

The Clinical Trials Industry in South Africa: Ethics, Rules and Realities



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Abbreviations

abbreviation	in English	in original language
A&E	Accident and emergency	
AIDS	Acquired immunodeficiency syndrome	
BMJ	British Medical Journal	
CAPRISA	Centre for the AIDS Programme of Research in South Africa	
CEDAC	Canadian Expert Drug Advisory Committee	
CHMP	Committee for Medicinal Products for Human Use	
CIOMS	Council for International Organizations of Medical Sciences	
CRA	Clinical research associates	
CRO	Contract Research Organisation	
DoH	Declaration of Helsinki	
EMA	European Medicines Agency	
FDA	Federal Food and Drugs Agency	
GCP	Good Clinical Practice	
GP	General Practitioner	
HIV	Human immunodeficiency virus	
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use	
ICS	Inhaled corticosteroid	
LLC	Limited liability company	
MCC	Medicines Control Council	
NGO	Non-Governmental Organisation	
NHREC	National Health Research Ethics Council	
NHS	National Health Service	
pMDI	Pressurized Metered Dose Inhaler	
RA	Rheumatoid Arthritis	
REC	Research Ethics Committee	
SADAG	South African Depression and Anxiety Group	
SOMO	Centre for Research on Multinational Corporations	Stichting Onderzoek Multinationale Ondernemingen
TB	Tuberculosis	
UK	United Kingdom	
US	United States	
USA	United States of America	
WHO	World Health Organization	
WMA	World Medical Association	
ZAR	South African Rand	

Foreword

This report focuses on the current status of **clinical trials in South Africa**. It is part of Wemos' ongoing research and advocacy aimed at ensuring the **better regulation** of clinical trials and stronger protection for all those taking part.

Over the past decade, South Africa has become an important destination for many international pharmaceutical companies looking to carry out clinical trials. Despite the progress made in the country in recent decades, the divide between rich and poor remains significant. Given the current state of South Africa's struggling public health sector, it is clear that in many cases, people are not in a position to access or afford the medicines or specialist treatment they may need. Therefore the opportunity to participate in clinical trials and receive treatment for free is a tempting proposition for many. This scenario is not unique to South Africa, but a widespread problem in many countries with vast inequalities in income and healthcare provision.

This report includes a number of interviews with medical professionals and industry watchers who were able to highlight the pressing issues of concern, risks and flaws regarding South Africa's clinical trials industry. Ethical questions surrounding **the use of placebo-controlled studies** (chapters 4, 5 and 6) and **post-trial access to treatment** (chapter 7) were raised consistently throughout the research and are therefore discussed at length in this report.

One placebo-controlled study was being carried out by the British-Swedish company AstraZeneca who were trialling an existing children's asthma drug against a placebo treatment. The trial was being carried out on asthmatic children as young as six who were given a placebo inhaler instead of their usual medication for a period of six weeks. Many health experts believe that the withdrawal of regular medication puts children at unnecessary risk of a serious asthma attack and Wemos agrees that such trials should be reconsidered. From the viewpoint of AstraZeneca, placebo-controlled trials such as this have been deemed safe and necessary to satisfy 'regulatory requirements' by the United States' (US) Food and Drug Administration (FDA) which in 2008 dropped the need for compliance with the Declaration of Helsinki (DoH) in clinical trials conducted outside the US.¹

According to some experts, the placebo trials discussed in the current report are not meant for the development of new drugs, but are intended merely **to protect the market share of the company** by adding minor variations to an already existing drug with which they hope to preserve their revenue stream once the patent of the old drug has expired.

In countries such as the Netherlands and Germany, new treatments usually become accessible to most patients quite quickly. This is not the case in South Africa where expensive new drugs often take years to become affordable in public hospitals and clinics. Some doctors and investigators believe that even if the drugs trialled in South Africa do not

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

become affordable to the masses until many years later, the general global benefits of new treatments justify South Africa's expanding role in the global clinical trial industry. But some critics say **South Africa is simply being exploited** by the international drug companies to boost patient numbers and that **the trials provide no long-term benefit** for either the patients or local research staff. To them it seems unethical that patients who risked serious adverse-effects while participating in clinical trials for billion-dollar blockbuster drugs are left to relapse without access to further treatment after the trial ends. Both opinions are outlined in this report which aims to provide both an overview of the current situation and highlight the areas which still require improvement and further review.

Wemos takes the position that the well-being and rights of the individual trial subject must always take precedence over all other interests. The cases described in this report highlight the importance of a thorough ethical review in order to protect the rights of trial participants. Globally, the protection of trial participants is under threat because the FDA no longer requires compliance with the DoH for clinical trials conducted outside the US; and because of more recent regulatory proposals by the European Commission which are a step back in terms of protection of the rights and safety of trial participants.² **We call on pharmaceutical companies to comply with international ethical principles instead of simply 'hiding' behind the regulator's demand for placebo-controlled trials for scientific reasons. Responsibility lies with regulators, governments and ethics committees to create a system in which the risk for exploitation is minimised and some form of post-trial access to treatment is guaranteed.** Wemos is lobbying politicians, policymakers and regulators for this purpose, while constantly demonstrating that the present situation is far from acceptable. **We also call for a modification of the current model in which the drug companies use clinical trials to protect the market share of their company, resulting in drugs that have little added value for public health.**

Wemos, July 2013

² A. den Boer and I. Schipper. 2013. 'New EU regulation on clinical trials: the impact on ethics and safeguards for participants.' In: *Indian Journal of Medical Ethics* Vol X No. 2 April-June 2013. See <http://www.issuesinmedicaethics.org/212com106.html> (last consulted on June 28, 2013).

Methodology

This report is the culmination of three months (December 2012-February 2013) of intensive research and interviews by Nina Lakhani, an independent journalist from the United Kingdom (UK), with leading health experts, academics, and representatives from the Contract Research Organisations (CROs) who are commissioned by the drug companies to manage and monitor clinical trials. The research was primarily done in South Africa but interviews were also conducted with experts in a number of other countries including the UK, the United States of America (USA), India and Canada.

The decision to focus on the situation in South Africa was motivated by the popularity of the country as clinical trial destination for the multinational pharmaceutical industry. The clinical trial business in South Africa is now valued at around 250 million Euros but very little information, other than business and profit analysis, is available. Therefore it seemed timely to investigate the current status of South Africa's clinical trial business in more detail, looking in particular at the ethical questions of patient recruitment, placebo-controlled trials, post-trial access to treatment and the role of Research Ethics Committees (RECs).

Before determining the key line of enquiry and pursuing interviews, the first step of the research was to review all current literature on the subject, notably academic journals, medical papers, research reports and media articles. The lack of media coverage on the subject of clinical trials was quite surprising. Given the increasing presence of drug companies and CROs in a country with high rates of poverty and illiteracy, the potential for ethical and human rights violations should be considered high. Equally surprising was the lack of local Non-Governmental Organisations (NGOs) or activists focusing on the monitoring of clinical trials or patient rights.

The initial stage of the field research was spent in the cities of Johannesburg and Durban – two of the country's leading clinical trial hubs. Here Nina Lakhani was able to speak at length to medical doctors and clinical trial investigators overseeing trials in both the public and private sector. She was also able to carry out interviews with individuals from the RECs, CROs, and various NGOs and academic institutions. Her investigations revealed that hundreds of clinical trials, notably for conditions such as asthma, schizophrenia, HIV/AIDS (human immunodeficiency virus/acquired immunodeficiency syndrome) and rheumatoid arthritis are underway in South Africa. As a result of the research and discussion with many of those involved, she was able to document a number of unethical trials.

Following the compilation of the information and data gathered in South Africa, Nina Lakhani then approached a number of international pharmaceutical companies, particularly those involved in ethically questionable placebo-controlled studies, to ensure their views and right to reply were included in this report. Wemos also shared draft versions of chapters 4 and 5 with AstraZeneca and Janssen for comments. The world's two biggest drug trial regulators, the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA), were also contacted for their response to a number of questions relating to the regulation of placebo-controlled trials.

Despite some difficulties in terms of accessing information about clinical trials in South Africa, both the independent journalist and Wemos have endeavoured to source, verify and cross-check all the information presented to them, either in the form of written literature or verbal accounts. Please contact Wemos with any comments.

1. Clinical trials in South Africa

Current overview

Over the past decade, South Africa has become an important destination for many international pharmaceutical companies looking to carry out clinical trials. According to the online registry ClinicalTrials.gov³, in February 2013, over 1,600 clinical trials had been registered in South Africa. The registry shows that South Africa's clinical trial sites are largely based in and around the main cities of Johannesburg, Pretoria, Durban, Cape Town, Port Elizabeth and Bloemfontein. These urban areas are home to most of the private medical establishments and specialist public hospitals, making them attractive trial locations for the drug companies. However trials in more rural primary care clinics are also becoming common, notably for HIV and tuberculosis (TB), two of South Africa's most prevalent diseases.

Why do pharmaceutical companies look to South Africa?

“The pharmaceutical industry has had a long presence here, it is a well-oiled industry,” says Professor Jerome Singh, Head of Ethics and Law at the Centre for the AIDS Programme of Research in South Africa (CAPRISA). “South Africa is unique for clinical trials – while it is not as cheap as India, the population is more genetically diverse, we have a good exchange rate, high burden of traditional and lifestyle diseases and limited access to healthcare for the majority of the population. But there is also a well-established research infrastructure and plenty of experts which make it a prime place to do clinical trials.”

Easy and rapid patient recruitment has also added to South Africa's appeal as a global clinical trial hub, especially for private companies hired specifically to find patients willing to participate in clinical studies. “Recruitment in South Africa can outstrip many countries including the big players – we are often called upon to rescue recruitment,” claims Urmilla Bridgmohun from Inc Research, a CRO. “It (patient recruitment) is very easy here... so it works out quicker and therefore cheaper than other countries. For example, in an asthma trial we can beat recruitment in other countries because there are fewer competing trials, the same goes for schizophrenia, bipolar disorder, and alzheimer's,” she adds.

Other medical professionals point out that South Africa is a country in which inequalities in wealth and health are rapidly widening, meaning "diseases of the affluent" such as diabetes, heart disease and hypertension are on the increase. This also makes the country an attractive location for the pharmaceutical companies to test drugs they hope will generate huge profits from the western markets.

³ ClinicalTrials.gov is a registry and results database of publicly and privately supported clinical studies of human participants conducted around the world. It is a service of the United States' National Institutes of Health. See www.clinicaltrials.gov.

