filing a claim.

THE ROLE OF CONTRACT RESEARCH ORGANISATIONS

Contract research organisations (CROs) play a major role in the conduct of industry-sponsored trials wherever clinical trials are outsourced. The role of CROs in Egypt is particularly significant as they not only conduct the trials but also have a role in the oversight and monitoring of trials. Given the absence of a unified set of regulations, CROs also play an important role in Egypt for the approval of international clinical drug trials.

The CRO is defined as a person or organisation (commercial, academic or other) contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions. This means that the sponsor (the pharmaceutical company) contracts the CRO to perform part or all activities related to conducting a clinical trial. However, the pharmaceutical company is ultimately responsible for the data and safety of patients and for ensuring the CRO is abiding by guidelines, local regulations and duties in the contract.

A former employee of Quintiles, one of the major international CROs operating in Egypt, explains the regulations governing the licensing process of CROs in Egypt. Licensing applications are submitted to the MOH, after which the MOH examines the application and visits the CRO offices. If approved, the CRO receives a registration number under which it is allowed to operate and conduct trials. It is possible to conduct trials without being officially registered as



Journalist Alyaa Abo Shahba interviewing a participant to a clinical trial in a university hospital.

BOX 3: PERSPECTIVES OF CLINICAL TRIAL PARTICIPANTS**OM NEAMA'S STORY**

Om Neama is a 60-year-old housewife and widow. In 2012 she noticed a lump in her armpit and a swelling in her breast. When she finally went to see a doctor at the National Cancer Institute, the doctor told her that her tumour was at a late stage and that she needed urgent surgery to remove it from her breast and lymph nodes.

"Hearing this I was totally shocked as I do not have insurance and I barely managed to pay my first daughter's marriage expenses. I was hoping that my youngest would be able to finish her education. Receiving medical care at public expense is difficult, takes a lot of time and its procedures are so complicated, whereas the doctor said that my case is not to be delayed," said Om Neama.

Om Neama managed to have the surgery as one of her neighbours was friends with the son of one of the private hospital owners in Mohandeseen. Luckily, both the hospital owner and the doctor agreed to do the surgery for free when they became aware of her financial situation.

About a year after the surgery, Om Neama fell ill again. The doctor at the Kasr Al-Aini oncology department told her that she had to run some important tests. "The expenses for the radiology and lab tests really exhausted me financially. Then I learned the shocking truth: I have liver cancer. I wasn't financially ready for this and my daughters weren't able to finish the procedures required to help me receive medical care at public expense."

"When the doctor told me I would have to go through a clinical trial to receive my treatment, I couldn't understand at first, then he explained to me that I will receive the treatment and medication for free, also all the other lab tests and radiology will be free too. He told me that the effect of the medication I am going to have resembles the one I am currently taking, if not better. So, having no other choice, I immediately consented."

Om Neama's daughter said that the family did not hesitate to let her mother go through the clinical trial for the new drug. She read the contract terms with the company Roche and signed at once. "Our biggest concern was to receive free medication," she said. By the end of 2014, Om Neama started her clinical trial, receiving 34 therapeutic doses. She does not know yet when the experiment will be over.

"After entering this clinical trial, I felt that all my worries were lifted as I managed to receive my medication for free, especially after I had to pay so much money for the scans and lab tests. I was so happy to know that they would continue following up my condition after the end of the experiment," said Om Neama.

UM HASSAN'S STORY

We met Um Hassan,⁹² a lady in her 40s, in the Clinical Research Centre of the Faculty of Medicine, University of Alexandria. She said, "I'm from Kafr el-Sheikh. Currently, I work as a gatekeeper in the neighbourhood of Heliopolis in Cairo. My older son is sick with sickle cell anaemia, and needs to have a blood transfusion every fortnight."

When her son became ill at four months old she consulted doctors in Kafr el-Sheikh who were not able to diagnose him. The boy was referred to al-Shatbi Hospital in Alexandria, where Um Hassan found a reasonable level of care in its specialised centre. She learnt that a new drug was on trial so she applied. "I felt from the way they explained that this treatment would be good for my son," she said.

Her 10-year-old son looked like he was only four because of his illness. His mother said that he had to be operated on to remove his spleen. She was encouraged by the fact that transport to the centre and testing were free, and that she was hopeful that the treatment would be effective.

a CRO by the MOH, but in such cases it is not legal to publish the results of the trial.

Companies also sometimes contract a third party to audit the work of all stakeholders to ensure the appropriate procedures are being followed, including signing the informed consent, and receiving medical examinations and a medical follow-up at all stages. However, these internal audits are not made public.

When we asked Roche for its position, the company stated that it is standard practice worldwide to use profes-

sional CROs for monitoring of clinical trials across multiple countries. In Egypt, as well as globally, Roche has conducted internal audits (using Roche employees) or third parties, including CROs.⁹³

AbbVie also confirmed it relies on CROs for the monitoring of its trials (besides their own employees) in Egypt, but also as third party auditor.⁹⁴

MONITORING OF CLINICAL TRIALS

When a trial is underway, it is supposed to be subject to constant monitoring. In Egypt, the MOH Central Administration for Research and Health Development is responsible for the monitoring of clinical trials through annual reports that have to be submitted to them by the entities conducting the trials. In-house IRBs also oversee the trials at an institutional level, and IRBs receive reports biannually. Based on these reports it is decided whether or not the trial should continue.

Some researchers reported that the MOH in Egypt does not exercise its supervisory role on the tests as required. Due to time and budget constraints, monitoring performed by the IRB at the clinical trial site is generally considered to be weak.

Many of the medical professionals interviewed confirmed that the sponsor company mandates independent companies to monitor the whole process to ensure there is no conflict of interest among the different entities involved. According to Noha Abdul Raziq, Pharmacist in the Research Centre of the Oncology Department, Cairo University, monitoring is carried out by the sponsor company and a third party audit.

It is unclear who this third party auditor is. Also the role of CROs in overseeing trials is problematic. This kind of monitoring by parties hired by the sponsor of the trial cannot be considered trustworthy, since they will not share audit reports or methodology. This means that decisions on the continuation or discontinuation of a trial are taken on the basis of information supplied by those who potentially have a conflict of interest.

Asked to comment, AbbVie claims that Independent Data Monitoring Committees are used during studies in order to ensure that there is no conflict of interest. Besides “the CRO is blinded to treatment assignment in placebo controlled trials. Therefore, the theoretical situation where the CRO could purposefully manipulate information to cause trial continuation is avoided”.⁹⁵

The authors of this report still believe that CROs have an inherent conflict of interest that is problematic in relation to important decisions – such as recommending the ending of ongoing clinical trial when the participants are at risk – as this may compromise their further business prospects with the TNC.

CONFLICT OF INTEREST

There are multiple other potential sources for conflicts of interest when conducting clinical trials in Egypt. As mentioned above, the monitoring mechanism is not transparent and it is difficult to obtain any information about ongoing or completed clinical trials, or their success or failure.

To give just one example, the IRB at the Liver Institute in Menoufiyah requires a signed acknowledgement of the

lack of any conflict of interest between the researcher and the sponsor prior to the approval of a clinical trial. This applies to any possible conflicts of interest, whether they arise from personal, professional or kinship relations with any of the hospital staff, says Hisham Abdul Dayem, Assistant Dean of the National Liver Institute, Menoufiyah University and member of the REC.

Hany Sleem, President of the Egyptian Network of Research Ethics Committees (ENREC), says that eliminating conflicts of interest could be clearly provided for by the law. As far as he is concerned, the contracts that pharmaceutical companies sign with researchers are legal and public, including the issue of compensation. Moreover, companies train research teams so that the research is conducted according to a uniform protocol.

Yasser Abdul Qader, Professor of Oncology and Director of Clinical Research Unit, Department of Oncology, Cairo University Hospital (Kasr el-Aini) states that revenue from trials goes to the research facility, and that researchers receive payments that are not commensurate with the effort exerted. “The research coordinator, for instance, receives around US\$ 60 per patient throughout the whole period of the trial, which is a very small payment.”

He clarified that trials provide income to support the budgets of the Faculty of Medicine and the hospital serving all patients, in addition to the educational value, which also places Egypt on the scientific map. “Foreign pharmaceutical companies commend our work, and this is a source of pride,” he says (see Chapter 2). “The new generation of young researchers is enthusiastic. More experienced researchers try to help them and attract pharmaceutical companies to do research. The return is divided according to the law. We do not make any personal financial gain from such trials.”

Emad Hamada, Chair of the Oncology Department at Cairo University, agrees that compensation for the work of researchers is very small and argues that it needs to increase. He says that revenues from clinical trials are divided according to the planned budget: 20 per cent for the faculty, 25 per cent for the research facility and 55 per cent for the research team.

In Chapter 2, Abdul Azim mentions that a number of research facilities exist due to the fact that clinical trials are a good source of funding for research bodies. This financial dependence could lead to a less critical appraisal of research proposals by these research bodies, which may be related to the questionable clinical trials described in Chapters 1 and 5.

In this report (and in similar field studies carried out by Public Eye (former Berne Declaration) and Wemos in other low- and middle-income countries), several examples of potential undue influence or conflicts of interest that may put the protection of participants at risk have been mentioned. This includes, for example, the financial interest of hospitals that host international clinical trials or the fact that researchers involved in industry-sponsored clinical

trials, as well as medical doctors providing patients, are being paid by the sponsor or the CRO, usually well above average national salary standards.

WHAT HAPPENS IN CASES OF ADVERSE EVENTS?

A specialist of gastroenterology and hepatology at the Liver Institute, Cairo University, who wished to remain anonymous, explained what happens in the case of an adverse event in a clinical trial. “There are standards for monitoring adverse events. An immediate report is filed to the Research Ethics Committee and the sponsor to ensure speedy response to any symptoms showing on the patient. Also they are resorted to whenever any changes occur, such as pregnancy, if the drug is contraindicated in cases of preg-

nancy. Any modifications to the protocol are monitored by the IRB of the research facility.”

The specialist states that the trial must be suspended immediately, should the study fail. “The criterion of failure is the number of deaths.” Heba Khafagy, Lecturer in the Oncology Department of Cairo University Hospital (Kasr El-Aini), agrees.

For other professionals we interviewed, the bar to a suspension of the trial is set lower. Rafat Ragae Abdul Malek, Assistant Professor of Oncology at the Faculty of Medicine, Cairo University, indicates that the trial would be suspended if there were too many side-effects. Hisham Abdul Dayem, Assistant Dean of the National Liver Institute, Menoufiyah University and member of the IRB states that, if there are any worrying results, the trial is immediately stopped.

BOX 4: EXAMPLE OF A FAILED TRIAL ON CHILDREN

The Egyptian media has occasionally reported on the misconduct of clinical trials. Magd Kotb, Professor of Paediatrics and member of the Institutional review board at Cairo University, recounts an incident that is still under official investigation since 2008. Kotb uncovered details of trials conducted on children at one of Cairo University’s hospitals, providing evidence that only 9 per cent of the children improved while most of the cohort receiving treatment developed hepatic failure, lethal pneumonia, otitis media and ascites with high incidence of death.⁹⁶

“I proved with documents that out of 734 children suffering cholestasis, 401 children were administered Ursodeoxycholic acid (UDCA). However, only 9.35 per cent of those receiving the drug were cured, while 86.54% of those who received this bile acid deteriorated.”

Another medical professional in the same hospital confirmed that not only was this drug – whose brand name was Ursosalk – inefficient in treating children, but it was harmful. The findings of the research showed that 35 per cent of the children who were administered the drug responded, while 65 per cent did not. The result was that those children suffered hepatic failure.

Kotb stated that the drug Ursosalk is produced by the German company Dr Falk Pharma GmbH, which disappeared from the Egyptian scene after the failure of the trial. Later, the Egyptian Centre for the Protection and Support of the Drug Industry filed an official report on the same incident.⁹⁷ Also, a report was filed against the regulatory body, the Egyptian Drug Authority.

In relation to the example described in Box 4, serious concerns about the efficacy of UDCA were already known years before the trial,⁹⁸ but the unfavourable safety profile of UDCA appears to have been hidden by its allegedly broad “hepato-protective” profile that encouraged a wide off-label use⁹⁹ for many unapproved indications.¹⁰⁰ UDCA is not licensed for use in children, as its effectiveness and safety have never been established.¹⁰¹

The risks of involving infants and neonates in the UDCA clinical trial at the Cairo University Children’s Hospital were known from the beginning and seem to have been disproportion-

tionate compared to the benefits. Although the trial was halted, the damage was already done to many participants and it is not known whether the families of the victims received any compensation related to these serious adverse events.

