

Clinical Drug Trials in Argentina: Pharmaceutical Companies Exploit Flaws in The Regulatory System



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1. Introduction and summary

Pharmaceutical companies are increasingly conducting clinical drug trials on people in developing countries or emerging economies. In addition to China, Brazil and South Africa, Argentina is a primary destination for this activity. Although the country's regulatory standards are often cited as exemplary, the actual conduct of clinical trials there is anything but perfect. From enrolling babies from among the population's poorest segments to improperly using placebo on schizophrenic adolescents, and even using a "standard" unapproved treatment, pharmaceutical companies too often exploit the flaws in Argentina's regulatory system to avoid their ethical obligations.

"Phase III" trials (i.e. the final step before a drug is marketed) require large numbers of patients. To save time and money, simultaneously conducting the same trial in several countries is in the best interest of pharmaceutical companies. Almost half of all drugs marketed in Europe are currently estimated to have been tested in "non-traditional" countries (countries outside Western Europe, the United States and Japan, which hosted all clinical trials until the end of the last century). Such offshoring of clinical trials is known to increase the risk of ethical violations. In "non-traditional" countries, pharmaceutical companies can benefit, both from regulatory systems that are often flawed, and the vulnerability of certain populations.

The Swiss companies Hoffmann-La Roche and Novartis are regularly among the world's top three pharmaceutical companies in terms of amounts invested in drug research and development (R&D). These two pharmaceutical giants headquartered in Basel conduct numerous clinical trials worldwide, including in southern and eastern countries.

Argentina is one of Latin America's primary destinations that pharmaceutical companies choose for their clinical drug trials. The aim of this report is to gain an understanding of the legal framework within which the Swiss companies – which have a significant presence in Argentina's trials

market – operate, and to what extent they observe current ethical rules.

The research upon which this report is based was conducted in Argentina during the first three months of 2013, by reviewing scientific literature, official documents or press articles and conducting interviews with ethicists, doctors, patients, those in charge of regulatory agencies and representatives of pharmaceutical companies.

Despite Argentina's lack of specific national legislation governing clinical trials, both the Argentinian Ministry of Health and certain provincial authorities do regulate clinical trials. Generally, major players in clinical research have judged monitoring standards and observance of ethical rules as "mostly good".

Our investigation, however, has revealed worrying flaws in the system, which, in addition to allowing disturbing abuses, have sparked much controversy. Over the past few years, certain companies have taken advantage of regulatory gaps to avoid their obligations. The violations that have come to light relate in particular to the enrolment of babies from among the population's poorest segments, the improper use of placebo, discontinuation of treatment after trials are concluded, and the lack of commitment to provide compensation if problems arise from trials.

For strategic reasons and to maximise profits, industry-sponsored clinical drug trials on human subjects are increasingly offshored in developing and emerging countries. In those countries, pharmaceutical companies can find a large pool of vulnerable people willing to take part in drug trials as it represents often their only treatment option. In addition, weak regulatory environments enable the pharmaceutical multinationals to shorten clinical trials duration. This increases significantly the risk of ethical violations. Concerned about this situation, the Berne Declaration launched several investigations in 2012 and 2013. Four field studies took place in Argentina, India, Russia and Ukraine to better understand these contexts in which numerous clinical trials take place. How is the regulatory system performing? Are the ethical standards respected? How do Swiss firms conducting clinical trials behave in these countries? A research was also carried out in Switzerland to understand how Swissmedic – the Swiss medicines agency – functions and carries out the ethical control of clinical trials that were conducted in third countries. The field studies were done by investigative journalists and by an NGO specialised in the field. The five investigation reports are available on www.ladb.ch or upon request at info@ladb.ch.

This report is based on the research conducted in Argentina by **Gustavo Kuhn**, an investigative journalist.

2. Clinical trials in Argentina: appearances can be deceptive

Pharmaceutical companies have regularly chosen Argentina for conducting multi-centre clinical trials. As a country, it does offer numerous advantages with regard to testing the efficacy and safety of drugs that are still at the experimental stage. But its regulatory system also has significant flaws that have resulted in serious ethical violations. The country may often be cited as exemplary, but the way clinical trials are actually conducted there is anything but perfect.

The overall context in which clinical trials operate

The aim of this investigation was to find out whether the attraction that Argentina holds for pharmaceutical companies lies in “practical” considerations alone, or whether the standard of monitoring there effectively frees the industry from the obligations imposed upon it by the countries of Western Europe and the United States, thus saving it time and money. We focused in particular on the Swiss companies that have a significant presence in Argentina’s clinical trials market.