Lack of access to adequate healthcare and patient recruitment

As mentioned above, rapid recruitment has been cited as a reason to carry out trials in South Africa, but the reason why it is so easy to recruit trial subjects, namely widespread poverty and lack of access to healthcare, is rarely explored in any great detail.

South Africa's apartheid era policies left a legacy of sub-standard healthcare for most of the non-white population in South Africa and many people still find it difficult to access and afford the care they need. These inequalities persist and meaningful change has been slow. Many health workers are also now concerned that a lack of political will, poorly paid and inexperienced staff and corruption have eclipsed racism as the main obstacles to good public healthcare for all South Africans. The country's public health system is still predominantly used by the country's impoverished black population and is in a serious state of decline. Despite progress in formulating new laws guaranteeing equal access to quality healthcare, shortages in medicines, doctors and hospital beds today remain the rule rather than the exception.

Widespread corruption also contributes significantly to the stark inequalities in the country's health service. Certain amounts of health expenditure are believed to be lost through corruption as officials siphon off public money, and bribes and kickbacks are accepted from potential suppliers for coveted medicines and equipment contracts. According to health experts such as Professors Ames Dhai and Yousaf Veriava from the University of the Witwatersrand, "Corruption is a major and unambiguous contributor to the poor health of South African citizens."⁴

Given the flaws and chronic problems which plague South Africa's public health system, many people in the poorest communities often don't have access to adequate or affordable healthcare. This means that the opportunity to take part in clinical trials is often seen by the most vulnerable as a way to get free treatment. And drug companies are quick to exploit this opportunity. "(Clinical trials) give people access to medicines that are not available in public hospitals. People are attracted to the fact the clinical trial will fund expensive medicines and medical assessment," explains Professor Dhai. "The misconception among many vulnerable South Africans is very sad, because they feel the only chance of getting access to healthcare they need is to enter a clinical trial. But the intervention is not proven and could work adversely against them. This is ultimately down to a failure of the health system to deliver care on the ground which forces people into a state of further vulnerability."

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

⁴ A. Dhai and Y. Veriava. 'Health inequity in South Africa – a by-product of injustice'. *Australian and New Zealand Journal of Public Health* Volume 36, Issue 6. Article first published online on December 10, 2012. See <http://onlinelibrary.wiley.com/doi/10.1111/j.1753-6405.2012.00953.x/pdf> (last consulted on June 10, 2013).

CASE STUDY: A tale of a clinic

Ebony Park, Johannesburg

Almost 100 women and children were waiting in line to see the nurse at the Ebony Park clinic in the rural outskirts of northern Johannesburg. Many had come for an HIV-test or for ante-natal checks on their unborn babies. Others patiently waited their turn for TB tests, their hands firmly grasping containers of sputum samples precariously covered with paper towels. When their turn finally came, the six clinic nurses were friendly, efficient and used to the daily influx of South Africans living with common diseases such as HIV, TB and high blood pressure. The competence and dedication of these nurses, and so many like them across the country, is especially critical if we consider that a trained doctor only comes once a week to Ebony Park clinic and that the nearest hospital is 10 kilometre drive/walk away.

This scenario in Ebony Park is not uncommon in South Africa. Over 80 per cent of South Africa's population rely on these small health centres, known locally as Primary Care Clinics. And with the country's world class private health sector still only accessible to around 18 per cent of the population, these clinics are the backbone of the country's public health service. Both specialists and medicines are however in short supply. In Ebony Park, the staff was dealing with an unexplained shortage of medicines such as paracetamol and antiretroviral drugs. Also depleted was the stock of rubber gloves which are essential for any physical examination. "The money is there but the pharmacy cannot get the stock," explained the clinic manager. "It's very serious and we don't know what has happened," he added.

However, next door in another part of the clinic, two clinical trials were taking place: one for a prevention of mother-to-baby HIV transmission study, the other for a new TB drug. Here, there were no queues, no supply shortages and the trial participants each received 12 Euros (150 Rand (ZAR)) per monthly visit to cover costs like transport and lost earnings. The payment may not seem a lot, but with one quarter of the population unemployed, it is a fortune to those living on the breadline and dependent on the public health sector. "We do participate in a lot of clinical trials here at our clinic," the clinic nursing manager confirmed. "But we (nurses) are not involved at all, apart from helping recruit patients. The patients are taken care of by the research staff," she added, making reference to the private companies who send in research staff to conduct the trials. When asked if people taking part in the clinical trials later benefitted from access to the new drug, the nurse said that post-trial access was not guaranteed and depended on government policy after the trial.

2. Checks and balances

Regulation and the role of Research Ethics Committees

In South Africa informed consent for clinical trials is a requirement enshrined in the constitution. Stringent guidelines for clinical trials are also guaranteed within South Africa's National Health Act 2003 and the Good Clinical Practice (GCP) guidelines, both of which outline the regulatory framework and standards for clinical trials in the country. Before going ahead, all clinical trials must have approval from the Medicines Control Council (MCC), and be registered with the official South African National Trial Register, which was established in 2005.⁵ The MCC and National Health Research Ethics Council (NHREC) stipulate that every clinical trial conducted in South Africa must adhere to the latest version (2008) of the DoH, and its rules on the use of placebo controls and post-trial access to treatment.

The introduction of such stringent guidelines was welcomed by ethicists and health professionals and by some CROs. "Ten years ago, we (South Africa) were considered one of the cheapest and easier countries to do clinical trials in. But since then, the regulatory environment has been properly constituted and I am proud to be part of what has been established. Many of the drug companies find it very frustrating – but there is greater scrutiny and it is much safer now," says Urmilla Bridgmohun from Inc Research.

South Africa is also home to one of the world's oldest ethics committees founded at the University of the Witwatersrand in Johannesburg in 1966. Before any trial can proceed in South Africa, the drug company must have the approval from at least one officially registered REC.

South Africans take a lot of pride in country's stringent regulatory health system which, since 1994, has made significant progress in universal protection for clinical trial patients. But this does not mean the system cannot be improved or that problems don't exist. "South Africa has better ethical governance than all other African countries but that doesn't mean there are no problems. It is certainly better here than it was even two years ago when committees didn't have to be registered and anyone could set one up, regardless of qualification or training," says CAPRISA's Professor Jerome Singh.

In 2012, the NHREC undertook an audit on 22 registered South African RECs and revealed some concerning insights. The data showed that six RECs approved 100 per cent of the health research protocols that were submitted to them. Only one per cent of all submitted health research protocols that were processed, was not approved. The audit also revealed that 45 per cent of the RECs were not sure whether researchers adhere to conditions of approved research protocols. The NHREC audit concluded that "there are high chances of violations of rights of participants in those approved research studies where active

⁵ www.sanctr.gov.za

monitoring is none existent." The NHREC audit also found that approximately one in three committees said they did not have procedures to address conflict of interests for members.

"Though the audit was very important it was about processes not analysis, so it was only the first step," believes Professor Dhali, who is also deputy chair of the NHREC. "We were looking at composition, functioning and regulatory requirements, the next step should be an analysis of the decision making. This is essential if we are to accredit RECs as required by the National Health Act. The fact that many institutions don't provide any support to RECs is a huge problem that the (NHREC) Council must grapple with. How can they do their work and fulfil their mandate without resources for training or admin support – institutions have to commit to this."

Despite the fact the MCC and NHREC both require that every clinical trial must adhere to the latest version (2008) of the DoH, evidence from RECs and CROs strongly suggests that compliance varies. "Some drug companies are trying to use whichever version of the Declaration that suits them," says Professor Dhali. "But we are very clear that the only valid version is the one on the World Medical Association (WMA) website. The MCC also sticks to the 2008 version so even though some companies are trying to get away with it, we won't allow it." Professor Peter Cleaton-Jones, Chair of the Wits Health Research Ethics Committee in Johannesburg, adds: "The Declaration of Helsinki is sacrosanct – we will turn trials down if they don't agree to latest version."

But certain REC members believe that flexibility should be applied for each individual trial. "Some committees are very strict about following the Declaration to the letter, but we are more flexible, we ask for justifications and may ask for additional safety measures," says Marzelle Haskins, Managing Director of the REC Pharma-Ethics. She adds: "We take it on a case by case basis. A few years ago drug companies used to try their luck with ethics committee 'shopping' but I think there is too much communication between us now and guidelines are stricter, though no doubt some will still." The CROs interviewed made it clear that compliance with the latest DoH was not set in stone. "Some RECs are stringent about the inclusion of the 2008 Declaration of Helsinki – but it varies and some are much less fixated on it. But every trial has an obligation to comply with the South African GCP guidelines," says Urmilla Bridgmohun from Inc Research.

Several interviewees also mentioned that the degree of communication between ethics committees has improved and as a result, ethics committee "shopping" had become much more difficult over the past 2 years.

Improving transparency

Monitoring trials by independent researchers and academics can be greatly helped by a public trial registry. The information available on the South African National Clinical Trial Register is limited and the search engine is not user friendly. In addition the existing registry is not transparent in a number of areas. For example, on the website of the Register the following is stated: "... trials whose primary goals are to assess major unknown toxicity or determine pharmacokinetics (Phase 1 trials) are excluded from the trial information being made publicly available." Furthermore investigators and companies can apply for information to be

kept hidden because of concerns about innovation or timely patient recruitment. For those trials publicly listed key information is often missing, for example the name of the sponsor, the research sites and numbers of patients to be enrolled. The information that is available, is often well out of date. These omissions mean the publicly available information is of very limited use to participants, journalists, researchers and academics.

3. The silent partners

The influential role of Contract Research Organisations

It is currently estimated that around half of the world's clinical trials are now contracted out by drug companies to private organisations known as CROs. The CROs are hired to oversee many aspects of a clinical trial, including securing the approval from the ethics committees, finding suitable locations and recruiting patients and the medical investigators. Patient recruitment is an important aspect of CRO work, indeed the ability to recruit and retain enough patients is essential to a CRO's success. Many investigators already have an extensive patient database and are often selected by the CROs because of their outreach potential.

According to a recent report⁶ by Visiongain, a business information provider for the pharmaceutical industry, the profit from the global CRO industry is set to reach over 32 billion dollars by 2015. This is already a significant increase from the 20 billion dollar gain made by the industry in 2010. Much of this growth is expected to come from a 20 per cent annual increase in the number of CRO contracts given out for clinical trials taking place in India and China. There are over 1,100 CROs globally.⁷ American CROs such as Quintiles and Parexel are amongst the largest with offices across the world.