For the authors of this report, this example indicates a dysfunctional oversight system. We could find no publicly available information about the official investigation that was launched following this incident, which would have been helpful in determining the responsibilities of the different actors involved and to contribute to the improvement of the oversight system.

4 HEPATITIS C DRUG TRIALS IN EGYPT

HCV: A MAJOR HEALTH PROBLEM WORLDWIDE

Hepatitis C virus (HCV) infection is a major health problem affecting more than 170 million people worldwide. The effects of chronic infection include cirrhosis, end-stage liver disease and liver cancer, although most infected people are unaware of their infection (it is mostly asymptomatic for a number of years if not decades).¹⁰² Globally the morbidity and mortality attributable to HCV infection continues to increase. According to WHO, approximately 700,000 people die each year from HCV-related complications. The hepatitis C virus can be eliminated but access to treatment remains low in many settings.¹⁰³ There are six major genotypes of HCV, with genotypes 1 and 3 together accounting for more than three quarters of HCV infections.¹⁰⁴

New, direct-acting antivirals (DAAs) that came onto the market in late 2013 are transforming the treatment of HCV as they can be administered orally, directly at the point-of-care, and over a shorter time period (on average 8–12 weeks) than the interferon-containing regimens that were used before them. DAAs can eliminate the virus in more than 90 per cent of cases and are associated with fewer serious adverse effects.¹⁰⁵ However, they have also sparked heated

debate because of their exorbitant cost – the most often-cited being sofosbuvir (Sovaldi®) produced by US-based company Gilead, with its US\$ 84,000 price tag for a three-month treatment course (US\$ 1,000 a pill). Even high-income countries struggle to cover treatment costs, although some were more successful than others in negotiating price reductions. The prices, nevertheless, remain far beyond those that would be affordable for widespread use in low- and middle-income countries.

Since 2013 many other DAAs have been launched by various TNCs (see Table 4).

Not all DAA are equally effective against all HCV 6 genotypes, hence the need to look for fixed-dose combinations (FDCs).

The latest treatment guidelines¹⁰⁶ can be summarised as follows:

- It is recommended that DAA regimens be used for the treatment of persons with hepatitis C infection rather than regimens with pegylated interferon and ribavirin.
- The preferred regimens for persons affected by genotype 4 are daclatasvir/sofosbuvir or ledipasvir/sofosbuvir.
- The duration of treatment is usually 12 weeks, up to 24 weeks for patients with cirrhosis.

TABLE 4: Overview of recent DAA treatments for HCV

First worldwide registration	Active ingredient	Brand name	Company	Initial cost in the USA for a 12-week course (US\$)
27/09/2013	Simeprevir	Olysio™	Janssen	66,000
06/12/2013	Sofosbuvir	Sovaldi®	Gilead	84,000
04/07/2014	Daclatasvir	Daklinza®	Bristol-Myers Squibb (BMS)	63,000
10/10/2014	Sofosbuvir/Ledipasvir	Harvoni®	Gilead	94,500
25/11/2014	Ombitasvir/Paritaprevir/Ritonavir/Dasabuvir	Viekira Pak®	AbbVie	83,319
28/01/2016	Elbasvir/Grazoprevir	Zepatier™	Merck	54,600

Sources: UNITAID and various media reports



"I used to inform the physician responsible for my follow-up about the side-effects and he used to photograph them and prescribe medicine," says Dania. "Many times the pain would be unbearable."

THE HCV SITUATION IN EGYPT

Egypt has the highest prevalence of viral hepatitis C in the world, making it a major public health challenge. The chronic infection rate is estimated at 10 per cent among 15-59-year-olds,¹⁰⁷ with some estimates reaching as high as 14 per cent.¹⁰⁸ This represents well over six million people, with an estimated 150,000 new cases annually.¹⁰⁹ These high rates are due to the mass campaign of intravenous anti-schistosomiasis treatment carried out by the Egyptian government in the 1960s–80s.¹¹⁰

HCV is a bloodborne virus and the most common modes of infection are through unsafe injection practices; inadequate sterilization of medical equipment; and the transfusion of unscreened blood and blood products.¹¹¹

To overcome these public health challenges, a National Committee for the Control of Viral Hepatitis (NCCVH) was established in 2006 with a mandate to develop a National Control Strategy. The first strategy was developed for 2008-2012, with an annual budget of US\$ 80 million.¹¹² In 2007, it launched an ambitious national treatment plan using two established medicines: interferon and ribavirin. It switched to the new treatments as soon as they were available, with over 140,000 Egyptians being treated free of charge with sofosbuvir and/or simeprevir by September 2015.¹¹³ The Egyptian government's ambitious goals are to

treat 300,000 hepatitis patients a year starting in 2016 and to drive the national infection rate below 2 per cent by 2025.¹¹⁴

The arrival of the new generation of DAA treatments on the market has generated new hope but also heated debates about treatment prices and the opacity surrounding negotiations between the government and the US company Gilead (see section 'The Sovaldi deal: controversy about the process').

Another important medical aspect that needs to be taken into consideration is the fact that HCV genotype 4 (GT-4) is the most prevalent in Egypt. As can be seen from the treatment recommendations above, sofosbuvir alone is not sufficiently effective against GT-4. The recent marketing approvals of sofosbuvir/ledipasvir (Harvoni®, Gilead) and of daclatasvir (Daklinza®, Janssen) in Egypt will increase the effectiveness of treatments, but this will come with an additional cost.

Last but not least, Egypt also historically has a vibrant generic industry that has been very active on the HCV front, contributing to improved access to life-saving medicines. Given the absence of patent protection, several Egyptian companies were able to produce generic versions of DAAs for the market. Generic sofosbuvir products on the market include Gratisovir® (Pharco), Viropack® (Marcyrl) and Augispov® (AUG Pharma) sold in a package with Olysio® (simeprevir, Janssen). Generic daclatasvir (Dacla-

virocyl®) produced by Marcyrl is sold in a package with its sofosbuvir product (Viropack®).

Two Egyptian companies have been licensed by US company Gilead (producer of sofosbuvir and ledipasvir/sofosbuvir) as part of their global voluntary licensing agreement announced in 2014.¹¹⁵ The limited geographical scope of this voluntary licensing agreement has been heavily criticised by advocacy groups and patients' organisations as it excluded some hard-hit low- and middle-income countries.¹¹⁶ The anti-diversion strategy put in place by Gilead to prevent cheaper sofosbuvir (US\$ 900 for a three-month treatment course as compared to over US\$ 60–80,000) making its way onto high-income country markets was also fiercely criticised as it, “violates patient privacy and autonomy, undermines confidentiality of patient data, introduces coercion and policing upon medical providers and may result in treatment interruptions for patients, leading to treatment resistance and failure”.¹¹⁷

In April 2016 the Geneva-based Drugs for Neglected Diseases initiative (DNDi) announced it had entered into an agreement with Egyptian drug manufacturer Pharco Pharmaceuticals for the clinical testing and scale-up of a new, potentially pan-genotypic hepatitis C treatment re-

gime at a price of just under US\$ 300. Pharco has agreed to supply DNDi with the combination sofosbuvir plus ravidasvir for its clinical studies for US\$ 300 per course of treatment. For the scale-up of this regimen, once approved, Pharco has agreed to set the commercial price at US\$ 294 or less per treatment course.¹¹⁸

THE FREE TREATMENT PROGRAMME

In 2014 the government launched a national Plan of Action for the Prevention, Care and Treatment of Viral Hepatitis 2014-2018,¹¹⁹ including a new treatment programme using oral direct acting antivirals (DAAs), which are more effective than conventional pegylated interferon alone. The first of the new DAAs to be used was sofosbuvir, marketed as Sovaldi® by Gilead Sciences Inc. Another combination was recently introduced, ledipasvir/sofosbuvir, marketed as Harvoni® by the same company.

Patients who receive Sovaldi sign an agreement consenting to the use of test results, explains Wahid Doss, Professor of Hepatology, Cairo University and President of the NCCVH. Sovaldi has been dispensed to approximately

BOX 5: PERSPECTIVES OF CLINICAL TRIAL PARTICIPANTS

NE'IMAT'S STORY

It was by chance that Ne'imat¹²⁰ (over 60 years old) found out she was infected with viral hepatitis C. The news was shocking because her family could not afford treatment and she was not covered by a health insurance scheme.

Ne'imat, a housewife, benefited hugely when the state made available the hepatic treatment drugs Sovaldi and Olysio. The drugs were dispensed through the National Hepatology and Tropical Medicine Research Institute in Cairo for three months. Her elder son, Samir, applied on her behalf. Samir says, “I was able to secure the expenses of the blood tests, which is a required procedure for receiving the drug, and the cost of other monthly tests. We wouldn't have been able to [get] the treatment had it not been available for free.”

The protocol for receiving the treatment for free includes monthly follow ups with the physician in the medical facility offering treatment, and the receipt and filing of test results in patient files. “Because my mother moves with difficulty, I undertake all the procedures on her behalf,” says Samir. “I visit the doctor monthly and hand him the blood test. It became clear from the first month that he does not want to check her or her blood pressure; he only took the test results and noted them. Thus, I am the one who

files the results myself, instead of putting her under stress.”

Ne'imat undergoes PCR tests in the National Hepatology and Tropical Medicine Research Institute, with the costs covered by the state. The tests are not usually conducted on the same day that the monthly dose is dispensed. Thus, Samir receives the medication on behalf of his mother, with no objection from her physician.

Samir maintains, “I am so grateful for my mother's treatment free of charge. The drug proved effective from the very first month of receiving the dose. However, the procedures for dispensing the drug are complicated and tiresome: a visit to the MOH is required to obtain the official stamp of state-funded medical treatment. The office is on an upper floor, which is very difficult for elderly and sick people to reach. The person has to return to the Liver Institute to dispense the dose, while commuting between the Institute and the Ministry is not easy due to the crowded neighbourhood and lack of transportation.”

Samir was not aware that his mother's test results were part of an evaluation study to assess the efficacy of Sovaldi as a treatment, although he would not have objected in any case. He was surprised, though, that the physician never told him this.

BOX 6: PERSPECTIVES OF CLINICAL TRIAL PARTICIPANTS**ABDULKHALEQ'S STORY**

A chance to escape death was the only thing Abdulkhaleq¹²¹ had hoped for. He was suffering from acquired immune deficiency syndrome (AIDS), and his immunity level had declined. His CD4 count reached 65 and then 10 (between 350 and 1391 is normal). This situation already threatened Abdulkhaleq's life, but things got worse when he learned about his hepatitis c virus infection.

This pushed Abdulkhaleq to try a new treatment offered by Dr General Ibrahim Abdel Atti. "I was told that this treatment was a new discovery and can completely cure both AIDS and hepatitis c virus, yet no one told me it was just an experiment. I didn't sign any agreement or contract." He participated in the infamous "Kofta" treatment (see Chapter 3).

His immunity level declined significantly leading to a skin rash, severe headaches and inflammation of the lymph nodes, taking him to the fourth (and final) stage of AIDS. After the press coverage that declared the "Kofta" treatment false, a major scandal ensued and Abdulkhaleq was shocked. "I was surprised to learn that it was only an experiment, no one told me about this!"

At the beginning of November 2015, Abdulkhaleq was given a drug called Sovaldi for six months by Mahala Liver Educational Institute and Hospital, close to his village. "I hid the fact that I had HIV and nobody asked me about it, also the initial tests didn't include an HIV test. When I told the doctor who was following my case at the Abbasid Fever Hospital, he let me know that it was good to hide this information as he was worried they would refuse to further provide me with the medication."

130,000 patients so far. Consent involves the condition of the patient being monitored and documented in their medical record before, during and after treatment. "Treatment protocols are international. Using peg-interferon with Sovaldi in the beginning was an international trend, and not only in Egypt. We continuously revise treatment protocols, and we try to offer the easiest and cheapest treatment possible," says Wahid Doss.

Magdy El-Serafy, Director of the National Hepatology and Tropical Medicine Research Institute, and Member of the NCCVH, states that upon selection of patients, priority is given to moderate cases such as young men suffering no chronic diseases, and to those who have received no treatment before.

The stories in boxes 5 and 6 describe patients' experience of this unprecedented treatment programme that was recently described by the *New York Times* as, "an experiment the size of Egypt".¹²²

THE "SOVALDI DEAL": CONTROVERSY OVER THE PROCESS

In early 2014, Egypt's NCCVH was the first of all low- or middle-income country governmental bodies to negotiate preferential pricing for sofosbuvir with manufacturer Gilead. Soon after, the patent for Sovaldi was denied by the Egyptian Patent Office, which also helps explain the hastiness with which Gilead started negotiations.¹²³ The deal reached (US\$ 300 per month of treatment) was deemed a "success" by Minister of Health Adel Adawy, but it soon sparked criticism because of the lack of transparency in negotiations, Sovaldi's much higher price on the private

market (over US\$ 2,000 per month if bought outside the national treatment programme), and the fact that it set a minimum global benchmark well above the actual production cost of sofosbuvir.¹²⁴ Another criticism expressed by the Syndicate of Pharmacists was that the deal had been struck and the drug distributed even before sofosbuvir was officially registered in Egypt, thus favouring a foreign company over domestic companies.¹²⁵

The NCCVH, represented by Wahid Doss, Dean of the National Hepatology and Tropical Medicine Research Institute, has been subject to fierce criticism following the deal, primarily for not disclosing its terms.