It should be stated from the outset that nobody questions the need for clinical trials. They are intended to prove the safety and efficacy of products before they are marketed and consumed by tens of thousands – millions even – of patients throughout the world, and thus represent a mandatory stage in the development of new drugs or medicines. Clinical trials must therefore demonstrate that the product being tested offers more benefits than risks for the patients into whose bodies it is absorbed.

Clinical trials must, however, comply with a certain number of methodological and ethical rules. For the latter, the main emphasis is on respect for the basic rights of the human beings who lend their bodies and health to medical science.

Noteworthy in this context is the fact that numerous professionals warn that, in the current economic climate, a certain number of trials are not of new molecules intended to treat incurable diseases but of new doses, new combinations or new uses for existing and/or very slightly modified medicines. This practice allows pharmaceutical companies to continually launch new products onto the market and/or extend the exclusive rights (or monopoly) conferred by patents.

More importantly, many ethicists and other observers of clinical trials alerted us to the fact that, to improve profitability, most pharmaceutical companies will try almost anything to accelerate the process of licensing their drugs – even if this means trampling on certain ethical concepts or freeing themselves of certain obligations towards those participating in their clinical trials. Abuses of this kind are mainly seen in developing countries, where the legal framework and monitoring standards are less “rigorous”

than in Western Europe or the United States and where an increasing number of clinical trials are taking place.

The growth of trials in Argentina

Argentina had a high level of activity in the field of clinical research during the second half of the 2000s. According to our calculations, based on the figures published by the National Administration of Medicines, Food and Medical Technology (ANMAT) (1), an average of 176 trials were authorised in the country each year between 2006 and 2012, as against 96 between 2002 and 2005. CAEMe, the umbrella organisation of the multinational pharmaceutical companies with a presence in Argentina – which proudly announced that its member companies conduct 95% of the clinical trials that take place in the country (2) – listed 509 “active” clinical trials there for the year 2012. This corresponds to the total number of new protocols approved that year and trials authorised earlier but still ongoing in 2012. These trials were conducted in 3132 “centres” and involved 23,892 patients. In comparison, the number of active clinical trials in 2003 was 230.

Most clinical trials conducted in Argentina take place in the capital, Buenos Aires, in the province of Buenos Aires – the most populated in the country – or in the province of Cordoba, in the centre of Argentina. For example, the census of clinical trials for 2010 (3) showed that more than a third of the approximately 21,000 patients who participated in a clinical trial that year did so in the capital, 22% were recruited in the province of Buenos Aires and 20% in Cordoba. Santa Fe, Argentina’s third most populated province, accounted for 11% of participants. Whereas in 2010 only a few patients were recruited in the least populated provinces in the country’s interior, this is not always the case. As the scandalous case of GlaxoSmithKline’s COMPAS study (see section 3) shows, trials of vaccines, which require a very large number of “subjects”, are regularly conducted in various other provinces.

Argentina is an important country for Swiss companies as far as conducting clinical trials is concerned. Jorge Cuneo, Medical Director at Novartis Argentina, for example, says that since the 90s, his subsidiary “has been a pillar” of the group at the global level: “In 2012, we invested 23 million

dollars in Argentina, and 19 million the year before". ANMAT's website displays a list of clinical trials approved in the country (4) that shows 148 clinical trials registered in the name of Novartis since 2002, or almost 9% of a total of 1667 research projects listed by mid-May 2013. These figures show this Swiss company as the clear leader among the pharmaceutical companies conducting the most clinical trials in Argentina. Next is the US company, Bristol-Myers Squibb, with 112 trials listed, the British GlaxoSmithKline (104), two further US companies, Eli Lilly and Pfizer, with 76 and 65 respectively, and the Swiss company Roche with 56. Notably, other research conducted in Argentina was financed by Roche but registered in the name of its CRO (contract research organisation) – a service provider that carries out all or part of a clinical trial (5) on behalf of a pharmaceutical company.

Despite what is, after all, a large number of trials, Roche informed us, in a series of e-mail exchanges between March and May 2013 (5), that "only 7% of clinical trials globally are conducted in Latin America", and that Argentina accounts for less than 1% of patients participating in clinical trials worldwide.