Given the secretive nature of many CROs it can be difficult to get the full picture of their current operations in South Africa. OnQ and Inc Research were the only CROs who agreed to be interviewed. Quintiles, Paraxel and Covance were among those who refused to answer any questions.

Currently, an estimated 15 CROs are operating in South Africa. These range from local companies such as OnQ to global giants such as Quintiles and Parexel, many of which have bought-out smaller companies in recent years. "In the global market place, CROs are very much the specialists in conducting clinical trials – we know how to do it and we do it best... I have worked in both CROs and the pharmaceutical industry and the way the global market is going, I think I am in the best place," believes Urmilla Bridgmohun from the CRO Inc Research.

As mentioned earlier, the CROs rely on their ability to recruit patients as a major selling point to the pharmaceutical industry and may put medical professionals under great pressure to deliver patients quickly. Dr Keith Pettengell, a gastroenterologist at Hillcrest Private Hospital in Durban, explains: "The usual scenario these days is that the CRO comes to you and wants 30 patients to be recruited in a week, because the study has been going on for five

⁶ Visiongain. 2011. *Pharma Clinical Trial Services: World Market 2011-2021*. See <http://www.visiongain.com/Report/641/Pharma-Clinical-Trial-Services-World-Market-2011-2021>.

⁷ M. van Huijstee and I. Schipper (editors). 2011. *Putting Contract Research Organisations on the radar. An exploratory study on the outsourcing of clinical trials by pharmaceutical companies to Contract Research Organizations in non-traditional regions*. See http://somo.nl/publications-nl/Publication_3615-nl.

years and they are desperate to get the numbers.” Dr Pettengell said he had recently rejected a trial because of this pressure. “We are seen more and more as the rescue country, and that’s why I turned the last one down – I don’t like not being able to do my best, and if you have less time to take over patient selection then you will inevitably have to enrol more and accept a higher dropout rate.”

Profile: The local CRO and its responsibilities

OnQ, the first South African CRO, was founded in 1999 and works with both multinationals and smaller biotech companies. The latter account for two thirds of their current client base. OnQ also conducts clinical trials outside South Africa in countries including Zimbabwe, Ghana and Mozambique, mainly for TB and malaria, and are considering opening a branch in Kenya.

Catherine Lund, managing director and founder of OnQ, says: “Patient recruitment is easy in South Africa. People are motivated by access to drugs, the fact they will be seen quickly, the doctors will be nice to them, they won’t have to queue all day. But I don’t see these factors as coercive. Our informed consent process is very robust. Many clinical sites have interpreters on board and it is not taken lightly like it used to be but some sites are definitely better than others – we are not completely there yet.”

“We often work with CROs in the US or Europe which don’t have a presence here and we will run their South African and other African sites. There’s a lot of subcontracting out and patients will not have the name of the CRO so I can see how transparency issues arise with layers of organisations, but we would always advise the principle investigator to refer the patient to the sponsor if there was a problem.”

CROs: How much oversight?

South African ethics committees currently rely on clinical trial monitors (employed by a CRO) to identify and report back any ethical violations. But given the CROs are often managing the trials themselves, there is a risk that the monitors could be unwilling to present any information which would delay or undermine the study.

Another area of concern is that monitoring of CROs by pharmaceutical companies is not always sufficiently stringent.⁸ The Access to Medicine Index published by the Access to Medicine Foundation in 2012, criticised the lack of oversight the drug companies often have over CRO procedures claiming, “Few companies have robust measures to ensure clinical trials conducted by contractors are safe and ethical with the majority providing no evidence of exerting real influence over the way their contractors conduct trials or adequate assurance of benefits returned to host communities.”⁹

⁸ See e.g. M. van Huijstee and I. Schipper. 2011. *Putting Contract Research Organisations on the radar. An exploratory study on the outsourcing of clinical trials by pharmaceutical companies to Contract Research Organizations in non-traditional regions*. See http://somo.nl/publications-nl/Publication_3615-nl.

⁹ Access to Medicine Index. See <http://www.accesstomedicineindex.org/sites/www.accesstomedicineindex.org/files/rd-2012-access-to-medicine-index.pdf> (last consulted on June 18, 2013).

The CROs said the level of contact with drug and biotech companies varied. The quality of monitoring and oversight can often depend on the size of the CRO or pharma company, explains Urmilla Bridgmohun from Inc Research. “The bigger companies trust us to get on with it, but the smaller biotech companies tend to micromanage, perhaps because they have a lot more invested in one product. We are not omnipresent at clinical sites, we have to rely on investigators doing what they said they would, we can’t be everywhere... There are checks and balances in place but it isn’t perfect of course. When the CRA [clinical research associates] do detect something, we will put the investigator through the right training.”

“The sponsors are all very involved, we have weekly teleconferences; the auditors will come before and during the study, but apart from that they leave us to it,” says Catherine Lund from OnQ. She adds: “My project managers spend 60 to 70 per cent of their time monitoring – looking at informed consent, exclusion criteria, site management – on average site visits take place every 4 to 6 weeks, but it can be as often as weekly.”

How to improve the quality of monitoring and transparency of clinical trials in South Africa?

Questions about the lack of independent oversight and effective monitoring of clinical trials are being asked both in South Africa and globally. Various leading South African ethicists including Professors Dhai and Cleaton-Jones are calling for a levy to be charged to drug companies so that trials can be monitored independently and patients are better protected from ethical violations.

“The drug companies need to pay more, if they are sub-contracting out to CROs and abdicating on their responsibilities so that someone else has to deal with standards, then they must pay. This would allow the committees or MCC to independently monitor the trials for ethical compliance,” believes Professor Dhai. Professor Cleaton-Jones also believes trial monitors should be completely independent from the CRO and that funding needs to be found to make this happen: “If it was a requirement to physically monitor every clinical trial our system would collapse. The right way to go would be if there was a team of accredited independent monitors accredited by the NHREC to monitor the monitoring. But the Council does not have the money for this so the only other way round it is for a levy on all the sponsors to pay for this independent monitoring – like in Denmark where 5 per cent are audited each year. Currently, if we hear of a problem or receive a complaint from the CRO monitor or investigator or patient, we can send an independent auditor but this costs 3,200 Euros [40,000 ZAR] per audit, so there is a resource issue.”

4. Controversial placebo-controlled clinical trials

According to a simple search on ClinicalTrials.gov, South Africa appears to have one of the highest rates of placebo-controlled trials in the world. Almost one in two of all registered trials in the country are placebo-controlled studies. This is comparable to Guatemala, Argentina, Chile, Bulgaria, Czech Republic, Slovakia, Estonia, Hungary, Romania, Russia, Ukraine, Latvia and Poland. However, South Africa has a much higher proportion of placebo-controlled trials than in countries such as the UK, US, Germany, Israel, Italy, France, Canada, and Netherlands where such trials only account for between one third and one fifth of all clinical trials.

There are generally two advantages of placebo-controlled studies for the pharmaceutical companies. Firstly, it is easier to show efficacy when testing a new drug against a placebo (instead of against an existing therapy). Secondly, studies which compare existing and new drugs require more patients and consequently more time and money.

Schools of thought

Placebo trials have been embroiled in controversy for many years and there are a number of schools of thought when it comes to the use of them. The DoH states that "extreme care must be taken to avoid abuse of this option". The DoH also underlines the use of a placebo as acceptable in studies where no current proven intervention exists; or where for compelling and scientifically sound methodological reasons the use of placebo is necessary. Yet, at the other end of the spectrum, regulatory authorities like the USFDA actually prefer to use placebo-controlled trials and do not require the drug companies to comply with the ethical standards enshrined in the DoH.

Amid huge controversy, in 2008 the FDA ruled that drug companies no longer needed to comply with the DoH in clinical trials conducted outside the US. This was a significant development as, in many cases, it made it much easier for pharmaceutical companies and their subcontractors to conduct clinical trials in countries with poor regulatory systems. The relaxation of the rules by the FDA in 2008 meant the international drug companies operating overseas only need to adhere to the good clinical practice guidelines developed by the International Conference on Harmonisation (ICH). The ICH is made up of drug regulators and industry representatives from only the world's richest countries – the US, European Union (EU) and Japan. The World Health Organization (WHO), the European Free Trade Association and Health Canada are observers. Unlike the DoH, the ICH GCP does not restrict the use of placebo-trials.

In Europe, the DoH is firmly enshrined in European regulations. In principle, European regulatory authorities such as the European Medicines Agency (EMA) require that pharmaceutical companies conduct placebo-controlled studies. However, the RECs in Western European countries are less likely to approve this kind of trials due to ethical

concerns. As a result, the drug companies are looking for locations outside Western Europe to carry out the placebo-controlled trials.

CASE STUDY: AstraZeneca CHASE 1 a placebo-controlled clinical trial on asthmatic children

Asthma is a chronic respiratory condition caused by the inflammation of the small tubes (bronchioles) which carry air in and out of the lungs. People with asthma have inflamed and sensitive bronchioles which can make breathing difficult when the lungs are irritated. The airways become narrow, the muscles around them tighten and there is an increase in phlegm (mucous) production. This leads to symptoms such as breathing difficulties, wheezing, coughing, and a tightening of the chest. The severity of the symptoms varies from person to person, but preventing acute attacks through regular medication is considered one of the mainstays of asthma treatment for most sufferers.

According to the WHO, some 235 million people currently suffer from asthma.¹⁰ It is the most common chronic disease among children. Most asthma-related deaths occur in low- and lower-middle income countries. In the UK every 18 minutes a child is admitted to hospital because of their asthma.¹¹

Asthma is increasingly common in South Africa, affecting almost 10 per cent of children nationally. Many asthma drugs are off patent meaning effective medicines for asthma are cheap and widely available. According to ClinicalTrials.gov, there are 44¹² asthma clinical trials registered across South Africa – 31 of which involve a placebo arm.¹³ One of them is from the British-Swedish company AstraZeneca that conducted a placebo-controlled clinical trial named CHASE 1¹⁴ on asthmatic children, using a widely used drug called budesonide, one of the drugs for preventing asthma attacks.

For the CHASE 1 study, AstraZeneca recruited asthmatics between 6 and 12 years old in the US, South Africa, Latvia, Hungary, Bulgaria, Slovakia and Poland¹⁵ who used daily preventive asthma medicines. One group of the children were randomized into a placebo group and received a dummy inhaler for six weeks. The other group received 160 micrograms (µg) of budesonide, an inhaled corticosteroid (ICS), twice a day.