Muhamad Ezz el-Arab, Professor and Director of the Cancer Treatment Unit in the National Hepatology and Tropical Medicine Research Institute, says, "I observed the inclusion of two members in the negotiation committee. The two members were also two major researchers in the trial conducted in Egypt. This is indeed a flagrant conflict of interest and a serious ethical problem. Both members should have refused to be members of the negotiation and the research teams simultaneously."

Following the deal, Sovaldi was approved for marketing in July 2014 in what has been a record fast-track approval. The first batch was received in Egypt soon after.¹²⁶

Ahmad Shaarawi, Dean of the National Liver Institute in Menoufiyah points to the monopoly of the physicians of the National Hepatology and Tropical Medicine Research Institute in Cairo on the Sovaldi transaction, and the default on providing it free of charge to the Menoufiyah National Liver Institute.

But NCCVH's Dr Doss defends his position. "I was not the only negotiator," he says. "I knew Gilead because I attend medical conferences. I simply liaised between Gilead

and Legal Affairs of the MOH, and didn't intervene in the pricing deal." Dr Doss believes that the NCCVH is being attacked for its success in obtaining low prices for both imported and locally produced sofosbuvir.

Dr Doss said that the negotiating committee of the Ministry of Health was comprised of 16 members who contribute to treatment protocols, not only three doctors as rumoured. "I assigned my financial compensation for this research to the Liver Transplant Unit at the National Hepatology and Tropical Medicine Research Institute," he says.

A CLINICAL TRIAL OR NOT?

Magd Kotb, Professor of Paediatrics, member of the IRB in the Faculty of Medicine and Director of the Preventive Medicine Centre in Cairo University Paediatrics Hospital says that Sovaldi was developed in the United States for different genotypes of Hepatitis C than the one most common in Egypt. Therefore this drug is not a treatment, claims Dr Kotb, but is instead prescribed for trial purposes. The question is whether the trial had been announced, and whether the results are known – information that should be published in order that treatment protocols can be developed. According to Dr Kotb, the situation as it stands is not right.

NCCVH's Doss objects, saying Sovaldi is not a clinical trial. But he adds, "Phase IV of any trial involves marketing and trying the new medicine, and Sovaldi is in Phase IV. It is possible to discontinue its use and withdraw it if it proved to be risky." According to the US NIH database, there is no Phase IV trial of Sovaldi currently underway in Egypt. A Phase III trial was completed in August 2014 – probably for registration of the medicine in Egypt.

Magdy El-Serafy, Director of the National Hepatology and Tropical Medicine Research Institute, and Member of the National Committee for the Control of Viral Hepatitis, states that Sovaldi is registered and approved by the European Medical Agency and the FDA. "We are always faced with the question of why we study the side-effects of the drug, which is what is known as post-treatment studies. We do so to evaluate the impact of the drug."

Wafaa Abdel Aal, Professor of Pathology and Head of Clinical Trials Unit at the Centre of Excellence, and Convener of Medical Research Ethics Committee, National Research Institute points to the fact that the trials of Sovaldi in Egypt prior to introduction to the market did not include trials on the type 4 virus. She is bewildered that a decision was taken to obtain Sovaldi and other drugs for hepatic viruses at reduced prices, without conducting clinical trials for such drugs.

ARE HEPATITIS C TRIALS IN EGYPT IN ORDER?

According to Ezz el-Arab, one of the main criticisms levelled against pharmaceutical trials of new hepatitis C treat-

ments (DAAs) is that research is the monopoly of a handful of physicians. He maintained that, "the former director of the National Institute was an endoscopist, with no connection to international research. However, when he came to power, all research was credited to his name. I demand putting an end to this bias and the monopoly of research on hepatic viruses by just four physicians due to their good connections to pharmaceutical companies."

Hany Sleem, Director of the Scientific Research Ethics Committee, National Hepatology and Tropical Medicine Research Institute and President of the ENREC, says on the issue of the monopoly of pharmacological experimentation of hepatic drugs by four physicians and the role of legislation in preventing such behaviour that international companies selected their national researchers based on the number of papers published in international periodicals and their track record of clinical trials.

Concerning the monopoly by specific researchers on pharmacological trials of liver drugs, El-Serafy stated that the track record of the researchers in terms of publication in international medical journals is important. This record makes the researcher preferred and more credible to foreign pharmaceutical companies. Thus, published scholars become key researchers in any team, which comprises younger researchers as well.

The Sovaldi deal generates diverging opinions among the Egyptian experts interviewed as to whether the national treatment programme is, in fact, a disguised, national scale clinical trial. We were told by Manal El-Sayed, Professor of Paediatrics, Ain Shams University, and a prominent member of the NCCVH, that data collected during the treatment are used exclusively by the NCCVH to evaluate the success rate of the treatment (disappearance of the virus in the blood). Had the data ended up or been the property of Gilead, we would have considered the national treatment programme a clinical trial, but that does not seem to be the case.

Hepatitis C is a national priority with fierce price competition between generic producers and TNCs. The state also plays an important role in subsidising treatments for those who cannot afford it. Hence the issue of post-trial access and availability/affordability of treatments is probably less acute than, for example, those for cancer medicines (see Chapter 5). In quantitative terms, the number of hepatitis C trials is much lower (about one-sixth) than the number of cancer trials.

Among the few active international hepatitis C trials, one that raised questions is sponsored by Gilead (NCT02487030) and entitled "Safety and Efficacy of Ledipasvir/Sofosbuvir Fixed Dose Combination, With or Without Ribavirin, in Egyptian Adults With Chronic Genotype 4 HCV Infection". What is the value of this Phase III trial – which is being conducted only in Egypt – when the experimental drug (brand name Harvoni) is already said to be effective against genotype 4 according to latest treatment recommendations¹²⁷ and has recently been registered in Egypt?



Dania with her friend who is helping her everytime she is coming to the hospital to take her dose.

5 CANCER DRUG TRIALS IN EGYPT

THE PREVALENCE OF CANCER IN EGYPT

A recent study indicated that the incidence of cancer in Egypt is rising rapidly and estimated that by 2050 there will have been a three-fold increase on 2013 levels.¹²⁸ Breast cancer is the most frequent cancer among Egyptian women, followed by liver cancer; among men, liver cancer is the most frequent, followed by bladder cancer. The incidence of liver cancer in Egypt is striking (it has the fourth highest rate in the world) and is thought to be related to the country's high incidence of hepatitis C.¹²⁹

WHY EGYPTIAN CANCER PATIENTS WANT TO PARTICIPATE IN TRIALS

Heba Khafagy, Professor of Oncology, Cairo University Hospital (Kasr El-Aini) says, "I started joining clinical trials systematically four years ago [as a researcher] through a research centre specialised in such trials. Prior to this date, trials were conducted on a small scale, where procedures for obtaining approvals were prolonged, and projects were mostly rejected."

She says that cancer patients, unlike other patients, wish to be part of clinical trials where they can receive drugs and treatment for free because the costs of treatment can otherwise rise as high as EGP 50,000 (approximately US\$ 5,600) per month. Moreover, state-funded health care does not provide full coverage of treatment costs and patients have to apply for health care services several times, which is very arduous for them. In addition, it can be difficult to be granted state-funded treatment for more than one round of treatment.

She adds that being part of a clinical trial ensures free tests, medical check ups, travel allowances if the patient is not a Cairo resident, post-trial follow up and even treatment in hospital if needed.

Raafat Ragae Abdul Malek, Assistant Professor of Oncology, Faculty of Medicine, Cairo University, says, "Participating in clinical studies for the treatment of cancer patients ensures treatment with therapies not available in Egypt. Treatment is also offered at no cost to the patient, the treatment facility, or even the state."

ETHICS OF CANCER TRIALS IN LOW- AND MIDDLE-INCOME COUNTRIES

These statements indicate that there is a fundamental inequality between trial participants in Egypt and more affluent countries. In Egypt, people with a life-threatening disease such as cancer see themselves faced with little other choice, which means taking experimental treatment with unknown side effects, simply because they cannot afford a standard proven treatment. Apart from exceptional situations where the standard treatment does not exist, is not effective or causes many side effects, patients should be given the standard treatment first.

Cancer patients in more affluent countries usually receive a proven treatment first and if that does not work they might engage in clinical trials. This could explain why Egypt is a popular destination for cancer trials – it is very hard to find treatment-naïve patients in more affluent countries. An investigation by the Indian Centre on Studies on Ethics and Rights described how treatment-naïve breast cancer patients were given experimental treatment in the context of a clinical trial. That study judged that the trial sponsor took advantage of the vulnerable position of breast cancer patients in India.¹³⁰

An article published in 2014 in the *Journal of Clinical Oncology* summarises the ethical stakes in relation to cancer trials in low-resource settings as follows:

"Despite the public health urgency of cancer in the developing world, along with the globalisation of industry-sponsored clinical research, the ethics of cancer clinical trials in low-resource settings have received little attention. What are the appropriate standards for the design and conduct of such trials?"

Two questions relevant to clinical trials in low-resource settings are particularly vexing. First, what is the proper control group for evaluating investigational treatments in this setting? As with HIV, investigators conducting cancer trials – especially those based at developed-world institutions or funded by developed-world sources – must decide whether trials should compare novel interventions to the developed-world standard of care, or if it is acceptable, or even preferable, to evaluate them against locally available treatments. Second, must these trials have the potential to benefit the host population?"

These questions, which encompass what sponsors and investigators owe both to study participants and to host communities, remain unsettled to this day."¹³¹

The authors of this report believe that every participant in a clinical trial, wherever it takes place, is entitled to the highest possible standard of care when allocated to a control group. Not only the investigational product but also the standard of care should be made available and affordable to the population involved in that research.

All these aspects are anchored in international ethical standards such as the Declaration of Helsinki or the CIOMS

Guidelines. As expressed in a recent comment published in *The Lancet Haematology*, “If there are reasons to believe that these conditions will not take place, the [CIOMS] guidelines deem it unethical and exploitative to do the research in that country.”¹³²

In light of these principles, the following trials identified during our study raise ethical concerns.

EARLY-STAGE CANCER TRIALS

1. A Pharmacokinetics Study to Investigate the Effect of Rifampin on Vemurafenib in Patients With BRAFV600 Mutation-Positive Metastatic Malignancy (NCT01765543)

Sponsor: Roche

Investigational drug(s) of sponsor: vemurafenib (Brand name: Zelboraf)

Drug(s) of other companies: rifampin¹³³

Original approval of the investigational drug: 08/2011 (FDA), 02/2012 (EMA), 10/2011 (Swissmedic)

Critical analysis: Phase I trial, active (recruiting). Experts consulted believe the trial may make sense because of the immunosuppressive effect of vemurafenib, but participation is very demanding on patients because many blood samples have to be taken. The risk/benefit ratio is unclear as there is no information on how long after this trial phase (first cycle) the drug will be provided free for patients. An active extension study (NCT01739764) is underway until March 2018, but it is unclear what might happen afterwards for patients.

Comments of Roche (excerpts):¹³⁴ “(...) This study was conducted specifically to meet a post-registration requirement Roche received from the FDA at the time of the first approval of vemurafenib. We recognize that sampling in pharmacokinetic studies may be burdensome for patients, however, it is required to adequately assess the PK [phar-

macokinetic] profile for the drug in question and deliver the primary endpoint [be able to measure the main result planned] as defined in the protocol. The study has completed enrolment in four countries including the USA, Croatia, Egypt and South Africa. The clinical study report is currently under preparation. The status of clinicaltrials.gov will be updated soon to reflect the study status.

“After patients participated in study GO28052 [NCT01765543], they were offered to participate in the extension study GO28399 [NCT01739764] through which they could continue to receive vemurafenib as long as they receive benefit. It is estimated that the study will end in 2018 (...); however, Roche internal policies ensure prolongation in case included patients continue to benefit from vemurafenib. (...)”

Based on the above comments, the trial seems reasonable. We may however wonder if it is ethical to conduct a trial in Egypt to meet a requirement of the FDA – that is, a trial linked with the marketing authorisation process in the US. Will Egyptians also benefit from it? The MOH REC and the relevant IRB should verify whether all participants of this study will be included in the extension study and make sure that Roche fulfils its commitment to continue providing vemurafenib – if proven beneficial – to patients who need it beyond March 2018.