Benefits for the country

The pharmaceutical industry and certain departments of the Argentinian government portray this surge in biomedical research as an opportunity for the country. Thus, CAEME promotes clinical trials, claiming that it made it possible for 190 million dollars to enter the country in 2012 (2), for cutting edge technology to be imported, professionals to be trained and patients to be given access to latest generation products.

ANMAT is taking a similar tack, claiming that "the involvement of Argentinian researchers in the clinical trials brings several advantages with it: 1) Professional training; 2) Development and knowledge of professionals at an international standard; 3) Access for patients to new treatments; 4) Practical experience with new medicines for researchers. (1)."

For its part, Roche stresses the development of facilities: "Roche's investment in research and development (R&D) is improving the infrastructure of the centres in which clinical trials are held. Once Roche has identified a centre that is qualified to successfully conduct a clinical trial, it provides that centre expensive facilities and equipment to ensure that it is able to do the work correctly, including deep freezers in which to keep the product, medical equipment, monitors, generators, drip chairs, thermometers and computers." (5) The Argentinian subsidiary of the company also told us that this equipment, and the training of clinical-trial personnel, "are made use of sooner or later and help [the population] in a general way." Finally, Roche estimates that "direct

remuneration of the professionals (researchers, nurses, pharmacists, assistants and administrative staff), and of the institutions themselves, is a major source of funding for both the institutions and the professionals."

Novartis Argentina's Medical Director, Jorge Cuneo, also told us that his company equips the centres that are to be used for clinical trials, and that the equipment remains there afterwards. He also believes that clinical trials give doctors and patients access to innovative drugs that they could not otherwise obtain.

Criticism is mounting

Not everyone approves of such a portrayal of benefits conferred upon the countries in which international clinical trials are conducted. Many who criticize the offshoring of clinical trials effectively say that the benefits for the host countries are overvalued. They are of the opinion that the money invested only benefits a small number of professionals and that the increase in medical infrastructure as a result of clinical trials is negligible. It should be said that the quality of Argentina's existing structures is often cited as one of the country's main strong points as far as conducting international clinical trials is concerned.

Roche also stressed this advantage in its correspondence with us (5), asserting that Argentina "has a system that offers wide access to healthcare through both public and private institutions offering high quality medical treatment, with health professionals benefiting from solid scientific and technical training. Being able to count on high quality personnel and facilities is fundamental to the decision to conduct a clinical research project."

Even more abhorrent to certain ethicists is the argument that "patients who participate in trials have access to breakthrough drugs". Dr Sergio Gonorazky, who chairs the Institutional Review Board (IRB) for research trials at the Hospital Privado de Comunidad (HPC), the private community hospital in Mar del Plata, says in fact that the product tested during a clinical trial cannot be cited as a "breakthrough drug" when the very principle of the trial is to determine the product's efficacy. Dr Gonorazky, a neurologist, also reminded us that a significant number of phase III clinical trials (the final stage of a trial before marketing) are concluded without the drug being studied having demonstrated any real efficacy (6), and further research is simply halted early because the drug in question causes undesirable side effects that far outweigh the expected benefits. The presentation of a trial conducted by Roche on a molecule called ocrelizumab, tested on patients suffering from a form of lupus, a disease of the immune system, will also illustrate this point (see section 3).

Ethical double standard

The main criticisms of the globalisation of clinical trials however, are not aimed at the manner in which the trials are portrayed, but rather at the manner in which they are conducted. A further criticism is that the host countries are not capable of absorbing such an increase in the number of trials conducted at their centres, especially with respect to the monitoring of good clinical and ethical practice.

According to numerous ethicists and health professionals, multinationals take advantage of the slightest flaw in the system that will allow them to speed up the process of bringing a new product to market or to reduce research costs. According to Dr Jorge Yabkowski, President of FESPROSA, Argentina's union of health professionals: "These days, almost 90% of pathologies can be treated effectively with drugs for which the patents have expired, and the laboratories' profit margins are down. As a result, they have allowed themselves to become engaged in a commercial war in the search for new molecules, new combinations of drugs and new uses for existing ones. In this race for profit, multinational pharmaceutical companies will sometimes resort to anything." His organisation was behind the accusation that triggered the GlaxoSmithKline COMPAS scandal (see section 3). In the view of Dr Yabkowski and many other players in the sector, multinationals "apply an ethical double standard", depending on whether a trial is conducted in an industrialised country or a developing country.