AstraZeneca says the FDA required a further clinical trial before it would consider approving AstraZeneca's combination inhaler Symbicort pMDI (pressurized Metered Dose Inhaler) – which contains budesonide and another drug, formoterol – for use in

¹⁰ <http://www.who.int/mediacentre/factsheets/fs307/en/> (last consulted on June 18, 2013).

¹¹ <http://www.asthma.org.uk/asthma-facts-and-statistics> (last consulted on June 18, 2013).

¹² <http://www.clinicaltrials.gov/ct2/results?term=Asthma+South+Africa&cond=Asthma&pg=3> (last consulted on June 11, 2013)

¹³ http://www.clinicaltrials.gov/ct2/results?term=Asthma+South+Africa+Placebo&recr=&rslt=&type=&cond=Asthma&intr=&titles=&outc=&spons=&lead=&id=&state1=&cntry1=&state2=&cntry2=&state3=&cntry3=&locn=&qndr=&rcv_s=&rcv_e=&lup_s=&lup_e= (last consulted on June 18, 2013).

¹⁴ Title of the study: A 6-week Study in Asthmatic Children aged 6 to <12 Yrs Comparing Budesonide pMDI 160ug Twice Daily With Placebo (CHASE 1). This study has been completed according to ClinicalTrials.gov. See <http://www.clinicaltrials.gov/ct2/show/NCT01136382?term=CHASE+1&rank=1> (last consulted on May 21, 2013).

¹⁵ See trial sites at http://clinicaltrials.gov/ct2/show/study/NCT01136382?show_locs=Y#locn (last consulted on June 18, 2013).

children between 6 and 12 with moderate/severe asthma in the US. “The CHASE 1 study is part of the plan agreed with the FDA for investigating our asthma medicine Symbicort pMDI (a combination of budesonide and formoterol) in children. As part of that plan the FDA asked that we look at the dose of the mono-components in a pMDI formulation. CHASE 1 is to confirm the efficacy of the budesonide dose (160 µg bid), while a similar study called CHASE 2¹⁶ is evaluating the formoterol mono-component”, says the company.¹⁷

Ethical and safety concerns

Denying or withdrawing a proven treatment for the sake of a placebo-controlled trial has raised the alarm amongst a number of health professionals. A nurse from an asthma charity¹⁸ in the UK: “The key to managing your asthma is to be aware of your asthma triggers, do what you can to avoid these, and most importantly to ensure that you take your medicines as prescribed.”

“We would be very concerned about any situations where children or adults were not taking asthma treatments, and what affect this may have on their health. Stopping someone’s medicine can lead to a deterioration of their symptoms and ultimately an asthma attack which can be a terrifying experience and can prove to be fatal; tragically three people [mainly adults] die every day because of their asthma in the UK.”

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

When asked about the potential health risks posed to children taking part in the trial, AstraZeneca gave assurances that the children enrolled in the study had relatively mild asthma, that the study design used the shortest placebo-controlled period likely to show clinical response (6 weeks) and that rescue treatments were provided. Furthermore, AstraZeneca stated that it had included safeguards to minimize the risks for the placebo group such as regular clinic visits, lung function assessments and an asthma safety plan.¹⁹

“We as well as the FDA believe that the current study designs are ethical, otherwise we would not be conducting them. ... Again, these trials are being performed according to a study plan agreed with the FDA. Study approvals have also been granted by ethics committees in the countries where the study is conducted, and by the relevant regulatory agencies. In South Africa specifically, approval was granted by the South African Medicines Control Council”, says the company.²⁰

¹⁶ CHASE 1 and CHASE 2 are completed.

¹⁷ Quote from email correspondence AstraZeneca-research journalist, February 2013.

¹⁸ At the request of the charity, the name of the organization and its spokespersons are not mentioned in this report.

¹⁹ Based on email correspondence AstraZeneca- research journalist, February 2013.

²⁰ Quote from email correspondence AstraZeneca- research journalist, February 2013.

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

According to AstraZeneca, the FDA formally agreed to a placebo trial for the combination budesonide/formoterol inhaler in writing: "This trial is being conducted in response to a formal written request from the FDA and is performed according to a study plan agreed with the FDA aiming at an approval of the medicine in children aged 6-12 years in the US," explains the company.²¹ It also says: "The best way to determine the true magnitude of effect is to compare it to a placebo baseline. To perform a comparator study would take many more patients and could potentially expose more children than necessary to an ineffective therapy. We would surely perform the comparator study if a placebo controlled study was not ethical to perform; however, this is not the situation in this case."²²

For Dr Amar Jesani, editor of the *Indian Journal of Medical Ethics*, the use of placebo-controlled trials undertaken when proven treatment is available is a serious breach of ethics standards: "The Helsinki Declaration, the Council for International Organizations of Medical Sciences (CIOMS)²³ guidelines are very clear that placebo controlled trials can be conducted only in those conditions where there is no proven treatment/prophylaxis/prevention method available.... By admitting that the international pharmaceutical companies are doing placebo trials just for regulatory reasons, they are admitting the large scale violation of ethical guidelines of the medical profession and the World Health Organization."

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

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

"This trial is hard to justify and it has been very hard to recruit," says private Paediatrician Dr Ahmed Ismail Manjr who has been involved in recruiting asthmatics for the CHASE 1 trial. "I think it is of dubious scientific value, I know the FDA wants it but we have no problems with it in South Africa where it [budesonide] has been licensed for use in

²¹ Quote from email correspondence AstraZeneca-research journalist, February 2013.

²² Quote from email correspondence AstraZeneca-research journalist, February 2013.

²³ The Council for International Organizations of Medical Sciences (CIOMS) is an international, non-governmental, non-profit organization established jointly by WHO and UNESCO in 1949.

children aged 6 and up for more than 20 years – the MCC is not asking for any more information... it is an old molecule.”

Symbicort pMDI has not yet been approved for use in children aged between 6 and 12 in South Africa.²⁴

Benefits for the company

Symbicort is one of AstraZeneca’s leading, most lucrative brands, with global sales of almost 3.2 billion US dollar in 2012.²⁵ In the US, the patent on Symbicort (combination) will expire in 2014, whilst the patent on the pMDI device will expire in 2026.²⁶

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

This is a commonly heard concern among experts. Dr Adrian Morris, an asthma specialist working in the UK and South Africa, says: “There is always space for research but I am not convinced that we need new drugs, the ones we have are pretty good if used properly. The trials are all about the pharmaceutical industry wanting to develop new drugs that they can market under patent because all the old patents have run out and anyone can make them now, at a fraction of the cost. This is about their financial needs not any huge clinical need. “

Viewpoint: Professor Lainie Ross, bioethicist at the University of Chicago: “Moral responsibility”

In 2004, Professor Lainie Ross, a paediatrician at the University of Chicago conducted a systematic review of all US asthma clinical trials involving children carried out between 1998 and 2001. The findings of her research published in the journal *Paediatrics* revealed that enrolling children with asthma in the placebo arm of a clinical trial was often “common, harmful and ethically unjustified”.²⁷ She concluded that children who needed asthma medication were being placed at unnecessary risk because medication was being withheld from them, rendering them twice as likely to suffer harm as those given the standard treatment. She also discovered that three times as many children had withdrawn from the placebo trial because of worsening asthma attacks. In response to Ross’ conclusions that these placebo-controlled trials were unethical, the trial investigator back then said they were crucial because they studied the safety and efficacy of a new mode of delivery of budesonide and a placebo trial was necessary for FDA approval.

²⁴ Personal communication AstraZeneca South-Africa - Wemos, June 2013.

²⁵ AstraZeneca Annual Report 2012, page 4. See http://www.astrazeneca-annualreports.com/2012/documents/eng_download_centre/annual_report.pdf (last consulted on June 18, 2013).

²⁶ AstraZeneca Annual Report 2011, page 35. See http://www.astrazeneca-annualreports.com/2011/documents/pdfs/annual_report_pdf_entire.pdf (last consulted on June 18, 2013).

²⁷ See <http://www.uchospitals.edu/news/2004/20040105-ross.html> (last consulted on June 18, 2013).

Fast forward 13 years and it would appear the same justifications are being used for the CHASE 1. Dr Ross says: "We have heard this same excuse for 15 years, it is time to get beyond this. The FDA needs to re-think how it can use well-done international data. The pharmaceutical companies need to acknowledge their moral responsibility. It is not justifiable to do a placebo-controlled trial when similar trials have been done in many other countries such that the safety and efficacy data are already known. I am sure that there are good scientific reasons to want a "clean crisp trial" - the FDA prefers placebo-controlled trials because they are "neater", need fewer subjects, easier endpoints – that does not justify doing the study. We must respect prospective participants and this exposes them to unnecessary risk. Some ethics committees may argue that this is minimal risk and so it is okay because there are rescue meds in place. It is not minimal risk to take children off the medications that are life-saving."

5. Clinical research on the mentally ill

The gap between South Africa's rich and poor is clearly reflected by the degree of equal access to quality mental healthcare. A 2012 article published in the *African Journal of Psychiatry* mentions that 16.5% of adults have suffered a common mental disorder in the past year and only a quarter of these people had received treatment during this time.²⁸

In South Africa's poor townships and rural areas, high rates of violence and substance abuse contribute to particularly high levels of acute mental health problems including cases of suicide. Access to good quality mental healthcare is severely limited for a great deal of the population. This is clearly illustrated by the fact that two thirds of the country's 350 psychiatrists work solely in the private sector and only two public-sector psychiatrists cover two of the country's poorest regions. The government is trying to attract and train more psychologists, but many head straight for a career in the more lucrative private sector. For many people in need of psychiatric help, sometimes their only option is to travel miles to a public hospital and wait for hours to be seen. Or enter a clinical trial.

Over the past few years, South African patients have participated in numerous psychiatric clinical trials for multinational companies, the majority of which have been conducted almost exclusively in private practices and often with the use of placebos.

The use of placebos in psychiatric clinical trials remains highly contentious because of the distressing and sometimes life threatening symptoms patients can experience during a relapse linked to the withdrawal of treatment. Common relapse symptoms in patients suffering from schizophrenia and other psychotic illnesses include hearing voices, paranoia and disorderly thoughts. More seriously ill patients may need to be hospitalized and they may harm themselves or others.

CASE STUDY: The charity, the psychiatrist and the CRO

The South African Depression and Anxiety Group (SADAG) is the country's largest mental health charity which has helped to set up 200 self-help groups, mainly in rural areas. It also runs telephone helplines – manned from a small office in Sandton, an affluent suburb in Johannesburg – mostly sponsored by drug companies, for example the 'AstraZeneca Bipolar line' and 'Sanofi sleep disorder line'. In return, the companies receive regular reports about how many people are calling and where they are located, which is useful information for their pharmaceutical representatives, says SADAG founder Zane Wilson.