2. A Multi-Center Study of Biomarker-Driven Therapy in Metastatic Colorectal Cancer (NCT02291289)

Sponsor: Roche

Investigational drug(s) of the sponsor: bevacizumab (Brand name: Avastin), vemurafenib (Brand name: Zelboraf), capecitabine (Brand name: Xeloda), atezolizumab (No brand name yet)

Drug(s) of other companies: cetuximab (Brand name: Erbitux, Imclone), oxaliplatin/fluorouracil/folinic acid (chemotherapy regimen named FOLFOX)

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

Critical analysis: Phase II trial, active (recruiting). The design of this study is “completely chaotic” according to oncology experts, and results will be unclear given the large number of



subgroups. This study is meant to benefit more the pharmaceutical company than patients and it is thought that it is being undertaken to get doctors to prescribe certain medicines such as bevacizumab. Using such a complex study design to test new medicines in such a large number of countries (24 in total, including many low- and middle-income countries) is extremely worrying given the high risk of study errors. Besides, the limited number of participants and the fact that the study uses two surrogate endpoints (or markers) – which are often poor predictors of actual clinical benefit and overall survival – considerably limits its power. Vemurafenib is being used off-label in this study as it has been registered only for treatment against melanoma, not against colorectal cancer. There is a risk also of delayed effect of the initial therapy (bevacizumab + chemotherapy) into the maintenance phase, thus affecting the tumour response and increasing the risk of bias in the final results. The fact that atezolizumab is not yet approved in high-income countries contravenes Egyptian regulations that state that only medicines approved in their originating country can be used in foreign sponsored clinical trials in Egypt. Finally, all experimental combinations involved in this study are potentially very toxic and are expensive, which raises this issue of their future availability and affordability for Egyptian cancer patients.

Comments of Roche (excerpts):¹³⁵ “(...) Patients who did not receive prior therapy are initially treated with an approved regimen containing bevacizumab for the first four months; this portion of the trial is referred to as ‘induction’. The second part of the treatment, which is referred to

as ‘maintenance’, takes into consideration the molecular signature of a patient’s tumors, and based on the tumor characteristics the treatment becomes more targeted. The innovative and highly adaptable trial design permits modification of current experimental arms and inclusion of additional treatment cohorts based on the latest scientific evidence. All experimental treatments are directly compared to the current standard-of-care.

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

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

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

3. A Clinical Study Conducted in Multiple Centers Comparing Veliparib and Whole Brain Radiation Therapy (WBRT) Versus Placebo and WBRT in Subjects With Brain Metastases From Non Small Cell Lung Cancer (NSCLC) (NCT01657799)

Sponsor: AbbVie (prior Sponsor, Abbott)
Investigational drug(s) of sponsor: veliparib (No brand name yet)
Drug(s) of other companies: None (placebo-controlled)
Original approval of the investigational drug: None found (drug still in development)

Critical analysis: Phase II placebo-controlled trial completed, no trial results posted. This study seems to make sense in terms of its design, but raises the ethical issue of a placebo-controlled cancer trial in a low- or middle-income country and there are risks related to the toxicity of the drug. The results of the Phase I study are not indicated – if they were positive the placebo-controlled design in Egypt could be seen as unethical. The trial used a clinical outcome (overall survival) rather than surrogate endpoints (markers), which is a positive feature. The fact that veliparib is not approved in high-income countries contravenes Egyptian regulations that state that only medicines approved in their originating country can be used in foreign sponsored clinical trials in Egypt.

Comments from AbbVie (excerpts):¹³⁶ “The design of this trial is veliparib or placebo added to standard therapy (which is radiotherapy). All subjects in the trial receive standard therapy. The phase 1 results (tolerability, PK [pharmacokinetics], and anti-tumor activity) were described in the study protocol. The phase 1 trial was a single arm trial that did not prove a benefit of veliparib. Therefore, the ethical issues referenced are probably not applicable to this study.

“We/AbbVie have received approval to conduct interventional studies with compounds that are still in investigational phase and not yet registered in originating country.”

The explanation given by AbbVie is not convincing. We question the rationale for proceeding with Phase II testing if the Phase I results proved no benefit. In addition, AbbVie mentioned that the Phase 1 results were described in the study protocol—this document is however not publicly accessible and we are thus unable to confirm this. The US NIH database summary sheet, on which we based our analysis, does not mention anything about these results. This is a clear deficiency of the sponsor company—whose duty it is to update the registries regularly—and highlights the problems linked with the lack of accessibility to important documents (such as protocols or clinical study reports) related to clinical trials. This makes public scrutiny of such operations very challenging.

Recent developments indicate that transparency is not among AbbVie’s key priorities. In 2013 it filed a lawsuit against the EMA to stop it releasing three clinical study reports on its blockbuster arthritis drug adalimumab (Humira®).¹³⁷ An out-of-court agreement between EMA and AbbVie was reached in 2014, which granted public access only to redacted versions of the reports.¹³⁸ The European Ombudsman has just published its inquiry, questioning EMA’s “continued reliance on the protection of commercial interests” to the detriment of public health.¹³⁹

This is troubling, as it suggests that AbbVie received approval to conduct trials on at least one medicine that was not registered in its originating country. Whether this is due to laxity on the part of the Egyptian authorities – contravening their own regulations – or to strong arguments from the sponsoring company justifying an exception is unclear.

This trial is complete, but there is another active Phase III trial (NCT02106546) in Egypt testing veliparib for lung cancer that should remain under scrutiny by the Egyptian authorities. Veliparib is still not registered in the US.

4. A Study of Sunitinib In Young Patients With Advanced Gastrointestinal Stromal Tumor (NCT01396148)

Sponsor: Pfizer
Investigational drug(s) of sponsor: sunitinib (Brand name: Sutent)
Drug(s) of other companies: None
Original approval of the investigational drug: 01/2006 (FDA), 07/2006 (EMA), 04/2006 (Swissmedic)

Critical analysis: Phase I/II safety trial, active (recruiting). The primary outcomes are all physiologic measures – estimated

steady-state maximum plasma concentration, estimated oral clearance, etc. – on children and adolescents. Sunitinib is approved only for use in adults, but in this trial is tested in children, hence we argue that this trial does not comply with Egyptian regulations (only drugs approved in foreign countries can be used in clinical trials in Egypt). According to the Swiss Compendium of Medicines,¹⁴⁰ only patients with resistance or intolerance to imatinib should be treated with sunitinib. However if we look at the inclusion criteria, not only young patients with resistance to imatinib are included but

also those that cannot obtain imatinib in their country. According to one oncology expert this should never be used as a reason not to give imatinib, which is considered the best-proven standard treatment. This trial is conducted in 12 mostly OECD countries (with the exception of Egypt and Singapore); three countries (Canada, Poland, Portugal) were removed in the course of the study for unknown reasons.

Pfizer was asked for comments, but the company did not respond despite two reminders. The question of whether it is ethical to deprive the children and adolescents participating in this trial of the best-proven standard treatment (imatinib) just because it cannot be obtained in Egypt remains open. This trial should remain under close scrutiny by the MOH REC and the relevant IRB.

General comments about these early-stage trials

In general, early-stage trials are considered to be riskier for the health of trial participants than late-stage trials when more is known about the efficacy and safety of a drug or a combination of drugs.¹⁴¹ In January 2016, a Phase 1 trial in France killed one participant and left several others severely injured.¹⁴² The results of the official investigation launched by the French health authorities, communicated last May, “found that the company had not properly informed volunteers and had followed a flawed testing protocol”.¹⁴³ This tragic incident in France also led the European Medicines Agency to start reviewing guidelines regarding “first-in-human” clinical trials, including what data are needed to enable their appropriate design and to allow initiation.¹⁴⁴

Phase 1 trials require close monitoring to safeguard the safety of trial participants, and it is therefore unsurprising that several Egyptian experts have expressed criticism of early-phase trials in Egypt as described in Chapter 1. Cancer patients are extremely vulnerable because of the severity of their disease, and Egyptian cancer patients may be even more vulnerable because of limited access to treatment and care. It is unclear whether trial sponsors take these vulnerabilities into account when engaging in early-phase trials in Egypt. Oncology experts have been critical of the design of the early-phase oncology trials described above, and we hope the Egyptian authorities will monitor these trials more closely.

LATE-STAGE CANCER TRIALS

A Study of Avastin (Bevacizumab) + Xeloda (Capecitabine) as Maintenance Therapy in Patients With HER2-Negative Metastatic Breast Cancer (NCT00929240)

Sponsor: Roche

Investigational drug(s) of sponsor: bevacizumab (Brand name: Avastin), capecitabine (Brand name: Xeloda)

Drug(s) of other companies: None

Original approval of the investigational drug: bevacizumab: 02/2004 (FDA), 01/2005 (EMA), 12/2004 (Swissmedic)
capecitabine: 04/1998 (FDA), 02/2001 (EMA), 06/1998 (Swissmedic)

Critical analysis: The purpose of the study is to, “compare maintenance therapy with Avastin (bevacizumab) + Xeloda (capecitabine) versus Avastin alone, in patients with HER2-negative metastatic breast cancer who have not progressed during first-line therapy with docetaxel + Avastin”. The study started in 2009 and was completed 2014. According to the US NIH Database, as well as in Egypt the trial took place in Brazil, China, India, Saudi Arabia, Poland, France, Italy, Spain and Turkey.

The study raises concern for several reasons. In 2011 the US FDA announced that its Commissioner Margaret Hamburg would revoke the agency’s accelerated approval of the breast cancer indication for Avastin (bevacizumab).¹⁴⁵ According to the FDA, Avastin used for metastatic breast cancer has not been shown to provide a benefit (in terms of delay in the growth of tumors) that would justify its serious and potentially life-threatening risks. Nor is there, according to the FDA, evidence that Avastin will either help women with breast cancer live longer or improve their quality of life.

Regarding side effects, the FDA stated that women taking Avastin for metastatic breast cancer risk potentially life-threatening or serious side effects, such as bleeding and haemorrhaging; heart attack or heart failure; extremely high blood pressure; and the development of perforations in different parts of the body such as the nose, stomach and intestines. The EMA does not concur with the FDA’s opinion and still allows Avastin for metastatic breast cancer.¹⁴⁶

One expert oncologist stated, “I would not participate in this trial myself”. As a rationale she mentions the negative benefit/risk ratio similar to the FDA opinion described above.

Looking at the severity of the side effects and the lack of benefit for breast cancer patients raises questions as to why the trial was not halted in 2011, when the FDA revoked approval of Avastin. It seems that the sponsor of the trial knowingly exposed breast cancer patients to serious health risks and unnecessary suffering. When we look at the completion date (June 2014) we read that, “final data collection for primary outcome measure” took place. But what kind of relevant measure or analysis could the sponsor possibly make knowing the unambiguous withdrawal of the indication by the FDA?

Comments of Roche (Excerpts):¹⁴⁷ “While the FDA has revoked the indication of bevacizumab for the treatment of metastatic breast cancer, the European Medicines Agency (EMA) and other authorities do not share this opinion and continue to consider bevacizumab an appropriate treatment option as indicated in the label. Based on available

scientific evidence and in agreement with the authorities in the concerned countries, Roche did not see a reason to stop the IMELDA study after the FDA decision.

“The study was conducted in countries outside of the US (among others, France, Spain, Italy, Poland, Turkey and Egypt). During the course of the study, 10 Steering Committee meetings took place (from November 2010 until June 2014).

“In February 2011, the study was closed in Egypt upon request of the Ministry of Health, and eight active Egyptian patients were withdrawn. No other country took this decision.

“An IDMC [Independent Data Monitoring Committee] implemented and started its work as of June 2011 in agreement with further health authorities. (...) The IDMC was in charge of reviewing the patient safety in the trial. They never had concerns and let the study continue as planned until the end.

“The safety was as expected and didn’t show new safety signals.

“The study was published in 2014 (J. Gligorov et al, *Lancet Oncology*). The publication provides comprehen-

BOX 7: PERSPECTIVES OF CLINICAL TRIAL PARTICIPANTS

DANIA’S STORY

Dania (name changed to protect identity) is a woman in her 60s and subject of a clinical trial sponsored by the Swiss company Roche. “I don’t have health insurance. In the past I used to be paid a handsome salary. Thus, I didn’t care at the time to obtain health insurance, as this is the case [when you are] working in the private sector.”

In 2010 after the development of a large tumour, Dania underwent surgery, having received approval for state-funded treatment. The tumour was removed together with part of the breast and with 17 lymph nodes. Another approval for treatment was obtained so that she could receive chemotherapy.