Dr Juan-Carlos Téaldi, head of the ethics division of the hospital Clinicas in Buenos Aires, Argentina's main teaching hospital, told us that the government sees clinical trials as just another industry. It encourages them because they earn foreign currency and improve the country's trade balance: "The players who promote clinical trials even speak of 'an industry without a chimney' (Editor's note: an expression frequently used in Latin America to describe the economic interest of tourism). This is an image that encourages 'competitiveness' in the international market. It is important to be attractive to the pharmaceutical companies so that they conduct their trials here rather than elsewhere. This can result in a somewhat indulgent attitude towards clients who mustn't be angered, and thus in less heed being paid to ethical criteria. But we're not talking about tourism, or the production of milk, or cars or textiles. Medicine is a social good, and the research is done on human beings, who have rights."

Victoria Martinez, head of the office for the assistance of vulnerable groups at Argentina's Human Rights Secretariat also believes that the fact that clinical trials are "less well regulated here than in Europe and the United States makes Argentina attractive to the international pharmaceutical companies." Her office has formed a working group on

bioethics and is collaborating with various players in the sector on the creation of standards of good ethical practice in medical research.

She adds, however, that they "do not want to limit the number of clinical trials conducted in Argentina. The current government has been the most active in the history of the country in encouraging growth in research, the sciences and technology. That's good for Argentina; but we shouldn't let the multinationals take advantage of flaws in the regulatory system in order to violate patients' rights."

The pharmaceutical companies themselves deny the existence of a "double standard". What is more, they claim, as Laura de la Fuente, Novartis Argentina's spokesperson stressed to us, that it is precisely "the strict legal framework, and the world standard ethical requirements" imposed by Argentinian authorities that "make the country attractive". She explained that "the protocols of international trials are the same for all countries in which trials take place, although problems can arise in their application. Now in Argentina we can count on best ethical practice, which is very important if the results gathered are to be usable."

Jorge Cuneo, Medical Director at Novartis Argentina, agrees: "As a regulatory body, ANMAT is a model in the region. This is very important for us, because it guarantees the reliability of the information gathered in the course of trials."

Roche representatives also said that "the regulatory framework in Argentina, as far as requirements by the authorities are concerned, is one of the most demanding in the world, like the EMA in Europe and the FDA in the United States", and that, in the absence of such a "strict and clear" regulatory framework, Roche "would not even consider the possibility of conducting a clinical trial in the country." (4)

Why Argentina?

All the various players in the sector say that Argentina represents an attractive option for the pharmaceutical industry. First, at a structural level, it has well-trained health professionals, an ethnically varied population that is nevertheless genetically close to those of Western Europe and the United States, a vast network of medical establishments, and relatively low costs in comparison with other countries.

Second, recruiting patients there for clinical trials is relatively easy because the multi-tier medical system established during the 1990s makes certain treatments inaccessible to large segments of the population. Finally, it is important to mention the great respect Argentinians have for the medical profession: health professionals have no problem convincing their patients that participating in a "protocol" is the best option for them.

And, as already mentioned, ANMAT is considered a regional reference body with respect to the regulation of clinical trials (7), which makes it easier to record data gathered in Argentina.

The fact is that the Argentinian government encourages the growth in clinical trials: according to ANMAT, the Ministry of Health “is promoting all types of health-related research in the country”. This is confirmed by Jorge Cuneo, Medical Director at Novartis Argentina: “The Argentinian authorities’ support for research is very clear: any problems one might encounter are ironed out in the shortest time imaginable. This is particularly the case when equipment is held back in customs (Editor’s note: Argentina’s government has been implementing major import controls for several years). If such equipment is destined for clinical trials the problem is resolved very quickly.”

The legal framework within which clinical trials are conducted

Argentina has no national legislation governing clinical trials, which are governed by ANMAT Regulation 6677 of 2010 (8), and by resolutions 1490/07 and 1480/2011 of the National Ministry of Health (9). We also point out that Argentina is a federal country and that health care is primarily a provincial responsibility. Several provinces – namely, Buenos Aires, Cordoba, Santa Fe and Neuquén provinces, as well as the autonomous city of Buenos Aires, the country’s capital – have their own laws governing clinical drug trials.

Most ethicists and observers of clinical trials in Argentina agree that the absence of national legislation opens the door to abuse, and that certain laboratories take advantage of flaws in the system in order not to fulfil all their obligations to patients.

Novartis’ Jorge Cuneo believes that Argentina’s federalism with regard to health, and the fact that a number of provinces have their own laws on clinical trials, do not affect the quality and safety of the trials but complement them at an operational level.