SADAG is paid by CROs to recruit people into clinical trials. The CRO will devise adverts for SADAG to place in local newspapers and its own newsletter, and the volunteer counsellors are primed to ask potentially suitable callers if they are interested. Pre-screening questionnaires are done with potential recruits and sent to the clinical site

²⁸ K. Sorsdahl, D.J. Stein and C. Lund. 2012. 'Mental Health Services in South Africa: Scaling up and future directions'. In: *Afr J Psychiatry* 2012;15:168-171.

nearest the caller. SADAG has helped CROs recruit for around 30 trials now; 15 per cent of SADAG's funding comes from drug trials and pharmaceutical industry sponsorship.

Ms Wilson said: "In England there is lots of support from the government for mental health. In South Africa those who can't afford medical aid schemes have to rely on poor public facilities, so I think clinical trials can be advantageous for our uninsured patients. They will get high quality, one on one care and hopefully a drug that works for them. I don't recruit for placebos. We ask the drug company not to take patients off the drug immediately after the trial, to give them another month or so, but if they can't then we ask the investigator to write a letter they can take to the nearest public A&E [accident and emergency]."

But one SADAG volunteer was more critical about the arrangement with the CRO: "Clinical trials are a type of exploitation because patients cannot access treatment that is already available and will never afford the new drug even if it gets licensed," the volunteer said. "Also most people need counselling rather than medication, but at least we are helping them get something when they have nothing, even if it is for a few months."

Viewpoint: Dr Gerta Brink, private psychiatrist, Johannesburg: "Benefits are worldwide"

The waiting room in Dr Gerta Brink's private psychiatric practice in Johannesburg is upmarket, quiet and orderly. The only noise comes from the receptionists conversing in Afrikaans with each other. Since entering the private sector over 15 years ago, Dr Brink has been actively conducting clinical trials in her private practice. In fact, every Wednesday is dedicated to meeting with potential and current trial patients. "I started research in the public sector hospitals but then it was decided that this was unethical and it was stopped."

Dr Brink says she never has direct contact with drug companies as her contract is exclusively with CROs who come to her with trials. As a trial investigator she gets paid per patient, per visit, and for every test and assessment completed. Around half the recruits come through SADAG. "The benefits (of clinical trials) are worldwide, not just for here, and there are no risks to the patients. Even if the drugs are not affordable for the public sector patients at first, they will be at some point, and the companies have to make their money back because research is so expensive," she said.

CASE STUDY: Janssen Research & Development “withdrawal studies”

According to ClinicalTrials.gov, 28 clinical trials for schizophrenia and schizoaffective disorders have been registered in South Africa. Thirteen of these trials have a placebo arm.²⁹ Two such placebo-controlled trials have provoked particular criticism.

The **first study**, which started in September 2010, is to “evaluate the efficacy of monthly Paliperidone Palmitate injections in preventing the relapse of schizoaffective disorder.”³⁰ The drug sponsor in question is Janssen Research & Development, LLC (limited liability company). According to ClinicalTrials.gov, this study is currently *ongoing*. In addition to South Africa, study locations include the US, Bulgaria, India, Malaysia, Philippines, Romania and Ukraine.

Initially, all trial subjects receive paliperidone palmitate, a long-acting injectable form of paliperidone. Patients who meet pre-determined stabilization criteria will be eligible to continue. Half of them will receive paliperidone palmitate, the other half a placebo treatment. In order to prove the efficacy of the test drug, the patients in the placebo group must experience a relapse in their psychiatric condition more frequently and sooner than the paliperidone palmitate group.

The **second study**, sponsored by Janssen Scientific Affairs, LLC started in May 2012, aims to “evaluate the efficacy of Paliperidone Palmitate three-month formulation compared with placebo in delay of time to first occurrence of relapse of the symptoms of schizophrenia.”³¹ According to ClinicalTrials.gov, this study is currently *recruiting* participants.³² In addition to South Africa, study locations include the US, Brazil, Bulgaria, Colombia, Republic of Korea, Malaysia, Mexico, Romania, Russian Federation, Turkey and Ukraine.

This trial involves schizophrenia patients who started on paliperidone being switched (ratio 1:1) onto either three-monthly paliperidone palmitate or a placebo injection until the point of relapse.

Both Janssen Research & Development, LLC and Janssen Scientific Affairs, LLC are pharmaceutical companies of Johnson & Johnson. Janssen explained its choice of countries for these two trials: “Including patients in clinical studies from many different parts of the world provides clinical information about patients, all of whom have agreed to

²⁹

http://www.clinicaltrials.gov/ct2/results?term=south+africa&recr=&rslt=&type=&cond=schizophrenia&intr=&titles=&outc=&spons=&lead=&id=&state1=&cntry1=&state2=&cntry2=&state3=&cntry3=&locn=&qndr=&rcv_s=&rcv_e=&lup_s=&lup_e= (last consulted on 18 June, 2013).

³⁰ See <http://www.clinicaltrials.gov/ct2/show/NCT01193153?term=paliperidone+palmitate&rank=14> (last consulted on May 22, 2013). The website says: ‘This study is ongoing, but not recruiting participants.’ Countries include: the US, Bulgaria, India, Malaysia, Philippines, South Africa, Romania and Ukraine.

³¹ See <http://www.clinicaltrials.gov/ct2/show/study/NCT01529515?term=evaluate+the+efficacy+of+Paliperidone+Palmitate+three-month+formulation+compared+with+placebo+in+delay&rank=1> (last consulted on June 27, 2013).

³² When looking at the study locations, a striking number of locations report the status as ‘withdrawn’, meaning the study stopped early, before enrolling its first participant. This applies to one of the three sites in South Africa. The other two are described as ‘Not yet recruiting’.

participate in the studies, from different backgrounds and from countries where medical practice may differ.”³³

Differing viewpoints

Both of these Janssen “withdrawal studies” trials in South Africa give rise to debate and criticism amongst medical experts and activists. According to the DoH, this type of trial can never justify the use of a placebo because it involves withholding treatment from seriously ill patients who may run the risk of serious or irreversible harm. In addition, proven current interventions are available with which the investigational drug can be compared. Cases have been documented of clinical trials involving patients with schizophrenia in which a significant number of participants experienced a worsening of their disease and had to be hospitalized.³⁴ Already in 2007 *La Revue Prescrire*³⁵, a respected French drug bulletin, expressed outrage at the fact that paliperidone was tested against a placebo.

Of particular concern is that many of the countries included in the two Janssen studies have weak systems for providing healthcare and for monitoring clinical trial participants. Hence it is uncertain whether patients who experience harm as a result of a placebo (i.e. no treatment) will be adequately taken care of.

In a written response, a spokesman for Jansen said: “Independent local ethics committees carefully considered the design of the studies and the proposed measures to protect patient safety before giving approval, and health authorities reviewed the study designs. These studies have several design features that allow for close monitoring of patients during the period of time when patients may be treated with placebo. All researchers are carefully trained, and signs of worsening and relapse are carefully defined so that patients who may be in placebo groups can be withdrawn quickly from the studies and immediately treated with active medication.”³⁶

But David Healy, Professor of psychological medicine at Cardiff University and an expert in clinical trials for psychiatric drugs, refuted these claims: “It is disingenuous of Janssen to claim that patients are monitored closely and investigators carefully trained – I have been involved in many clinical trials and this is not what happens.” “It is well known that there have been clinical trials in South Africa where patients dropped out, quite possibly because of adverse events, but they were not followed-up – the investigators had no idea whether they relapsed or were dead.”

Aside from the ethical dilemmas of withdrawing treatment from patients, the design of the two studies is considered questionable because physical withdrawal symptoms can sometimes be mistaken for disease symptoms and thus compromise the quality of the data. “Withdrawal studies are well-known to be a very bad design,” says Professor Healy. “Some patients will get worse not because of the illness, but because of withdrawal symptoms from the drug.” However, Janssen states: “If study patients do not receive their

³³ Quote from email correspondence Janssen-research journalist, February 2013.

³⁴ Schipper, I. and F. Weyzig. 2008. *Ethics for Drugs Testing in Low and Middle Income Countries* (see page 63). See http://somo.nl/publications-nl/Publication_2472-nl.

³⁵ La Revue Prescrire. *Schizophrenia: no to placebo-controlled clinical trials*. September 2007 <http://english.prescrire.org/en/81/168/45750/0/2007/ArchiveNewsDetails.aspx?page=2>

³⁶ Quote from email correspondence Janssen-research journalist, February 2013.

medication or receive a placebo injection as part of the withdrawal phase of the study, it may take many weeks for them to develop symptoms. Physical withdrawal symptoms in this case are not likely to be confused with a return of symptoms of the underlying illness.”³⁷

Experts also point to a less obvious backstory regarding the Janssen paliperidone trials. According to drugpatentwatch.com³⁸, four of Janssen’s lucrative risperidone injection patents expire in 2014, another four by the end of 2017. The company has been busy conducting clinical trials across the globe to evaluate monthly and three monthly paliperidone injections. This has led some experts, including Professor Joel Lexchin, to suspect that the latest trials are an opportunity to have a new injectable brand-name drug available once the patent on the older one runs out, thereby preserving Janssen’s revenue stream.

Janssen insists that there are important differences between paliperidone and risperidone. According to the company, paliperidone has a lower potential for drug-drug interactions compared to risperidone. Furthermore, the paliperidone palmitate injections do not require refrigeration and may be administered less frequently.³⁹ However, the UK’s National Health Service (NHS) North-East Treatment Advisory Group noted uncertainty regarding clinical efficacy and was not satisfied that cost-effectiveness had been adequately demonstrated. It does not recommend paliperidone depot injection for schizophrenia.⁴⁰ The Canadian Expert Drug Advisory Committee (CEDAC)⁴¹ was not convinced of the clinical advantage of paliperidone and recommends that paliperidone should not be listed. In a written response⁴², Janssen states that national health appraisal bodies for Scotland and Wales have each independently appraised and recommended paliperidone palmitate as cost-effective. Indeed, the Scottish Medicines Consortium⁴³ accepted paliperidone, commenting however that the paliperidone injection was more effective than a placebo but merely non-inferior to existing antipsychotic depot injections.