Two years later, she suffered from a severe cough, described by her doctor as a tracheitis and by another as pneumonia. She was unsure which of the two opinions to trust until she visited a well-known allergist, who told her that the cancer tumour could have attacked the lungs.

Undergoing more specific tests, she realised that this was the same type of cancer she suffered in her breast, adenocarcinoma. When she consulted an oncologist she was offered the chance to participate in a clinical trial to test the efficacy of a new drug. The main incentive was that treatment, tests, and follow up would be free. She agreed readily.

Prior to joining the trial, and with the preliminary tests, Dania learned that the tumour had metastasised to the brain as well. “I had read the informed consent form quickly without paying much attention to detail because I was happy with the treatment team. Moreover, the trial was in the name of a well known oncologist.”

In 2013, Dania started the clinical trial. Since the beginning of the trial, Dania said she suffered from many almost unbearably painful symptoms. The symptoms included her nails falling out, skin burns and severe diarrhoea. She also suffered from incontinence and had to undergo two cataract operations at her own expense because researchers told her that this symptom was not related to the trial drug. The ophthalmologist explained that this cataract was formed because of a brain tumour, which caused inflammation of the brain membrane. “I used to inform the physician responsible for my follow up about the side-effects and he used to photograph them and prescribe medicine. Many times the pain would be unbearable.”

Dania says she was always keen on spreading optimism among all her colleagues in the trial whom she used to meet during chemotherapy sessions. “I used to be grouped with a patient who spoke about death all the time,” she recalls. Through the Cancer Patients Aid Association, Dania learned about diets, yoga and meditation therapy. “I talk to my body and I talk to the tumour, telling it that it does not have any power over my body,” she says.

sive positive efficacy and favorable safety data that could answer your questions, and we are happy to provide any additional information as needed.”

According to Roche, the trial was halted in 2011 in Egypt on request of the Egyptian authorities, but no further details were given. The date of the decision coincides with FDA’s revocation of the marketing approval of the breast cancer indication for bevacizumab, which suggest that both events are linked. If that is the case, the Egyptian authorities may have reacted in a much more precautionary way than the EMA. Roche claims that everything was monitored very closely and no safety issues were identified. An article published in 2015 in the medical journal *JAMA Oncology* mentioned that this trial showed “no differences among different subgroups in terms of overall survival, and no significant changes in quality of life measures. These results are difficult to apply to clinical practice because there was no control arm investigating capecitabine without bevacizumab”.¹⁴⁸ Beside the question of efficacy, this analysis suggests methodological flaws that potentially un-

dermine the value of the trial – and hence the benefits to the host countries. In our survey on the affordability of certain medicines that have been tested in Egypt, a one-month supply of bevacizumab bought in an Egyptian pharmacy costs more than 20 times the official monthly minimum wage (see Chapter 6).

The vulnerability of Egyptian cancer patients is illustrated by the testimonies of trial participants (Box 7 and 8).

BOX 8: PERSPECTIVES OF CLINICAL TRIAL PARTICIPANTS

WALAA’S STORY

Walaa¹⁴⁹ is a patient participating in a lung cancer clinical trial. Two years ago she noticed her left eyelid sagging (medically known as blepharochalasis). She consulted more than one ophthalmologist, until one of them advised her to visit a neurologist. The tests showed she had lung cancer.

“I learnt of this and I felt scared because I am not insured,” Walaa said. “I am a housewife. My husband is a retired engineer. I have three sons, all of whom have graduated. Over two years we spent all of our savings despite receiving state-funded treatment.”

After her diagnosis she had surgery for the removal of the rare tumour, at the expense of the state. She received chemotherapy sessions, followed by radiotherapy. Walaa continued to feel sick. It was discovered that the tumour still existed and was affecting the left side of her body.

Only part of the tumour had been treated but follow up surgery would be difficult. She added, “I was working on the papers for receiving state-funded treatment, a very difficult and lengthy procedure, and in the meantime I was taking some treatment sessions at my own expense. I had to sell some of my belongings.”

Hope was restored when she received a phone call informing her of the chance to join a trial. Walaa said, “I was so

happy to have an opportunity for treatment after having lost hope. I signed the informed consent form immediately and did not care to read it in detail. I believe the pharmaceutical company was American. My left side was almost paralysed. The decision to continue the treatment was made by my family, due to the difficulty of securing EGP 120,000 (about US\$ 13,500) annually. I was about to sell my last property.”

Walaa added, “The new drug has different effects such as causing my hair to fall [out]. It has also caused me severe anaemia, which required [a] blood transfusion and my blood type is very rare. However, we managed to find it, only to suffer greatly before I could reach a hospital that would give me the blood. It was very costly.”

She held a package of medicine on which was written “for clinical trials only”, and that in Egypt only two persons are subject to this trial. She said, “The trial drugs disturb my stomach and I did not know that, as I already have problems due to the large amounts of painkillers I took. Thus, I suffered once I received the first dose, and they prescribed stomach pain treatments.”

Walaa says, “I heard they would follow up my case after the trial, which is good, because I’ve spent so much money since I started treatment. All I care for is receiving medication.” When we met her again, Walaa had finished her trial but her condition had not improved. She hopes to be a part of a new clinical trial.

6 AFFORDABILITY AND ACCESSIBILITY OF MEDICINES TESTED IN INDUSTRY-SPONSORED CLINICAL DRUG TRIALS IN EGYPT

In terms of access to tested medicines after a clinical trial has taken place in a low- or middle-income country we should distinguish between two issues that involve different mechanisms, target groups, responsibilities and timelines:

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

POST-TRIAL ACCESS TO TREATMENTS FOR TRIAL PARTICIPANTS

Leading international ethical guidelines such as the Declaration of Helsinki and the CIOMS Guidelines include the right to post-trial-access to medicine (PTA) for participants in clinical trials. Article 34 of the Declaration of Helsinki states, “In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.”¹⁵⁰

DO TNCs REALLY LIVE UP WITH THEIR PROMISES REGARDING POST-TRIAL ACCESS?

Research by SOMO in 2015¹⁵¹ tried to identify elements of corporate best practice among nine of the biggest TNCs in relation to PTA. Whilst all companies included in the research refer in their policies to the Declaration of Helsinki, PTA is only provided in very specific circumstances on a case-by-case basis. PTA is even more exceptional in low- and middle-income countries, where the need is much greater. The scarcity of PTA arrangements by commercial sponsors in such countries is especially worrying. In fact, the limited number of PTA arrangements collected by SOMO's research has not provided enough information to identify elements of best practice.

Roche has developed several policies in relation to PTA—excerpts include:

- “As part of this commitment and in accordance with the Declaration of Helsinki, Roche offers patients who participate in Roche-sponsored clinical trials continued access to the investigational medicinal product that they received after trial completion, when appropriate”¹⁵² (emphasis added).
- “There are certain circumstances when, for the well-being of patients participating in a trial, continued access to the Roche investigational medicinal product is necessary. Examples are serious, life-threatening or disabling diseases such as HIV/AIDS, cancer, or lupus, when no alternative treatment is commercially available”¹⁵³ (emphasis added).

Novartis has a similar provision:

- “Where applicable, e.g. in the case of life-saving therapies or serious consequences if the medication was withdrawn, research participants may, after trial completion, be offered participation in an extension study until marketing authorization”¹⁵⁴ (emphasis added).

Hence cancer is considered by the two companies that account for half of the industry-sponsored trials presently conducted in Egypt as valid ground for PTA, but their policy is drafted so that they can ultimately decide when and where they rely on this mechanism. Even if alternative treatments officially existed on the Egyptian market, they would be unaffordable for the majority of their trial participants who would thus rely on the sponsor company to avoid any treatment interruption.

Is PTA happening in Egypt? Few experts and participants interviewed during this research spontaneously mentioned this issue and were able to give concrete examples.

Heba Khafagy, Professor of Oncology, Cairo University Hospital (Kasr El-Aini) says follow-up continues even post trial.

Nihal el-Habashi, Medical Physiology Professor, Academic Director of the Clinical Studies Centre at Alexandria University, clarifies that the protocol of the study sets the standards for admitting patients: “We face problems in follow-up and continued access by the patient to the drug, especially in chronic diseases. We had a successful attempt in the treatment of psoriasis in 2012. We asked the research sponsor company to continue to supply the patients with the drug. However, the MOH refused, despite the fact that it should be the one enforcing this condition.”

In this report, several experts and participants interviewed have said clinical trials are an opportunity to access free treatment; but what happens after the trial? This is difficult to know as only FDA-regulated trials labelled as “expanded access studies” are registered on the NIH Database – and there are only two of those with a branch in Egypt. Other extension studies – which are also a way to guarantee PTA – are labelled as Phase IV studies. The regulatory aspects to allow the provision of treatment under compassionate use schemes or similar in Egypt are also unclear, as the refusal of the MOH mentioned above shows.

We could not gather strong evidence of PTA provisions being applied in Egypt – this would require further research. We suspect that PTA arranged and paid for by a commercial sponsor is the exception rather than the rule, as expressed in the SOMO study.

This was confirmed by our discussions with Roche representatives. When we met them in Cairo, they claimed the company relies on a clear PTA policy. But when asked if they could give us concrete examples of what is currently being implemented in relation to cancer trials, they admitted they had no PTA mechanism presently active in Egypt.¹⁵⁵ We asked Roche to review this assertion and it reiterated that its respective policies “stipulate clearly that PTA is a rule” in all their studies “as appropriate, also taking into account accessibility from a financial point of view of patients”. Based on the sole example of the previously discussed vemurafinib study (see Chapter 5), they claim that their policies “are effectively being adhered to”. As they provided no other example, we consider that their PTA policy is not applied to all their trials.

We argue, as expressed in a recently published paper,¹⁵⁶ that there is urgent need for consideration of PTA benefits and to agree on practical recommendations for addressing or improving current practices, especially in low- or middle-income countries where participants have limited access to health care and medicines through public schemes.

AVAILABILITY OF MEDICINES TESTED IN EGYPT

The Declaration of Helsinki states that, “Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.”¹⁵⁷

The CIOMS Guidelines also stress the importance of sharing the benefits: “Even if research addresses a question that has social value for the community or population where it is carried out, the community or population will not benefit from successful research unless the knowledge and interventions that it produces are made available to the population.”¹⁵⁸

Alaa Awad, Professor of Hepatology, Theodore Bilharz Institute, Cairo, says that the draft law failed to address the benefit to Egyptians at large from conducting such a trial, such as the responsibility of the sponsor company vis-a-vis the state to make the drug available, after approval, in the Egyptian market at lower prices, or even grant domestic manufacturing rights of such a product.

TNCs also have clear written policies in place in this regard. Roche states that, “Where there are no plans to apply for marketing authorisation of a particular medicinal product in a low- or middle-income country, Roche will not conduct clinical trials with that particular medicinal product in the concerned low- or middle-income country.”¹⁵⁹ On its website, Novartis Oncology says that, “We commit to registering our new treatments in every country that has participated in the clinical trials and to making the treatments commercially available wherever feasible.”¹⁶⁰ During the company’s annual shareholder meeting in February 2014 and in a subsequent letter addressed to the Public Eye (former Berne Declaration), Mr Jörg Reinhardt, Chairman of Novartis, underlined that, “clinical trials will only be conducted in countries where marketing approval will be requested”.¹⁶¹

DO TNCs REALLY LIVE UP TO THEIR PROMISES?

Do TNCs practice what they preach? Do they really systematically apply for marketing approval in Egypt whenever they have tested medicines there? Are these medicines available and affordable?

To find out, we identified 58 medicines in the US NIH Database that were tested in industry-sponsored clinical trials in Egypt between 2005 and 2015, excluding those conducted by Egyptian companies.¹⁶² We then shortlisted 24 out of these 58 medicines for the purposes of this survey, based on several criteria: type of medicines, variety of companies, and date of marketing approval in other countries (EU, US, Switzerland).

The list was given to researchers at Shamseya, a non-profit organisation for innovative community health care solutions that works closely with the Egyptian Initiative for Personal Rights (EIPR). The researchers were mandated to investigate if and when the medicines were approved for marketing in Egypt. Next they tried to find information on the prices of the medicines and if they were reimbursed by the Egyptian social security system – or if they had to be paid for out-of-pocket (see Methodology section).

With this survey we aimed to find out if Egyptians benefitted from the knowledge, practices or interventions that result from the research conducted in their country, as required by the World Medical Association in the Declaration of Helsinki.

The list of selected medicines together with an overview of the results of the survey obtained in February 2016 are set out in Table 5.