In Roche’s view, Argentina’s federalism “has so far not created any insurmountable barriers to the implementation of clinical research projects involving researchers and patients from several different provinces.” Speaking for Novartis, Jorge Cuneo estimates that it “would obviously be simpler with national legislation, but it is extremely difficult to reach a consensus on this type of subject.”

Although two draft bills have been drawn up in the last few years, they never reached the stage of being debated in Argentina’s National Congress, even though they were introduced by members of the elected majority. “We are working on creating a proper law on clinical trials, but there

is a lot of resistance to it”, the national Human Rights Secretariat told us.

To illustrate the difficulty with – or lack of interest in – legislating on these matters, several people we talked to spoke of the fate of the Public Production of Medicines Law. This legislation, which was intended to safeguard the “national interest” and promote the research and public production of medicines, drew wrath from the pharmaceutical industry (10 and 11). Although both legislative chambers adopted the legislation in mid-2011, the health minister never drew up the regulations governing its application, which meant that the law so decreed by the pharmaceutical companies never came into force.

ANMAT, Argentina’s regulatory body

As mentioned above, ANMAT is the governmental body that regulates and monitors everything to do with drugs and medicines in Argentina (1 and 12). Under the authority of the Ministry of Health, it draws up rules on good clinical practice and monitors compliance with current standards and laws on clinical trials.

According to Dr Juan Carlos Téaldi, head of the ethics division of the Hospital Clinicas in Buenos Aires, however, ANMAT does not really monitor the ethical standards of a protocol. “There is a legal vacuum on this point”, he told us. “ANMAT’s real role is to regulate actual drugs. There is no proper institution with a clear mandate to monitor respect for the rights of trial participants. ANMAT more or less ‘absorbs’ this function, given the vacuum that exists. But it doesn’t really evaluate the risk–benefit balance for patients. It seems unable to follow up; it is not competent to evaluate the risk to people.” This is confirmed by the bioethics team at the Human Rights Secretariat, which explained to us that ANMAT, for example, “simply checks that there is in fact a consent form approved by an ethics committee, without reviewing the content of the form.” And this, despite the fact that these forms pose major ethical problems: “Most people don’t really understand what they are signing. Quite simply, they lack access to the health system, and so accept what a doctor suggests to them, without really knowing what it entails.”

In Dr Téaldi’s view, ANMAT has become less vigilant over the past few years: “Since director Martinez was pushed out in 2010, ANMAT has become much more permissive. To some extent, Dr Ricardo Martinez put the brakes on the demands of the multinationals. By promising the government more investment, the industry managed to get him removed”. Several other observers also believe that the former director of ANMAT was dismissed for his “lack of indulgence” towards the pharmaceutical industry.

According to these interviewees, the complaints of companies in the sector related in particular to the

GlaxoSmithKline COMPAS affair. The COMPAS clinical trial, conducted on thousands of new-borns, many from the poorest segments of the population, led to 14 deaths and numerous irregularities. An inquiry was opened, and both GlaxoSmithKline and several of the researchers responsible were fined (see section 3). In that matter, the pharmaceutical companies are said to have reproached Dr Martinez over the zeal of the inspectors in charge of the investigation and the amount of the first fine imposed on the British company (subsequent fines were decided by Dr Martinez's successor, Dr Carlos Chiale, on the basis of investigations ordered by Dr Martinez). An interesting detail is that the director of ANMAT was replaced less than a week before the courts confirmed the sanctions imposed by the reviewing body on GSK and on the main COMPAS researchers in Santiago del Estero. When contacted for his views on the matter, Dr Martinez refused to talk about it.

The two points on which ANMAT is said to have become more lax in recent years are placebo use and patient access to medication once a trial is over. These problems are discussed in more detail below.

Two professionals working for the industry also raised these "changes from 2010" but in a very different way. During our conversation, Jorge Cuneo, for example, remarked that ANMAT's authorisation process had greatly improved. According to him, the period between 2008 and 2010 had been difficult, but "the new management has improved a lot of things since then. The evaluation teams are very receptive." When asked earlier about these "improvements", the Medical Director at Novartis Argentina had said that new regulations had made it possible to anticipate some of ANMAT's actions and that the move to a computerised system meant that a lot of time was saved during the protocol authorisation process.

Pablo Liuboschitz, director at the CRO Research & Development RA SA, was also very pleased about how much less time the reviewing of protocols before authorisation was taking: "Until 2010, ANMAT used to take a long time to review protocols, which was hardly an attraction for the pharmaceutical industry. The situation is much better now, though."