“This is business, pure and simple,” believes Professor Healy. “These [clinical trials] have nothing to do with medicine. Paliperidone is pure marketing; it is just (the same drug as) risperidone at a higher cost with no increased benefits for patients.” Professor Healy added that part of the problem was that the public wrongly assumed drug regulators guarded against unneeded clinical trials or medicines. “The regulators like the FDA are not in the business of saying there are enough anti-depressants or anti-psychotics on the market or whether a drug is good or bad, they treat new drugs like they treat new butter or olive oil, the company just has to jump through the regulatory hoops – which includes having two placebo trials even when these have no scientific value.”

³⁷ Quote from email correspondence Janssen-Wemos on July 1, 2013 (see Annex 3 for full statement).

³⁸ www.drugpatentwatch.com (last consulted on May 23, 2013).

³⁹ Based on email correspondence Janssen-Wemos on July 1, 2013 (see Annex 3 for full statement).

⁴⁰ See <http://www.netag.nhs.uk/files/recommendations/NETAG%20decision%20summary%20notice%20-%20Paliperidone%20depot%20injection%20-Xeplion-%20-Mar%202012.pdf> (last consulted on June 20, 2013).

⁴¹ Canadian Expert Drug Advisory Committee (CEDAC) Final Recommendation. 2011

⁴² Based on email correspondence between Janssen-Wemos on July 1, 2013 (see annex 3 for full statement).

⁴³ Scottish Medicines Consortium. Re-submission paliperidone palmitate 50mg, 100 mg and 150 mg prolonged release suspension for injection (Xeplion). 7 October 2011

Professor Joel Lexchin is also amongst those questioning why the paliperidone withdrawal studies were authorised in the first place. "Clinical trials for products developed to protect market share which have little or no benefits to patients are always ethically questionable. But I don't understand why regulators and ethics committees would allow placebo clinical trials for these anti-psychotics... they are failing people. A relapse in schizophrenia can be very serious, it can lead to hospital, self-harm or harming others. From my point of view these trials should never be allowed." Lexchin's concern was the focus of a 2012 article in the respected *British Medical Journal* (BMJ) in which he and professor Donald Light of the Department of Psychiatry, University of Medicine and Dentistry of New Jersey concluded that drug companies "devote most of their research money funds to developing scores of minor variations that produce a steady stream of profits."⁴⁴

Janssen finished by stating: "We are deeply committed to conducting clinical research in the most ethical manner possible, with patient safety as a prime consideration, and we strive to find innovative therapies to treat unmet medical needs of patients around the world."⁴⁵

⁴⁴ D. Light and J. Lexchin. 2012. 'Pharmaceutical Research and Development what do we get for all that money'. In: *British Medical Journal* 2012;345:e4348.

⁴⁵ Quote from email correspondence Janssen-research journalist, February 2013.

6. What the most powerful regulators say about placebo-trials⁴⁶

In a written response, the **EMA** said: “In general, the European Medicines Agency and its scientific Committee for Medicinal Products for Human Use (CHMP) consider placebo-controlled trials important, where they can be used ethically. ... Whether they are required or not may vary for different therapeutic areas and in general depends on a multitude of factors which may be different for each medicinal product. Even if they are scientifically desirable they should only be conducted if they are ethically acceptable, no matter where they are conducted.”

The CHMP guideline on the clinical investigation of medicinal products, including depot preparation in the treatment of schizophrenia, states: “There is a debate about the use of placebo in clinical trials in the treatment of schizophrenia. Concerns about ethical issues and feasibility have been raised. However, assay sensitivity cannot be guaranteed even in well designed and conducted trials if a placebo arm is not included. Historical controls are not useful for current clinical trials, since the concept of the disorder, the diagnostic criteria and the efficacy criteria have changed. In recent trials in schizophrenia, the difference in efficacy between active treatments and placebo has tended to be smaller than the differences seen in the past. Therefore, a placebo control has been considered necessary for internal validation of non-inferiority trials comparing new drugs to an active control and is also highly desirable so that the 'absolute' effects (both therapeutic and adverse) of a product can be ascertained.”⁴⁷

“To avoid unnecessary risks for patients and others, placebo controlled studies should be performed in a highly controlled setting, with stringent follow-up to apply predefined escape criteria, rescue medication and stopping rules. Provided these safeguards are in place, the benefits of using a placebo arm will generally override any ethical reservations in short term controlled efficacy trials. Long term administration of placebo to patients in need of active treatment is ethically problematic and is associated with a high rate of premature withdrawals, making interpretation of the data difficult. For demonstrating maintenance of effectiveness of treatment in the long term, the use of a placebo arm is however possible and appropriate in a randomised withdrawal study in which patients stabilised on open label test treatment for at least 12 weeks are randomised to active test treatment or placebo. Patients who relapse meet study endpoint criteria and can receive active treatment immediately without compromising the study requirements. Provided the study is appropriately designed and conducted patients in the placebo group who become in need of active treatment will not be denied it and hence there should not be ethical problems.”⁴⁸

The **FDA** said: “You cannot put people at risk of harm by denying them a known effective treatment in order to do a placebo-controlled trial (ICH E-10). You can ask informed,

⁴⁶ The information in this chapter is based on email correspondence between the research journalist and regulators. All quotes come from this email correspondence.

⁴⁷ See

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/10/WC500133437.pdf
(last consulted on June 20, 2013).

⁴⁸ Idem.

uncoerced patients to endure discomfort in a trial, so long as it is wholly clear that they can leave the trial whenever they wish. There are some cases in which the placebo needed to ensure interpretability of the trial cannot ethically be used. In that case there may be no way to study a new drug in that disease unless it is superior to the available therapy.”

“Longer term trials of say, asthma prophylaxis, need a placebo because the effect of the control drug would not be predictable. (Many of those would be trials where drug and placebo are each added to baseline treatment and there are always rescue medications). Trials in diabetes of short duration can use placebo and are no threat to patients as long as they are well-monitored. Active control trials are also used, as are add-on trials, where drug and placebo are each added to other therapy, because the effect is rapid and large and the study is therefore interpretable. We do not think these present ethical issues.”

“We do not always require any placebo-controlled trial. We would not require one where use of a placebo would endanger the patient. Thus, in trials in serious infections, cancer (where there is an effective treatment), and other settings in which lack of the standard treatment would put a patient at risk, you cannot use a placebo, and the trials done are always active control trials. An active control trial where the new drug is more effective is always an acceptable option. This is very clearly set forth in ICH E-10.”

7. Post-trial access to treatment

The introduction of the principle of post-trial access into the DoH in 2000 was an attempt to address the potential exploitation of patients as trial subjects. This was a particular concern in poor countries where it was feared human research participants could be exploited for the sole benefit of affluent others. But despite this important development, even now 13 years later, post-trial access to medication remains a rare perk in South Africa.

What the Declaration of Helsinki says about post-trial access to treatment

The principle of post-trial access to drugs for people who participate in clinical trials was first introduced into the DoH in 2000. The Declaration stated: "At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study." The latest version of the Declaration, revised in 2008 states: "At the conclusion of the study, patients . . . are entitled . . . to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits. Article 17 requires that: "Medical research involving a disadvantaged or vulnerable population or community is only justified if ... there is a reasonable likelihood that this population or community stands to benefit from the results of the research." Article 14 also requires that any study protocol must describe how research participants can access beneficial interventions developed through the study. 'Other benefits' can also be presented to the research ethics committee for approval, for instance access to healthcare, support for local health infrastructure or health information campaigns.

The final passage from the DoH suggests that drug companies must do more to ensure trial participants are not just used to make up the numbers. There must be real, long-term, sustainable benefits for individuals and communities who participate in clinical research, often because they are desperately ill and poor – taking risks that may otherwise only benefit more affluent communities and drug company shareholders.

CASE STUDY: Clinical Trials for Rheumatoid Arthritis in South Africa: The Ethical Dilemmas

Negotiating post-trial access with the drug companies is often down to the ethics committees. Rheumatoid Arthritis (RA) illustrates the current situation in South Africa.

RA is a chronic, painful, auto-immune disease affecting around 1 per cent of the world's population. It usually develops between the ages of 40 and 60 and is three times more common among women. This crippling disease can affect any part or organ of the body but most commonly causes swelling and damage in joints and can lead to severe disability.

South Africans have the same primary genetic marker as European sufferers; for West Africans and their American descendants, this marker is different. Research has shown that higher rates of poverty can significantly worsen the impact of RA in South Africa. According to Professor Mohammed Tikly, Head of Rheumatology at the Chris Hani Baragwanath teaching hospital in Soweto, in South Africa, this debilitating disease tends to strike people, on average, a decade earlier than in the west.

The conventional treatments are not effective in one third of patients. Therefore there are many clinical trials investigating biologics – a relatively new class of ‘genetically engineered’ drugs to target the body’s inflammatory response. These can cost between 6,000 and 8,000 Euros [70,000 to 100,000 ZAR] per year so they are unaffordable for most South Africans, even for those with private health insurance as only the top-tier schemes pay.

Professor Tikly’s outpatient clinic department is always full of RA patients, mainly black, waiting up to or at least 3 hours to be seen. “The patients seen here are privileged as most district hospitals can do very little for people with severe RA,” the professor explained. “Some travel hundreds of kilometres from rural areas and Port Elizabeth (1000 kilometres) to get access to rheumatology care. Even conventional treatments are still only available to the privileged few in urban areas. There are two main challenges for us: the shortage of human resources and access to early diagnosis and treatment with traditional drugs. For those with the most severe disease, the lack of access to biologics is another problem, but a much smaller one.”

According to Professor Tikly, for patients who cannot afford private healthcare or expensive medication, clinical trial participation can be a good opportunity to access treatment that would otherwise be unaffordable. However, the question of what happens after the trial has finished and the continuation of treatment for a patient often remains a difficult one. “Some patients given access have done very well,” says Professor Tikly. “But the ethical problem is what happens at the end of the trial – they have to come back into the system and some have really struggled because their disease has relapsed. We tell patients that they may get a better quality of life for a year, 18 months, up to five years, depending on the trial, and these are people with severe disease so they agree. But it is very difficult for them and us if they get better during the trial but there is no access after.”

“We have 12 or so patients on them but that is out of around 250 who qualify clinically – there is still huge unmet need. The other challenge is the cost of reorganising services to administer [biologic] infusions, the extra demands on nursing care and lack of clinical space.”

“I still wrestle with the dilemma and don’t know if we are doing clinical trials for just selfish reasons – but patients at least have a few years of better quality of life and hopefully after a few years we will come up with an alternative – but maybe this is naive thinking.”