TABLE 5: **Availability and affordability of 24 medicines tested in Egypt**

No	Company/ Sponsor	Active ingredient tested (INN)	Brand name	Conditions for testing in Egypt	Testing period in Egypt
1	Bristol-Myers Squibb (BMS)	Daclatasvir	Daklinza	Hepatitis C	2010–2012
2	Eli Lilly	Prasugrel	Effient (US), Efient (EU)	Acute Coronary Syndrome	2008–2012
3	Eli Lilly	Pemetrexed	Alimta	Non-Small Cell Lung Cancer (NSCLC)	2008–2010
4	Janssen	Paliperidone	Invega	Schizophrenia	2007–2013
5	Novartis	Fingolimod	Gilenya	Multiple Sclerosis	2006–2011
6	Novartis	Indacaterol	Onbrez Breezhaler (EU) Arcapta Neohaler (US)	Chronic Obstructive Pulmonary Disease (COPD)	2006–2008
7	Novartis	Nilotinib	Tasigna	Chronic Myeloid Leukemia	2009–2014
8	Novartis	Everolimus	Afinitor	Kidney & Breast Cancer	2008–2014
9	Novartis	Tobramycin Inhalation Powder	Tobi Podhaler	Pulmonary Infection in Cystic Fibrosis Patients	2009–2011
10	Novartis	Valsartan / Amlodipine	Exforge	Hypertension	2009–2011
11	Novartis	Ranibizumab	Lucentis	Age-related Macular Degeneration	2013–2015
12	Novo Nordisk	Insulin Detemir	Levemir	Diabetes	2010–2012
13	Pfizer	13-valent Pneumococcal Conjugate Vaccine (13vPnC)	Prevnar 13 (US), Prevenar 13 (EU)	Pneumococcal Vaccine in Children with Sickle Cell Disease	2009–2013
14	Pfizer	Fesoterodine	Toviaz	Overactive Bladder	2011–2012
15	Pfizer	Irinotecan	Camptosar (US), Campto (EU)	Small Cell Lung Carcinoma	2008–2010
16	Roche	Bevacizumab	Avastin	Non-Small Cell Lung Cancer (NSCLC), Breast Cancer, Ovarian Cancer	2006–2015
17	Roche	Erlotinib	Tarceva	Non-Small Cell Lung Cancer (NSCLC)	2004–2014
18	Roche	Rituximab	MabThera (EU), Rituxan (US)	Non-Hodgkin's Lymphoma	2006–2011
19	Roche	Tocilizumab	Actemra (US, CH), RoActemra (EU)	Rheumatoid Arthritis	2010–2011
20	Sanofi	Irbesartan	Aprovel (EU), Avapro (US)	Hypertension	2006–2010
21	Sanofi	Clopidogrel	Plavix	Congenital Heart Defects in Neonates / Infants	2006–2010
22	Sanofi	Docetaxel	Taxotere (US, EU), Zentiva (CH)	Breast Cancer	1997–2013
23	Sanofi	Insulin Glargine	Lantus	Diabetes	2008–2012
24	Takeda	Alogliptin	Kazano, Nesina & Oseni (US), Vipidia, Vipdomet & Incresync (EU)	Diabetes	2009–2013

Sources: US NIH Database, FDA, EMA, Swissmedic, Egyptian Drug Authority, Egyptian pharmacies, Swiss Compendium of Medicines

RESULTS OF THE SURVEY

We could not obtain any date of marketing approval from the Egyptian Drug Authority (EDA) through their online drug database tool for 9 of the 24 selected medicines.

Of the 15 medicines for which a date of marketing approval existed, five were approved more than 10 years ago. According to a ministerial decree from 1974, drugs for

medical use are registered only for a duration of 10 years, after which approval in Egypt theoretically expires.

Even though their approvals seem to have expired, two of the five medicines are still widely available in Egyptian pharmacies (the diabetes medication Lantus and a treatment for hypertension, Aprovel, both by Sanofi). The research team attempted numerous times to get in touch with the EDA to enquire about the most recent website updates

Initial marketing approval of product in high-income countries (USA, EU, CH)	Registration date of the product in Egypt (as of 1.3.2016)	Average price in pharmacies for a monthly treatment (EGP)	Posology considered (source: compendium.ch)	Multiple of official monthly minimum wage (EGP 1200)	Dispensed by State-subsidised programme (PTES)
2014–2015	None found	—	—	—	Yes
2009	None found	—	—	—	No
2004–2005	1.3.07	No information	500 mg / month	—	Yes
2006–2008	7.5.09	5'880	28 tablets @ 6 mg	> 4	No
2010–2011	25.7.13	15'807	28 capsules @ 0.5 mg	> 13	No
2009–2011	21.6.12	231	30 capsules to inhale @ 150 µg	< 1	No
2007	10.3.11	6'175	28 capsules @ 200 mg	> 5	Yes
2009	2.8.12	19'100	30 tablets @ 10 mg	> 15	No
2011–2013	None found	—	—	—	No
2006–2007	3.7.08	76	28 tablets @ 10 mg/160 mg	< 1	No
2006–2007	None found	5'600	1 vial @ 10 mg/ml/eye	> 4	Yes
2003–2005	1.3.07	90	1 cartridge @ 3 ml (300 IU)	< 1	No
2009–2010	12.3.09	1'520	4 doses @ 0.5 ml (active immunisation)	> 1	No
2007–2008	None found	—	—	—	No
1996–1999	11.3.97	9'300	6 vials @ 100 mg/5 ml (for patient 70 kg/170 cm)	> 7	No
2004–2005	None found	25'000	2.5 vials @ 400 mg/16 ml (for patient 70 kg)	> 20	No
2004–2005	None found	26'000	30 tablets @ 150 mg	> 21	No
1997–1998	30.7.02	24'600	2 vials @ 500 mg/50 ml	> 20	Yes (For dose of 600)
2008–2010	None found	7'026	1.5 vial @ 400 mg/20 ml	> 5	No
1997	10.9.02	140	28 tablets @ 300 mg	< 1	No
1997–1998	18.9.13	205	28 tablets @ 75 mg	< 1	No
1995–1996	14.6.06	4'845	1.7 vial @ 80 mg/2 ml (for patient 70 kg)	> 4	Yes (For chemotherapy)
2000–2002	1.4.03	80	1 cartridge @ 5 ml (100 IU)	< 1	No
2013	None found	—	—	—	No

or if the registration of the drugs has been renewed. However, they did not respond. We also contacted Sanofi and the Egyptian Pharmacovigilance Center directly on this matter, without response.

To acquire the listed prices of the approved medicines, the research team contacted two small local pharmacies, one major chain of pharmacies and one online pharmacy. Overall, the majority of medicines were not available in

the small pharmacies but were available at the major chain.

Reimbursement by the Egyptian social security system is provided for by the Program for Treatment at the Expense of State (PTES). The eligibility criteria for participating in PTES are: not being enrolled in private insurance scheme or in the Health Insurance Organization, and evidence that the patient cannot afford treatment (usually determined by

FIGURE 4: proportion of marketing approvals

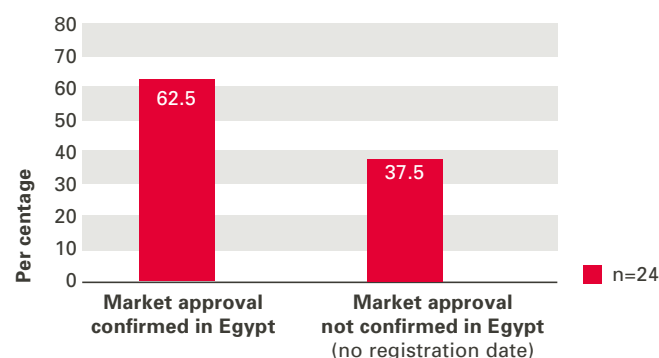
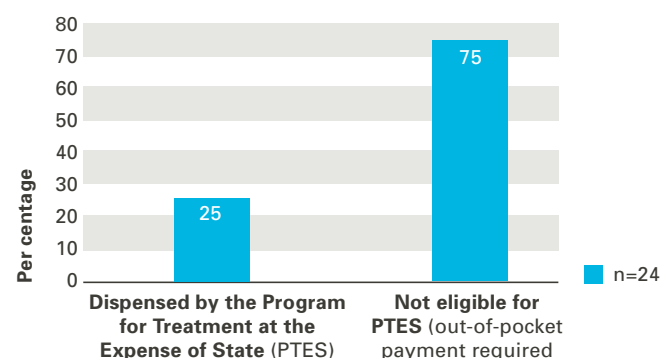


FIGURE 5: Proportion of medicines tested in Egypt eligible for a state-subsidised treatment



their employment status). To be eligible for PTES, the patient requires a medical examination at one of the hospitals offering the service. Treatment is dispensed according to availability, which often leads to patients financing a large portion of the medications out of pocket.

The results are appalling. As Table 5 shows, a monthly treatment with some of the medicines surveyed costs more than 20 times the official monthly minimum wage of the public sector – which today stands at EGP 1,200¹⁶³ (US\$ 135 at the 3 May 2016 exchange rate¹⁶⁴). A large percentage (75 per cent) is also not dispensed by PTES, which often represents the last chance for uninsured people to get access to costly treatments.

For wealthy people in Egypt it is often possible to obtain medicines through a pharmacy, even if the substance is not officially approved for local marketing. One example is Tarceva, an EGP 25,000 (approximately US\$ 2,800) medication for non-small cell lung cancer produced by Roche, whose price notably exceeds the average budget. Upon enquiring about it at one of the major local pharmacies, the survey team was informed that the medication could be ordered.

Subsequently the survey team was contacted by one of the pharmacy's employees who used his private phone for that purpose. "This is not really official," says Nevin El Nadi, survey coordinator at Shamseya. "Pharmacies have a parallel, informal system, comparable to a black market. This is also an explanation for the call through a private phone. Pharmacies want to know who is interested in the information and who they are sending it to."

RESULTS OF SIMILAR SURVEYS CARRIED OUT IN OTHER LOW- AND MIDDLE-INCOME COUNTRIES

The findings of this survey in Egypt echo conclusions of recent similar studies carried out in other low- and middle-income countries.

In Latin America, a cross-sectional study by Homedes and Ugalde published in the *WHO Bulletin* in 2015 aimed to assess whether new pharmaceutical products approved by the US FDA in 2011 and 2012 were registered, commercialised and sold at affordable prices in the Latin American

countries where they were tested. This study highlighted the following findings: of an expected 114 registrations, if the 33 products considered had been registered in all countries where tested, only 68 (60 per cent) were completed. Eight products were registered and commercialised in all countries but 10 had not been registered in any of the countries. With one exception, products for which pricing information was obtained (n=18) cost more than the monthly minimum wage in all countries and 12 products cost at least five times the monthly minimum wage. The authors conclude that many pharmaceutical products tested in Latin America are thus unavailable and/or unaffordable to most of the population. They recommend that ethical review committees should consider the local affordability and therapeutic relevance of new products as additional criteria for the approval of clinical trials, and that the opportunity costs of clinical trials be assessed.¹⁶⁵

Another study¹⁶⁶ published in 2015 in the *British Medical Journal* focused on India and South Africa. Its objective was to assess the relation between the number of clinical trials conducted in the period from 1 January 2005 to 31 December 2010 and the respective new drug approvals in those two countries. The study revealed that 39.6 per cent clinical trials in India and 60.1 per cent in South Africa led to market authorisation in the EU/USA without a new drug application approval in India or South Africa. The authors conclude that despite an increase in clinical trial activities, there is a clear gap between the number of trials conducted and market availability of these new drugs in India and South Africa. They recommend that drug regulatory authorities, investigators, institutional review boards and patient groups should direct their efforts to ensuring availability of new drugs in the market that have been tested and researched on their population.¹⁶⁷

Egypt is therefore no exception to what appears to be a global problem in relation to industry-sponsored clinical drug trials conducted in low- and middle-income countries when it comes to access to tested medicines. Beyond the promises that appear in their well-drafted policy papers, pharmaceutical TNCs have a clear and direct responsibility to make sure that people benefit from clinical research conducted in their country.

7 UPHOLDING INTERNATIONAL ETHICAL STANDARDS FOR CLINICAL TRIALS IN EGYPT

1. IS EGYPT ATTRACTIVE FOR INDUSTRIAL SPONSORS DESPITE THE UNSTABLE POLITICAL CONTEXT?

In recent years Egypt has been the second most popular destination for clinical trials on the African continent. Looking in particular at the two TNCs that run most of the clinical trials in Egypt, namely Swiss companies Novartis and Roche, it can be concluded that the Arab Spring events of early 2011 and its subsequent political unrest and dysfunctional democratic governance had no chilling effect on the number of active drug trials. On the contrary, the number actually increased for both companies between 2011 and 2016, reaching a peak in 2013.