Ethics committees: a lack of transparency and conflicts of interest

The way in which certain ethics committees operate merits scrutiny, primarily because Argentina's legal framework gives them a central role in devising clinical trials. In fact, according to ANMAT Regulation 6677-10 (8), their function is to "provide a public guarantee of the protection of the rights, the dignity, the safety and the wellbeing of trial participants". Resolution 1480/2011 (9) of Argentina's National Ministry of Health also states that

research ethics committees are "the central axis of vigilance and of protection of the rights of patients."

These ethics committees thus are the guarantors of respect for ethics and the defence of patients' rights during clinical trials, with ANMAT's role centred on the regulation of actual drugs and "technical" compliance of research protocols. The criteria for the composition and operation of these research ethics committees are not clearly defined, however, resulting in serious instances of dysfunction.

Dr Juan-Carlos Téaldi, head of the ethics division of the Hospital Clinicas in Buenos Aires, cannot find words harsh enough to criticise "private" ethics committees: "It's a major problem", he says. "The legal status of the research ethics committees is very vague, and there are no clearly defined guidelines as to what is ethical and what is not. On top of that, private institutions have set themselves up as "ethics committees", but they are in fact rubber-stamping organs for protocols filed by pharmaceutical companies. They approve all of them: and by doing so, they lend a semblance of legality to trials which may include serious ethical deficiencies. These "independent committees" are accountable to no-one, unlike the institutional committees. They have neither hierarchical superiors nor any responsibility towards their patients, given that they do not recruit them themselves. They portray themselves as "independent" committees, but they serve the industry, when it is they who should be the guarantors of patient rights. In fact, the only thing of which they are really independent is ethics itself."

The main thrust of this opinion is shared by numerous professionals in the sector who we met: researchers themselves, employees of the Human Rights Secretariat and heads of professional associations.

Furthermore, doctors Antonio Ugalde and Núria Homedes, President and Vice President respectively of the NGO Salud y Farmacos, devote a long passage in their book *Ética y ensayos clínicos en América Latina* (Lugar Editorial, 2012) to the problems raised by the existence of these "private" research ethics committees in Argentina. They explain, for example, that just two committees approve 80% of the clinical trials conducted in Argentina, one run by Professor Luis Maria Zieher – the "Comité independiente de etica para ensayos en farmacologia clinica" of the FEFyM (Foundation for Pharmacological Research and Drugs) – and the "Comité de Etica en Investigación Clínica (CEIC)", the research ethics committee run by Dr Carlos A. Barclay. This can be confirmed on ANMAT's website (3), where a brief presentation of all the trials authorised by the drug regulatory agency is published, including the name(s) of the ethics committee(s) that authorised the protocol in each case. These two committees – predominantly Dr Zieher's – seem to have approved an overwhelming majority of the

trials conducted in Argentina in the last ten years, although the proportion has fallen slightly in the last few months. And – also according to ANMAT's website – it is Dr Zieher's committee that the Swiss companies Roche and Novartis call on to review the protocols of almost 85% of all their clinical trials.

In their book, professors Ugalde and Homedes quote a particularly interesting article by Dr Sergio Gonorazky, entitled "Comités de ética independientes para la investigación clínica en la Argentina. Evaluación y sistema para garantizar su independencia" (13). In that article, Dr Gonorazky, who sits on the Institutional Review Board (IRB) for the review of research trials at the Hospital Privado de Comunidad (HPC), the private community hospital in Mar del Plata, explains that, in 2005 and 2006, the IRB analysed "36 protocols presented by the industry, together with their informed consent forms. Among those, 33 had been previously analysed by an independent, non-institutional ethics committee operating on a national scale". One of those research ethics committees had approved 30 protocols and the other, 3. The text does not clearly provide names of the committee members, but professors Ugalde and Homedes confirm that the main trial ethics committee implicated is in fact Dr Zieher's.

After analysing the protocols, the IRB issued 92 objections relating to items it deemed contrary "to national legislation or to standards and international declarations mentioned in ANMAT Regulation 6677/2010". These objections were relevant in 85% of the clinical trials reviewed.

A particular problem that the IRB observed was that, in its estimation, 64% of protocols limited the amount of compensation that could be paid to patients if they experienced problems to paying medical expenses arising from physical harm sustained. The IRB also noted that "24% of protocols made no mention of any kind of obligation towards patients following the end of a trial" but, in this context, "specifically referred to drugs which, if their efficacy had been demonstrated, should continue to be administered to patients after the end of the trial."