In South Africa, it is left to RECs to negotiate the best deal they can with drug companies. But as Marzelle Haskins, Managing Director of the REC Pharma-Ethics points out, there is only so much they can do: “We can’t force post-trial access as we have no legal clout in

this area but nor can they do the research without our approval – this means it is quite often a compromise. We have to look at the potential benefits of the clinical trial and we wouldn't want to reject it because of long term access.”

Catherine Lund, Managing Director of the South-African CRO OnQ, is of the opinion that post-trial access is not a realistic outcome: “Post-trial access is trial dependent, but you don't want to guarantee something that might not work... In my experience ethics committees don't ask about it – nice in theory but not really practical. In this cash-strapped environment it would be very expensive.”

Experts such as Professor Doris Schroeder, Director of the Centre for Professional Ethics at the University of Central Lancashire, concedes that the post-trial access questions are complex and not clear cut. “Yes, it seems eminently unfair to discontinue access to drugs to clinical trial participants who are responding well, when it is clear that their national health service will not pick up where the trial left off. It means refusing to help somebody whom one could easily help. And in the worst case, the participant dies. That's utterly horrendous, when help is so close.”

“However, when it comes to ethical guidelines, the story is much more complex. Post-study access to drugs exists only as one unsophisticated requirement in the Declaration of Helsinki and in similar guidelines. There are so many cases where providing post-study access to drugs does not make any sense (where the safety parts of the trial fail, for instance) or is not practically feasible (because the drug has not yet been approved or never will be). I don't think pushing for post-study access to trial drugs will go anywhere, legally or through activism, because it is too coarse a mechanism, even though it would fit [some] cases beautifully.”

She adds: “Ethical guidelines need fairly broad solutions and there can't be any on this topic. In my view, the activism has to be about access to healthcare as a benefit for vulnerable populations taking part in medical research and this access has to be provided through long-term partnerships with researchers and sponsors. The flying into areas of epidemics or the short-term search for individuals with fortuitous research characters (e.g. somebody who has never taken any drugs and certainly none at the time of the trial), is the problem.”

“Research clinics that build up local infrastructure and offer longer-term access to healthcare in return for trial participation could circumvent the above problems. Of course, there are other drawbacks, namely the withdrawal of staff from local hospitals into the more attractive foreign investor facilities. There are no easy answers here, as something like providing access to drugs post-trial needs to be regulated and regulations need consistency in approach; that's not possible if one says that participants are owed access to drugs, full stop.”

Exploitative relationships

There is little evidence that drug companies take capacity building of local researchers seriously, despite repeated claims by pharmaceutical industry that this is one of the benefits

of moving clinical trials to developing countries. There is also concern in some quarters that local doctors recruited by the CROs are not given fair credit for their professional research skills.

Professor Tikly says: "A disturbing issue for both [private and public] sectors is the fact most trials are designed and finalised before they are brought to us, with little if any room for changing the design or inclusion/exclusion criteria. ... Really they are using us for our numbers, they are not interested in any intellectual input we make in the developing world; it is only about the number of patients we can recruit. ... Let's be honest, the drug companies are just trying to sell their products and believe the experts are all in the Northern Hemisphere; we are non-entities."

"My concern is that our leadership [in research] doesn't commensurate with our contribution as too often we are the subservient partners in the research – and this needs to be re-balanced", says Professor Salim Abdool Karim, president of the Medical Research Council and director of CAPRISA. "We are not just here to recruit patients for data collection."

Catherine Lund of OnQ says that her CRO is committed to training local staff, particularly from disadvantaged groups. "There is a mandate from the Department of Health for capacity building in clinical research rather than using the same old clinics and investigators every time, especially among our black and other disadvantaged colleagues," she says. "So from 2012 we will be actively looking in the rural areas for new GP/Primary care sites for HIV, TB, cardiovascular system trials – we will not know them so will have to train and support them through."

8. Observations and remarks

Regulatory framework and RECs

In a country where twelve million people go to bed hungry every night and where the majority of the people that need healthcare cannot get it, it is no surprise that voluntary patient recruitment for clinical trials is relatively easy for the drug companies and the CROs. There is a genuine concern that clinical trial participants in South Africa are more vulnerable than participants in more affluent countries. Therefore, it is encouraging to note that the regulatory framework, designed to protect South African participants of clinical trials, has improved over the past decade. Ethics committees play an important role in the protection of clinical trial participants. Several interviewees mentioned that the degree of communication between ethics committees has improved and as a result, ethics committee “shopping” had become much more difficult over the past 2 years. Still, the findings of the NHREC audit indicate that many RECs are struggling to meet minimum requirements and as a result cannot always safeguard trial participants’ safety. Wemos welcomes the fact that prominent South African ethicists are calling for a levy to be charged to drug companies so that trials, once approved, can be monitored independently and patients better protected from ethical violations.

However, clinical trials in South Africa could be monitored more effectively by independent researchers through a more robust public trial registry that meets the WHO Registry Criteria.⁴⁹ Currently the information available on the South African National Trial Register is limited and the search engine is not user friendly. In addition, the Register currently leaves trial sponsors substantial room for not publicly disclosing relevant information. According to Wemos, this is not in the interest of clinical trial participants and severely limits public scrutiny.

Placebo-controlled trials and market share interests

Issues surrounding placebo-controlled trials have once again come to the fore in this report. South Africa appears to have a high rate of placebo-controlled trials, almost one in two of all registered trials, according to a simple search of ClinicalTrials.gov. This is comparable to other low and middle income countries. However, South Africa has a much higher proportion of placebo-controlled trials when compared to higher income countries where such trials only account for between one third and one fifth of all clinical trials. This observation – more placebo trials taking place in low and middle income countries – is supported by a study carried out by the Centre for Research on Multinational Corporations (Stichting Onderzoek Multinationale Ondernemingen, SOMO).⁵⁰

⁴⁹ See <http://www.who.int/ictcp/network/primary/en/index.html> (last consulted on 28th May 2013).

⁵⁰ Schipper, I. and F. Weyzig. 2008. *Ethics for Drugs Testing in Low and Middle Income Countries*. See http://somo.nl/publications-nl/Publication_2472-nl.

The outsourcing of such trials to countries such as South Africa, which are plagued by chronic poverty and insufficient independent clinical trial monitoring, is concerning to Wemos. If a trial subject suffers a relapse or comes to harm during a placebo trial, there is no guarantee that systems and safeguards will be in place to assist them.

Furthermore, according to leading experts, the placebo trials discussed in the current report are not meant for the development of new drugs, but are intended merely to protect the market share of the company. By adding minor variations to their blockbuster drugs, they are trying to get a 'new' product on the market by the time the patent of the old drug has expired, thereby preserving their revenue stream. Such clinical trials which have little or no benefits for patients are ethically questionable, according to Wemos.

This problem is key to what Professors Light and Lexchin call the 'hidden business model', as a result of which only one in ten newly approved medicines substantially benefits patients.⁵¹ According to experts cited in this report, drug regulators such as the EMA and FDA play an important role in sustaining this model as they do not require new drugs to be significantly better than drugs that are already on the market; neither do they evaluate whether there is a public health need for such a drug. Instead they treat drugs as if they were common commodities.

Furthermore, by requiring placebo-controlled trials⁵², the EMA and FDA actually create a situation in which ethical violations are imminent and pharmaceutical companies have little incentive to prioritise the protection of clinical trial participants.

Post-trial treatment access

Enforcing post-trial access to treatment is extremely challenging, and in South Africa it is left to ethics committees to negotiate it. Interviews with REC members suggest that some South African RECs are more successful in this area than others.

In Wemos' opinion, it is crucial in a country such as South Africa where many people have no access to healthcare, that some form of post-trial benefits are guaranteed. If not, the end of a clinical trial may also constitute the end of, what may be, the participants' only chance to treatment.

⁵¹ Light, D. and J. Lexchin. 2012. 'Pharmaceutical research and development: What do we get for all that money?' In: *British Medical Journal* 2012:344:e4348.

⁵² See a study carried out by SOMO. The study report states the following: "The European authorities granting market authorization for medicines require, in principle, that pharmaceutical companies conduct placebo-controlled studies (also for schizophrenia treatment); however, the Research Ethics Committees (RECs) in most Western European countries no longer approve this kind of trials due to the unethical aspects involved. As a result, the industry is compelled to look outside of Western Europe as these placebo-controlled studies are still required by the EMEA and the FDA for market authorisation." From: Schipper, I. and F. Weyzig. 2008. *Ethics for Drugs Testing in Low and Middle Income Countries* (see page 67). See http://somo.nl/publications-nl/Publication_2472-nl.

Annex 1 Interviewees

AstraZeneca: Esra Erkal-Paler, Head of Global Media Relations, London

Dr Adrian Morris: Asthma specialist with private practices in Cape Town, Durban, London and Guilford

Dr Ahmed Ismail Manjra: Paediatrician and allergy specialist at the Westville Private Hospital in Durban

Dr Amar Jesani: Coordinator of the Centre for Studies for Ethics and Rights in Mumbai and editor of the *Indian Journal of Medical Ethics*

Dr Doris Schroeder: Director of Centre for Professional Ethics at the University of Central Lancashire

Dr Gerhard Grobler: Chair of the South African Society of Psychiatrists and Head of Psychiatry at the Mr Steve Biko Academic Hospital, Pretoria

Dr Gerta Brink: Private psychiatrist in Randburg, Johannesburg

Dr Keith Pettengell: Gastroenterologist at Hillcrest Private Hospital in Durban, with 30 years experience as an investigator in pharmaceutical trials

Dr Lolo Doull: Consultant in Paediatric Respiratory Medicine and spokesman for Royal College of Paediatrics and Child Health

Dr Peter Cleaton-Jones: Chair of the Wits University Human REC in Johannesburg and member of the Human Sciences Research Ethics Committee

Dr VS Naidoo: Gastroenterologist from University of KwaZulu-Natal in Durban

European Medicines Agency: Unnamed spokesperson

Federal Drug Agency: Unnamed spokesperson

Janssen Research and Development, LLC: Greg Panico, Communications Leader, Neuroscience, Titusville, New Jersey

Mr Edwin Madibogo: Manager of Ebony Park Kaalfontein primary care clinic, Johannesburg

Mr Keymanthri Moodley: Associate professor and head of the Centre for Medical Ethics and Law at Stellenbosch University

Two nurses from an asthma charity in the UK

Ms Catherine Lund: Managing Director of the South African CRO OnQ and spokeswoman for the South African Clinical Research Association

Ms Loraine Schirlinger: Head of the Alzheimer's Society Gauteng office in Johannesburg