The factors that explain why the whole Middle East and North Africa (MENA) region has seen the number of clinical trials grow (at times faster than in any other region) also apply to Egypt. Pharmaceutical markets are growing significantly in these countries and provide even more space for expansion; they are called ‘pharmerging countries’ by some. Next to this, average cost of a clinical trial is 59 per cent lower compared to the average cost in the US. The required infrastructure is sufficiently available and timelines to conduct trials are shorter. Patient recruitment is faster and the desired patient groups are all present, including large numbers of treatment-naïve patients. What

makes Egypt especially ‘attractive’ is the large presence of certain diseases. There is a high prevalence of cancer and the prevalence of hepatitis C in Egypt is the highest in the world. The fact that a large section of the population has limited access to expensive treatments makes them easy to be recruited in a drug trial.

Although lower compared to other middle-income economies such as South Africa, China, India or Latin American countries, the number of active international drug trials suggests that Egypt remains among the favourite destinations for TNCs offshoring some of their testing. This is happening despite the political situation and what may be seen as regulatory hurdles and possible disincentives to conduct international trials in Egypt, such as the frequent delays in the approval procedure (as acknowledged by Roche representatives) or the difficulties in exporting biological samples to a centralised reference laboratory – a standard procedure in multi-centric trials – because of the need to obtain prior security clearance from the Egyptian government. This makes us believe that the incentives to conduct international trials in Egypt must be very strong.

2. DO UNETHICAL PRACTICES OCCUR IN INDUSTRY SPONSORED CLINICAL TRIALS CONDUCTED IN EGYPT?

The fact that participation in a trial is often the only way to receive treatment also means that patients are less inclined to take into account that their drug is experimental, i.e. that it may not be effective, or may have unknown side effects. Several patients stated that they were so desperate to receive treatment that they did not bother to read the informed consent form. It can be concluded that the lack of access to a standard treatment leaves them no choice to participate and therefore one cannot speak of voluntary and informed consent, which is an ethical violation according to the Declaration of Helsinki (paragraph 26). Based on the findings in this report we argue that the current Egyptian system in which clinical trials are being carried out does not provide adequate safeguards to vulnera-

ble groups and individuals to protect their safety and their human rights, which is also an ethical violation (DoH, paragraph 19).

The cancer trials described in this report provide the clearest illustration of the vulnerability of trial participants in Egypt and the profound inequality of their situation compared to cancer patients in wealthier nations. Cancer patients in more affluent countries will generally receive a proven treatment first, and if that does not work they may engage in clinical trials. Due to the high prices of cancer treatments, experimental drugs may be the only medication an Egyptian cancer patient will receive. As such they run an unknown risk of experiencing serious side effects whilst already suffering a serious disease.

Another example raising serious ethical questions concerns Phase I and Phase II trials. The situation is that in Egypt it is not permitted to conduct trials with foreign pharmaceutical products unless they are approved already in the country of origin. The regulation enforcing this was established to protect Egyptians from being used as guinea pigs; new foreign drugs cannot be tested first on Egyptians. Remarkably, 16 per cent of all active industry sponsored trials in Egypt in February 2016 are Phase I and Phase II trials. Early phase trials with already approved drugs only make sense scientifically if they are tested as a new indication or on a new type of population, however it is unclear if these conditions are systematically met. Scientifically unsound and repetitive clinical trials should be regarded as unethical as each clinical trial exposes participants to unnecessary risks. Our research also shows that, in at least 3 early stage trials, investigational drugs that are not yet approved in Europe or the US are tested, thus contravening the Egyptian regulations. Whether this is due to laxity on the part of the Egyptian authorities or to strong arguments justifying an exception is unclear.

During this research, we have seen no evidence of post-trial access to treatments mechanisms being put in place in Egypt, despite TNCs' promises expressed in their policy

papers. Leading international ethical guidelines such as the Declaration of Helsinki and the CIOMS Guidelines include the right to post-trial-access to medicine for participants in clinical trials.

While government oversight is lacking, commercial sponsors make use of contract research organisations (CROs) to oversee all stages of their research. CROs are mandated and paid by the sponsoring company to exercise a monitoring role that would normally be expected of government authorities. There is a conflict of interest in the dual role of CROs in Egypt: on the one hand being involved in the execution of a trial as a subcontractor of a pharmaceutical industry, and on the other hand being involved in the monitoring of trials. The second role may interfere with the first one, potentially leading to the cover up of unethical practices in order not to damage the position of the sponsor company. If this dual role of CROs is not specific to Egypt, the protection of subjects participating in such trials is even more at risk in a context where governmental oversight is considered insufficient.

3. ARE DRUGS TESTED IN EGYPT ALSO AVAILABLE TO AND AFFORDABLE FOR THE EGYPTIAN POPULATION?

Although the Egyptian government provides some form of health insurance and free treatment schemes, these provisions are often compromised due to bureaucratic hurdles. Furthermore they often do not cover all treatments, a second round of treatment or all the costs of a treatment, which is particularly problematic for cancer treatments. Hence, access to treatment was seen by several key informants as a positive effect of clinical trials in the country. However, clinical trials must remain scientific endeavours aimed at producing socially valuable knowledge – not at providing treatments for patients. For the latter, other mechanisms ensuring sustainable access to affordable treatments should be sought. Despite claims in TNCs' policy papers ensuring no clinical trial will be conducted in countries where there are no plans to request a marketing approval for the tested medicine, our research shows that this is far from being the case. Of the 24 medications tested in Egypt that we surveyed, we could obtain no date of marketing approval for nine (37.5 per cent) of them. The latter should be considered as officially unavailable. Of the 15 medicines for which a date of marketing approval existed, five were approved more than 10 years ago – beyond the duration of expiration foreseen by Egyptian regulations. Of the available medications, two in three cost more than the monthly

minimum wage for a monthly treatment – one in five costing more than 20 times the monthly minimum wage. A large percentage (75 per cent) is not provided by the state-subsidised free treatment programme, meaning uninsured patients will have to pay out of pocket. Most of these medicines are therefore out of reach for the majority of Egyptian patients.

According to international ethical guidelines, each clinical trial has to be beneficial for the population on which the medication is tested. Despite the fact that almost all pharmaceutical companies claim to apply for marketing authorisation in the countries where they test their medications, our research shows that this is far from being the case. It is unlikely that TNCs have applied for marketing approvals and been turned down by the Egyptian Drug Authority, since these medicines have all been authorised in high-income markets. This means that pharmaceutical companies do not uphold their own commitments and violate international standards such as the DOH and CIOMS Guidelines.

4. IS THERE REASON FOR INCREASED ETHICAL SCRUTINY AT THE EUROPEAN LEVEL WHEN PIVOTAL CLINICAL TRIALS FOR AN EU OR SWISS MARKETING AUTHORISATION PROCESS ARE CONDUCTED IN EGYPT?

During our investigation we found systemic flaws that would justify increased ethical scrutiny at European level in order to protect the rights and safety of trial participants in Egypt. The research has identified a number of 'red flags'.

First of all, Egypt is a lower middle-income economy with a large population of poor people and with a public health insurance system that covers roughly only half of the population. Egypt's government health expenditure is less than 1.5 per cent of GDP, resulting in 72 per cent of all spending on health care being out of pocket. This classifies the pool of potential participants as particularly vulnerable, which creates an increased likelihood of being wronged or of incurring additional harm. According to the Declaration of Helsinki, all vulnerable groups and individuals should receive specifically considered protection (DoH paragraph 19).

Secondly, to protect clinical trial participants, and especially to protect the vulnerable, a robust legislative framework with functioning independent control systems is a prerequisite, but this is clearly not present in Egypt. A fundamental flaw in the Egyptian system of clinical trials is the absence of comprehensive unified legislation. Instead, some of the aspects pertaining to clinical trials are referred to in various legislations and administrative decrees. This means that there is no clear guidance to those bodies charged with overseeing clinical trials or to those stakeholders involved in executing clinical trials, leaving room for different interpretations and making it more difficult to identify violations and impose sanctions. The political situation in Egypt has left the country with dysfunctional democratic governance and the absence of a legislative body for a long time. The parliament newly installed in January 2016 still needs to prove it can function as a democratic legislative body, and the fact that independent opposition has been marginalised is not very promising.

Although TNCs claim to follow high ethical standards such as those enshrined in the Declaration of Helsinki, PTA is only provided in very specific circumstances on a case-by-case basis. Few experts and participants interviewed during this research spontaneously mentioned this issue and were able to give concrete examples. On our question, Roche admitted they had only one PTA mechanism presently active in Egypt. This is ridiculously low when compared to the number of clinical trials the Swiss company is and has been conducting in Egypt. Given the overall difficulties for Egyptian patients to access essential medicines, in particular cancer ones, EU

and Swiss medicines agencies must examine whether PTA provisions were present in clinical trials conducted in low- and middle-income countries that serve for marketing authorisations in Europe. This would clearly be another red flag.

Another system flaw relates to Research Ethics Committees (RECs); they play a pivotal role in safeguarding the rights of clinical trial participants. In Egypt, trials need to be approved at central level by the REC of the Ministry of Health and by institutional review boards (IRB) at the relevant research institution where the trial will be conducted. Our research reveals that IRBs face serious challenges to carrying out their tasks of giving approval prior to the start of a trial and monitoring ongoing trials. A first challenge is the absence of uniform guidelines regarding membership composition and accreditation. A second challenge is that IRBs face budget constraints. A third challenge is the increasingly heavy burden on IRBs in recent years resulting from an increase in protocols to be revised and the rise of clinical trials with a more complex nature being carried out in Egypt. Several experts have expressed concern that these flaws lead to uneven and inadequate protection of clinical trial participants.

In countries such as India, media and civil society groups have played an important role in signalling and unveiling unethical clinical trials. Access to information is an important prerequisite for civil society to be able to play this role. In Egypt, access to information is quite challenging, particularly in the area of clinical trial registration and monitoring. Reports of ethics committees are not publicly available. Neither is the clinical trials database of the Ministry of Health's Research Ethics Committee (MOH REC) accessible to civil society organisations or journalists. This database includes data on industry-sponsored clinical trials submitted for approval by the MOH REC. While greater transparency is definitely needed in Egypt, this need extends to Europe as well. We asked the EMA how many inspections took place between 2010 and 2015 and were told that two inspections took place in that period, one in 2012 and one in 2014. Unfortunately we were not given any information about the companies involved and the findings of the report. Current regulations prohibit access to the inspection reports by parties other than the Commission, the EMA or the Competent Authorities, or the duly appointed experts of these parties, unless otherwise indicated by legislation.¹⁶⁸

8 RECOMMENDATIONS

RECOMMENDATIONS FOR MULTINATIONAL PHARMACEUTICAL COMPANIES

When pharmaceutical companies engage in clinical trials in low- and middle-income countries with limited access to treatment, they should ascertain that the safety and rights of participants are properly protected and that trial protocols and practice are in line with the highest ethical standards, such as the Declaration of Helsinki and the CIOMS Guidelines. Outsourcing a clinical trial to a contract research organisation does not absolve them from this responsibility.

In this report we have presented testimonies of seriously ill patients desperate to receive treatment, who as a result have not properly studied the informed consent form. We urge the pharmaceutical industry to ascertain that clinical trial participants are aware of the potential side effects of experimental treatment.

During our investigation we found that treatment-naïve cancer patients were enrolled in clinical trials – a practice considered iniquitous when compared to more affluent countries. We urge the pharmaceutical industry to provide these patients with the proven standard treatment (standard of care) first – assuming it exists and its risk/benefit ratio is acceptable – before they are enrolled in a clinical trial.

Our investigation also shows that several medicines tested on Egyptian populations are unaffordable once the treatment enters the Egyptian market. We urge the pharmaceutical industry that if they test new medications in

An abuse of research ethics should be considered a human rights violation (for example, clinical trials without proper informed consent from participants). In order to identify, prevent, mitigate and account for how they address their adverse human rights impacts, business enterprises should carry out human rights due diligence. The process should include assessing actual and potential human rights impacts, integrating and acting upon the findings, tracking responses and communicating how impacts are addressed, and provide remedy.

RECOMMENDATIONS FOR THE EU AND SWISS REGULATORY AUTHORITIES

In our investigation we found several practices that have been judged violations of ethical standards and/or scientifically flawed by several international experts. The European Medicines Agency has formulated several regulatory actions that give the European regulatory authorities ample opportunity to ascertain that medicines tested outside the European Union comply with the same ethical standards as those tested within the EU.

Before granting a drug market authorisation, EU and Swiss regulatory authorities should demand a justification from the relevant pharmaceutical company as to why vulnerable populations were involved in a clinical trial and should ask which provisions the trial sponsor took to adequately protect these vulnerable participants. One particularly relevant aspect is to provide a description on how informed consent was taken. Even if proper procedures were apparently followed in obtaining informed consent, EU regulatory authorities should be cognisant that many of the patients who participated in these trials may not have had any other option for obtaining adequate medical treatment.