After listing a long series of other deficiencies noted by the IRB, the author of the article estimates that an equally large number of errors in protocols approved by private ethics committees can only be explained by two possible factors: "the lack of independence of these committees and/or the absence of any real monitoring of protocols." He denounces the system's lack of transparency: "The research ethics committees are not independent. Sponsors and researchers pay for an evaluation and can choose which independent ethics committee is to evaluate them. It therefore seems logical to conclude that the more demanding an independent ethics committee is, the more it will hold up authorisation of the protocol and the more it will result in

complications for the sponsors and the researchers. One could thus assume that the party paying will choose the ethics committee that will cause it the fewest problems. But if the research ethics committee's financing depends on the sponsor, one could also assume that the committee would have to win over the client by causing it as few problems as possible. This conflict of interests demonstrates well the problems associated with this type of direct contractual relationship between the research ethics committee and the sponsors, which also do not comply with ANMAT's standards in other ways."

Although the article is about an analysis of protocols that was carried out between January 2005 and December 2006, its main conclusions highlight the continuing problems recently reported by numerous specialists. The author himself, who was interviewed on the telephone, says that the problems raised in this study persist. "We haven't continued with the systematic analysis of protocols approved by the private ethics committees, but we are still reviewing some of them. Overall", Dr Gonorazky assured us, "the situation is still the same".

We tried to arrange a meeting with members of the "Comité independiente de ética para ensayos en farmacología clínica" (independent ethics committee for clinical pharmacology trials) run by Professor Luis Maria Zieher. After our requests for interviews had been flatly turned down, we persevered, in writing, to get at least one reaction to the criticisms made of the way that the committee operates. Dr Rubén Iannantuono, Professor of Pharmacology at the Faculty of Medicine at the University of Buenos Aires and Vice President of the committee, was quite willing to share some thoughts on the subject, stressing that he was doing so in an individual capacity and not on the committee's behalf. He also stressed that it "would be highly beneficial if all the ethics committees were to publish the sources of finance for their activities, whether public, private institutional or, as described by many, private".

In response to criticism of ethical deficiencies and errors of design in clinical trials that were nevertheless approved by ethics committees, Dr Iannantuono attempted to minimise responsibility on the part of the research ethics committees, saying that they only represent one stage in the review process: "How many people have been wrong to give the go-ahead for a clinical trial with errors in its design or in the content of the informed consent form, when they knew that the principal researcher, the institution, the ethics committee and ANMAT (...) are all involved in the process of authorising a trial?" The professor also defends himself with a highly personal version of the expression "to err is human": "It [being wrong] can happen, just as it can happen that there are clear-headed, intelligent people with a greater

mastery of the discipline that enables them to detect errors that others were not able to detect”.

Also in response to criticism, Dr Iannantuono referred us to a study he himself published in June 2012 (14), in which he testifies to the great satisfaction of patients who have participated in clinical trials. This document, based on the voluntary return of forms sent out in 2009 to patients participating in trials approved by Dr Zieher’s committee, does in fact reveal that almost 98.5% of the approximately 1500 people who responded to the questionnaire included on the informed consent form stated that they were satisfied with that document and with the information received (55% judged it to be excellent, 34.7% very good and 8.5% good). A thousand patients responded to a second questionnaire, this time on the trial itself: 82% said that they were satisfied with the medical supervision during the trial, 91% said that they were prepared to participate in a different clinical trial and 92.2% of them would advise another person to do so.

In his “conclusions and comments”, Dr Iannantuono says he believes that these results are proof of Argentina’s satisfactory standard of clinical research. He remarks, however, that certain comments received – such as “I was never treated as well in that institution until I took part in a clinical trial” – can also be considered “an indicator of vulnerability associated with the characteristics of Argentina’s health system”. This point, which we address later in this report (in particular, in our presentation of the GSK/COMPAS case in section 3), is especially interesting and often emphasised when recruiting patients in Argentina. This argument can prove to be very problematic, however, as Dr Iannantuono himself points out.

Elsewhere, the case of Maria (borrowed name), also presented in section 3, shows that a high degree of satisfaction expressed by a patient who has participated in a clinical trial does not mean that the patient’s rights, or the ethical rules governing biomedical research, were actually respected. When we met the woman in question, she did in fact insist that she was happy to have participated in a Roche “protocol”. The trial was suspended before completion, however, because of the side effects of the drug being studied. The presentation of the trial on the informed consent form also contained at least one important error: no compensation was to be provided if a problem arose (apart from the cost of treatment for problems possibly caused by the trial) and the pharmaceutical company did not guarantee continuity of treatment once the trial ended.