Ms Marzelle Haskins: Managing Director of the private REC Pharma-Ethics

Ms Urmilla Bridgmohun: Project Manager with the American CRO, Inc Research – based in its Johannesburg office

Ms Zane Wilson: Founder of the NGO South African Depression and Anxiety Group SADAG

Professor Ames Dhali: Head of the Steve Biko Centre for Bioethics; deputy chair of the National Health Research Ethics Council; editor of the *South African Journal of Bioethics and Law*

Professor Charles van der Horst: HIV specialist from the University of North Carolina

Professor David Healy: Professor of psychological medicine at Cardiff University and an expert in clinical trials for psychiatric drugs

Professor Gita Ramjee: Head of the Medical Research Council's HIV Prevention research unit

Professor Jerome Singh: Head of Ethics and Law for CAPRISA, at University of KwaZulu-Natal. Adjunct Professor at Dalla Lana School of Public Health Sciences and Joint Centre for Bioethics at University of Toronto, Canada

Professor Joel Lexchin: Emergency room doctor and professor of public health at York University in Canada

Professor Mohammed Tikly: Head of rheumatology at the Chris Hani Baragwanath teaching hospital in Soweto, Johannesburg

Professor Salim Abdool Karim: President of Medical Research Council, Pro Vice-Chancellor (Research) at the University of KwaZulu-Natal and Director of CAPRISA - Centre for the AIDS Program of Research in South Africa

Annex 2 Reaction AstraZeneca

1 July 2013

Thank you for sharing with us Chapter 4 of your report related to placebo controlled clinical trials and the case study of AstraZeneca's CHASE 1 and 2 studies.

Overall, the report represents accurately, although selectively, the information we shared with the report's author earlier this year. There are two corrections we would request and one comment to highlight.

Page 4 of Chapter 4, the second paragraph states:

According to AstraZeneca, the FDA formally requested placebo trials for the combination budesonide/formoterol inhaler in writing: "This trial is being conducted in response to a formal written request from the FDA...."

To clarify - there is only one placebo controlled trial, not 'trials'. This is also repeated in the description (first page of Chapter 4) of the Case Study.

With regard to the reference to the FDA, it would be more accurate to state: "According to AstraZeneca, the FDA formally agreed to a placebo trial for the combination budesonide/formoterol inhaler..."

The Chapter 4 of the report only offers a partial representation of the Declaration of Helsinki on placebo controlled trials. We are concerned that truncating that passage could give a somewhat misleading impression to readers. The DoH states: "Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option."

More broadly, AstraZeneca is confident that the CHASE 1 and 2 study designs are ethical and we would like you to consider the following points about the use of a placebo controlled trial as part of those studies.

- The CHASE studies were intended (both are now completed) to support our paediatric supplemental New Drug Application for Symbicort pMDI (pressurized Metered Dose Inhaler) in children aged 6 <12 years in the US. The FDA specifically requested that AstraZeneca look at the dose of the mono-components in the Symbicort pMDI when used in children. The design of these studies was agreed with the FDA - CHASE 1 was intended to confirm the efficacy of the budesonide dose (160 µg bid), while CHASE 2 evaluated the formoterol mono-component.
- As CHASE 1 was a dose confirmation study, the best way to determine the true magnitude of effect is to compare it to a placebo baseline.

- Comparing to an active comparator leaves the results open to many variables regarding how the individual components perform. A placebo-controlled study reliably evaluates the safety and efficacy during the early phase development of a new treatment while minimising the number of necessary participants exposed to the treatment.
- Asthma in children is frequently more episodic in nature than in adults. When patients enter studies they may have higher levels of symptoms than at other times in the year and it is not unusual to see large improvements in asthma symptoms and lung function when patients receive placebo. This makes it difficult to select a minimally effective dose of active treatment. Inclusion of a placebo arm is the best way to adequately answer this question of singular importance to regulators.
- AstraZeneca is committed to following the highest scientific and ethical principles in the conduct of paediatric research, and studies involving children are only conducted once regulatory requirements are met and ethics committee approval is granted. The FDA agreed that the short-term withdrawal of low-dose ICS or leukotriene receptor antagonist monotherapy in children with stable asthma presents no greater than a minor increase over minimal risk, provided there are adequate safeguards for the patients. Study approvals were granted by ethics committees in countries where the study is conducted, and from relevant regulatory agencies. In South Africa approval was granted by the South African Medicines Control Council.
- Risks to the placebo group were mitigated with a robust asthma safety plan. Patients and their parents/carers were made aware of the study design and provide consent prior to the patient enrolling in the study. Parents or the treating physicians could withdraw the children from the study at any time. The paediatric population enrolled in the CHASE studies had relatively mild asthma. Patients in both arms of the studies, including the 'placebo' patients, kept the rescue medication that they were used to, in case those were needed.

The study used the shortest placebo controlled period likely to show clinical response.

The safety plan also included: regular clinic visits, lung function assessments to closely monitor the patient's asthma status.

Please do not hesitate to contact me if you have any questions or would like further information.

Best wishes
Esra Erkal-Paler

Head of Global Media Relations
AstraZeneca

2 Kingdom Street, London W2 6BD

Annex 3 Reaction Janssen Research & Development, LLC

July 1, 2013

Thank you for the opportunity to review the chapter you provided of the draft Wemos Foundation report on clinical trials in South Africa. We would like to add some additional perspective regarding the Janssen clinical trials that are mentioned in the chapter and also reinforce our longstanding commitment to public health, Neuroscience research, and to patients with brain disorders and their families.

For more than 50 years Janssen scientists have discovered and developed innovative medicines to treat serious mental illnesses. Our neuroscience researchers remain committed to discovering and developing new therapies to help patients affected by brain disorders such as Alzheimer's disease, schizophrenia, mood disorders, and chronic pain, which represent some of the most devastating and costly diseases faced by society.

We have provided responses to statements and quotes in the draft chapter, outlined below. We request that these comments be added to the report:

1. Janssen clinical trials are conducted at clinical-trial sites in many countries throughout the world. Study patients come to these sites for their appointments and evaluations. Regardless of the nature of the health-care system in the country where the research is being conducted, patients enrolled in Janssen clinical studies have a clinic and hospital where they can receive care and monitoring during the course of the clinical study.
2. Investigators in Janssen clinical trials are chosen based on their education, training, and medical qualifications. They also receive two days of training on the protocol, the assessments, safety reporting, and good clinical practices (GCP) for research. They are required to complete on-line training as well as attend in-person training for each study.
3. In all clinical trials there are certain study patients who are lost to follow-up for a variety of reasons. This occurs in routine clinical practice as well. In our clinical trials, investigators reach out to study patients and make every effort to bring them back to the clinic for follow-up care.
4. In regard to discussion of the validity of the Janssen study designs, we would like to emphasize that the medications being tested in these studies have a very long half-life of approximately one month or three months. If study patients do not receive their medication or receive a placebo injection as part of the withdrawal phase of the study, it may take many weeks for them to develop symptoms. Physical withdrawal symptoms in this case are not likely to be confused with a return of symptoms of the underlying illness.
5. There is a well-established need for clinical trials that study the ability of a medication to maintain therapeutic efficacy over longer periods of time and which

include a plan to study patients' withdrawal from the medicine as part of the study design. Health authorities around the world, including the U.S. FDA and the European EMA, require these studies and then review all of the efficacy, safety and tolerability data prior to approval. The appropriate long-term use of medications is an important question for patients, doctors and society and needs to be studied in clinical settings.

6. We do not agree with the statements by Prof. Joel Lexchin. There are significant differences between Janssen's oral antipsychotic medicines (risperidone and paliperidone extended release) and our various long-acting injectable antipsychotic medicines and between the specific Janssen injectable treatments as well, two of which are on the market (risperidone long-acting injection and paliperidone palmitate 1 month injection), and one of which is being studied in clinical trials (paliperidone palmitate 3 month injection). For example, paliperidone is metabolized primarily by the kidney, and thus has a lower potential for drug-drug interactions compared to risperidone, which is more metabolized in the liver. The one-month formulation of paliperidone palmitate is provided as a prefilled syringe which is ready to inject and does not require refrigeration or reconstitution, advantages over the earlier injectable medicine which was indicated for use every two weeks. The lack of need for refrigeration is an important consideration in many countries. The experimental three-month injection also has these newer features and may provide an option for treating symptoms of schizophrenia with four injections a year, compared to daily oral medicines or shorter-interval injections. The ability to attenuate the psychotic symptoms of schizophrenia with four injections a year may be particularly important in settings where much of the population is located some distance from clinical infrastructures.

Long-acting injectable antipsychotics are associated with effective treatment of symptoms of schizophrenia and delay of relapse. Longer intervals between treatments provide advantages for patients, providers, caregivers and health-care systems. Health authorities around the world rightly require companies to conduct clinical trials before they can market new or improved medications. Clinical trials comparing new medications to placebo and to older marketed medicines are how we demonstrate that they are effective, safe, and tolerable.

7. In England, the National Institute for Health and Care Excellence (NICE) has not reviewed paliperidone palmitate, which is why local and regional English National Health Service bodies, such as the North-East Treatment Advisory Group, which covers only the population in and surrounding the city of Newcastle-upon-Tyne, formulate their own views regarding the medicine. For balance, it is worth noting that the national health appraisal bodies for Scotland (Scottish Medicines Consortium – SMC) and Wales (All Wales Medicines Strategy Group – AWMSG) have each independently appraised and recommended paliperidone palmitate as cost-effective for use by the National Health Service in Scotland and Wales respectively. In addition, many other reimbursement authorities around the world have accepted the cost-effectiveness of paliperidone palmitate.

I would like to conclude by stating that Janssen has a long-standing commitment to improving public health, to providing innovative treatments for patients with brain disorders, and to conducting clinical research in an ethical and appropriate manner.

Thank you for the opportunity to respond to the draft report chapter.

Sincerely,

Greg Panico
Communications Leader
Neuroscience
Janssen Research & Development, LLC
Titusville, New Jersey, USA

wemos

Colophon

Title: The Clinical Trials Industry in South Africa: Ethics, Rules and Realities,
Document: GHG-M
Author(s): Wemos Foundation
Date: July 2013

The Wemos Foundation is an Amsterdam-based non-profit organization that advocates the right to health of people worldwide.

Wemos would like to thank all who contributed to this report.

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The Wemos Foundation is a public interest institution (Algemeen Nut Beogende Instelling – ANBI) and carries the certificate of the Central Office for Fundraising (Centraal Bureau Fondsenwerving – CBF).

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