We are deeply concerned about cancer trials being performed on seriously ill cancer patients in Egypt without sufficient ethical safeguards. Experts involved in clinical trials in Egypt mentioned that treatment-naïve participants were enrolled without receiving a proven treatment beforehand. We find it is the responsibility of the EMA and Swissmedic to ascertain that the same standards regarding clinical trials are complied with both within and outside their jurisdictions as data that serve for marketing authorisations in Europe are increasingly global.

Furthermore, before granting market authorisation, the EU regulatory authorities should ascertain whether the trial sponsor has made adequate provisions for post-trial

An abuse of research ethics should be considered a human rights violation.

Egypt, these medications should be made available in the country at an affordable price. They should put their own policies into practice.

We urge multinational companies to comply with the United Nations Guiding Principles on Business and Human Rights (UNGPR).¹⁶⁹ These stipulate that companies have a responsibility to respect human rights and that they should be held accountable for all their operations, including those taking place abroad and/or through subsidiaries.

treatment access for participants in Egypt. Finally, this report's findings and conclusions justify an increase of inspections of clinical trials in Egypt by European Regulatory Authorities.

The European Medicines Agency does not provide specific information regarding GCP inspections. Making inspection reports public would be an important step towards facilitating the public scrutiny needed to hold the pharmaceutical industry accountable.

RECOMMENDATIONS FOR EGYPTIAN AUTHORITIES AND STAKEHOLDERS

The following recommendations are addressed to Egyptian authorities in order to ensure that clinical trials conducted in Egypt benefit the population where the trial is conducted, respect the right to continued treatment once a trial is over, and ensure the capability and opportunity of participants to give informed consent voluntarily among other required core ethical standards.

1) The Constitution of 2014 states in Article 60 that: "The human body is inviolable. Any assault, defilement or mutilation thereof is a crime punishable by Law. Organ trafficking is forbidden, and no medical or scientific experiment may be performed thereon without a documented free consent of the subject according to established principles of the medical field as regulated by law."

Since such laws do not currently exist, it is necessary to develop a single, robust legislative framework with a functional independent control system. Any forthcoming versions of this new law on clinical trials should do the following:

- a. Clearly establish the agencies permitted to conduct pharmacological research, the conditions under which research can take place, and government regulatory bodies supervising clinical trials.
- b. Include specific regulations governing funding of clinical trials, monitoring procedures, compel pharmaceutical companies to transparently announce the results of trials and to assume legal responsibility – particularly vis-a-vis trial participants.
- c. Include specific regulations concerning how clinical trial participants' consent is obtained, their access to information, and place direct legal liability in cases of legal infringement on the company sponsoring the trial and not the researcher.
- d. Include legislative and regulatory measures to ensure full, post-trial access to treatment. Our investigation revealed appalling situations where one month's worth of treatment with particular approved medicines cost more than 20 times the official monthly minimum wage in the public sector.
- e. Maintain the safeguards preventing clinical trials sponsored by transnational corporations (TNCs) from being

conducted in Egypt unless the product they are testing has been granted market approval in its originating country. Exceptions should be made possible when new medicines are planned to be tested in Egypt against diseases that are primarily affecting low- and middle-income countries (also called Type II and Type III diseases by WHO¹⁷⁰), such as neglected tropical diseases or emerging infectious diseases

- f. Address the current legislative gap that does not tackle the legality of conducting Phase 1 and 2 clinical trials. This is particularly important since there are limited guarantees that, in these trials, patients in the placebo group (those not actually receiving a treatment) will have access to care if their pain or conditions worsen.
- g. Take the Declaration of Helsinki (DOH) and CIOMS Guidelines as their reference point for ethical standards specified in this new law.

While this legislative framework should take all the necessary safeguards against unethical or risky clinical trials, it should nevertheless do this without making the process for trial approvals particularly lengthy or bureaucratic. This will reduce the risk of TNCs resorting to corrupt practices to obtain their trial licences.

- 2) An online, regularly updated public registry of clinical trials conducted in Egypt should be created, ensuring the continuous update of the online drug database provided by the Egyptian Drug Authority (EDA, www.eda.mohp.gov.eg).
- 3) Regarding Phase 1 and 2 clinical trials, authorities should maintain vigilance over current ones and on any future early-stage trials, at least until a clearer national law has been agreed upon, to ensure the ethics of these trials in light of their sometimes questionable design and the fact that similar tests might well have already been completed elsewhere.
- 4) Policy-makers and government authorities should refrain from approaching clinical research as a mere vehicle for the delivery of unproven treatments to participants with limited financial resources. Instead, clinical research should be looked upon as a means to produce socially valuable knowledge that may or may not lead to new treatment plans. This change in mindset is key in a country where the state of the health-care system and cost of health-care make the pool of potential participants particularly vulnerable. This creates an increased likelihood of patients being wronged or of incurring additional harm, particularly in light of Egypt's deficient regulatory functions and lack of awareness and enforcement of patients' rights.
- 5) Knowledge about research design, methodology and ethical consideration should be readily included in the

formal curricula of medical schools or in post-graduate training programmes. Regulations should mandate that study sponsors should provide mandatory, fully funded training on research ethics and fundamental standards of clinical trials to the research team undertaking the trial. In the longer term, study participants' awareness of their rights during clinical trials should be mandated to prevent abuses. Dedicating a suitable national budget for clinical research would also reduce the reliance on private funding by TNCs in research institutions, and would enable a more sustainable, independent and ethical national research output.

- 6) Regulations covering the selection and composition of institutional review boards (IRBs) should be created. The current lack of legislation leads to a random composition of members in different IRBs in Egypt, with a heavy reliance on elderly members and alarmingly non-transparent processes and outputs. In addition, these IRBs should be equipped with the human and financial resources needed to ensure suitable oversight of ongoing clinical trials. This should significantly contribute to improving the quality and consistency of ethical reviews.

- 7) A nationwide patients' rights charter that clearly stipulates the rights of Egyptian patients regarding consent, access to information and participation in research should be adopted.
- 8) Ensuring access to information must be guaranteed as it is a fundamental prerequisite to enable civil society to play its role in signalling and uncovering unethical clinical trials practices. In Egypt, access to information proves challenging, particularly in the area of clinical trial registration and monitoring. Reports of ethics committees are not publicly available, nor is the clinical trials database of the MOH Research Ethics Committee (REC) accessible to civil society organisations or journalists. This database includes data on clinical trials submitted for approval by the MOH REC.
- 9) In addition, policy-makers, parliamentarians and the current administration are urged to respect, protect and fulfil citizens' right to health and access to affordable medicine, particularly for vulnerable people. This will markedly reduce the risk of them being exploited as participants in trials they perceive as an opportunity to freely access treatment they cannot otherwise afford.

One of the hospitals in Greater Cairo where clinical trials are conducted.



APPENDIX: LIST OF EXPERTS INTERVIEWED DURING RESEARCH

EGYPTIAN EXPERTS¹⁷¹

Doaa Abu-Talib

Professor of Law, Ain Shams University
(interviewed on 11 July 2015)

Mohamed Hassan Khalil

Coordinator, Defending the Right to Health Committee
(interviewed on 29 June 2015)

Manal El-Tibi

Member of the National Council for Human Rights
(interviewed on 29 June 2015)

Haitham Abdul-Aziz

Head of Government Pharmacists Committee in the
Ministry of Health
(interviewed on 30 June 2015)

Magd Kotb

Professor of Paediatrics, member of the Research Ethics
Committee in the Faculty of Medicine and Director of the
Preventive Medicine Centre, Cairo University Paediatrics
Hospital (Abul-Rish Children's hospital)
(interviewed on 8 July 2015, meeting on 17 February 2016)

Hany Sleem

Director of Scientific Research Ethics Committee,
National Hepatology and Tropical Medicine Research
Institute and President of the Egyptian Network of
Research Ethics Committees
(interviewed on 14 July 2015)

Alaa Awad

Professor of Hepatology, Theodore Bilharz Institute, Cairo
(interviewed on 2 September 2015)

Magdy El-Serafy

Director of the National Hepatology and Tropical Medi-
cine Research Institute (at the time of research), and
Member of the National Committee for the Control of
Viral Hepatitis
(interviewed on 7 September 2015)

Imam Waked

Professor of Medicine, National Liver Institute, Shebeen
El-Kom, Menoufiya; and Member of the National
Committee for Control of Viral Hepatitis
(interviewed on 23 December 2015, meeting on
17 February 2016)

Islam Muhammad

medical doctor and blogger, member of staff in
the drug research department in one of Egypt's private
pharmaceutical companies
(interviewed on 21 July 2015)

Wahid Doss

Former Director of the National Hepatology and Tropical
Medicine Research Institute, Professor of Hepatology
and President of the National Committee for Control of
Viral Hepatitis
(interviewed on 14 September 2015)

Diaa El Sayed

Trials Principal investigator, National Hepatology
and Tropical Medicine Research Institute
(interviewed on 26 October 2015)

Ayman Sabae

Researcher, Right to Health Programme, Egyptian
Initiative for Personal Rights
(interviewed on 8 September 2015)

Alaa Ghannam

Director of the Right to Health Programme,
Egyptian Initiative for Personal Rights
(interviewed on 27 September 2015)

Heba Khafagy

Professor of Oncology, Cairo University Hospital
(Kasr El-Aini)
(interviewed on 27 October 2015)

Noha Abdul Raziq

Pharmacist, Pharmaceutical Research Centre, Oncology
Department, Cairo University
(interviewed on 27 October 2015)

Alaa Shukrallah

Development Support Centre
(interviewed on 28 September 2015)

Ahmed Metwally

Public Health Specialist, National Research Centre
(interviewed on 29 September 2015)

Wafaa Abdel Aal

Professor of Pathology and Head of Clinical Trials Unit at
the Centre of Excellence, and Convener of Medical
Research Ethics Committee, National Research Centre
(interviewed on 20 October 2015)

Aida Abdel Mohsen

Professor of Public Health, Director of Clinics,
National Research Centre
(interviewed on 29 September 2015)

Nihal el-Habashi

Medical Physiology Professor, Academic Director of the
Clinical Studies Centre at Alexandria University
(interviewed on 12 January 2016)

Muhamad Ezz el-Arab

Professor and Director of the Cancer Treatment Unit,
National Hepatology and Tropical Medicine Research
Institute, Cairo
(interviewed on 7 July 2015)

Rafat Ragae Abdul Malek

Assistant Professor of Oncology, Faculty of Medicine,
Cairo University
(interviewed on 28 November 2015)

Yasser Abdul Qader

Professor of Oncology and Director of Clinical Research
Unit, Department of Oncology, Kasr el-Aini
(interviewed on 22 December 2015)

Emad Hamada

Chair of the Oncology Department at Cairo University
(interviewed on 22 December 2015)

Nadia Zaki

Director of Clinical Research Centre, Faculty of Medicine,
Alexandria University
(interviewed on 12 January 2016)

Hisham Abdul Dayem

Assistant Dean of Menufiyah Liver Institute,
and Liver Institute IRB member
(interviewed on 26 November 2015)

Ahmad Shaarawi

Dean of the National Liver Institute in Menufiyah
(interviewed on 26 November 2015)

Manal Hamdy El-Sayed

Professor of Paediatrics and member of the National
Committee for the Control of Viral Hepatitis
(interviewed on 9 January 2016, meeting on
14 February 2016)

Hamdy Abdul Azim

Oncologist, Former Head of the Oncology Department
and Founder of its Clinical Research and Studies Centre,
Cairo University
(interviewed on 25 November 2015)

Wagida Anwar

Public Health Professor, Member of MOH Committee
for Developing Cancer Treatment Protocols, Ain Shams
University
(interviewed on 28 October 2015)

Mohamed Raouf

Medical Director, Roche Egypt
(meeting on 17 February 2016)

Mohamed Swilam

Country Manager, Roche Egypt
(meeting on 17 February 2016)

EXPERTS OUTSIDE EGYPT**Dutch oncologist**

(prefers to remain anonymous)

Professor Cristiana Sessa

MD, Vice Head of Medical Oncology and Head of Clinical
Research, Oncology Institute of Southern Switzerland,
Bellinzona (Switzerland)

Professor Joel Lexchin

MD, School of Health Policy and Management, Faculty of
Health, York University, Toronto (Canada)

Dr Amar Jesani

Independent researcher in Bioethics and Public health,
Indian Journal of Medical Ethics, Mumbai (India)

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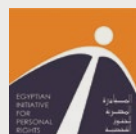
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