Argentinian ethicists also denounce the total lack of transparency regarding decisions of the ethics committees. There is in fact no national public register, or record – even if only for the professionals – of the handling of protocols before ANMAT authorises them. As Juan Carlos Téaldi says, “If the committee on which I sit rejects a protocol for not

respecting basic ethical principles, all the sponsor has to do is go to another committee, or go to another province, until they find a committee that approves it. That is in fact what happened in the Glaxo COMPAS affair.” According to Dr Téaldi, a register of rejected protocols would make it possible to harmonise the ethical criteria for clinical research in Argentina. The rejection of “BAY 11.643”, presented in section 3, illustrates these problems well.

In order to pre-empt errors, it is essential that both, flaws in protocols and ethical deficiencies identified by committees, can be reviewed by other committees asked to give a ruling on the same protocol, so that they can compare points of view and harmonise their decisions.

A first step in that direction has been taken with the recent creation of central ethics committees in certain provinces, such as the autonomous city of Buenos Aires and the region of that name. The main function of these committees is the creation of a database on which clinical trials and the decisions of the ethics committees are recorded. They are also responsible for the accreditation of research ethics committees and conducting spot checks on their operations, for promoting common evaluation criteria and advising the institutions in which clinical trials are conducted (15 and 16). It should be noted, however, that their authority only extends to their own province and that it is still too early to judge their real contribution.

Abuse of placebo

Most specialists identify the abuse of placebo as one of the most frequent ethical violations committed in clinical trials in Argentina. The relevant Argentinian regulations, based on international reference texts, however, do seem clear. For example, Resolution 1480 (A9 – P17) states that “the benefits and risks of any new intervention must be compared with those of the intervention that has proved to be the best so far. The use of placebo is only acceptable when no alternative intervention with proven efficacy exists, or when the technique in question is necessary for valid methodological or scientific reasons and the risk of harm or suffering is minimal.”

To illustrate what is “acceptable”, Roche gives the example of “trials to evaluate a treatment for slight or moderate pain or nausea that can still be treated subsequently; or, if the patient is unable to bear any pain, it will be possible to treat them without risk of permanent harm.”

Roche’s Argentinian subsidiary reminded us that “on the other hand, a good use of placebo is in comparing a treatment that is used in addition to a basic standard treatment. That is the case when, for example, a new oncological drug is being evaluated, where a (patient) group is given the most effective approved drug PLUS the new drug being studied. It is the control group that receives the

most effective approved drug PLUS placebo.” This is in fact considered ethical practice and is very common.

Novartis Argentina’s Medical Director, Jorge Cuneo, says that they always give patients basic treatment (“We always guarantee that patients receive the medication they need”) although he explained that in certain cases, using placebo enables them to better gauge trial results. He also said, however, that on several occasions, Novartis had to stop using Argentina as a location for certain multi-centre clinical trials that used placebo because ANMAT “maintains an extremely firm position on the matter”, even though the same trials had “been authorised in other countries”.

Against this background, one would expect that the use of placebo in Argentina is extremely limited and controlled, but the reality totally contradicts that theory. One trial (detailed in section 3), for example, which involved withdrawing all treatment from minors suffering from schizophrenia for an eight-week period was actually approved by ANMAT in 2010, before being suspended the next year and becoming the subject of an enquiry following an anonymous complaint.

That case, which concerns particularly vulnerable people, does not appear to meet any of the criteria listed above for the use of placebo. It shows that it is far from obvious that the use of placebo is “extremely limited and controlled”. After this scandal, which has not yet erupted outside the small world of clinical trials, ANMAT organised an “interdisciplinary forum” in 2012, the aim of which was to “continue to discuss placebo use in clinical research”. According to information we have received, this conference led to nothing conclusive.

Flouting the right to medication after a trial

Despite the requirements of reference texts (the Declaration of Helsinki, in particular), references in Argentina’s national regulations (Resolution 1480, sub-clause 2.6.4 (e) and Regulation 6677-10 sub-clause 4.11. (f)) and in several provincial laws, international pharmaceutical companies apparently balk at guaranteeing patients who participate in drug trials access to drugs judged to be safe and effective after the trials have ended. Certain specialists do in fact say that the texts could be deemed vague on this point and that many companies take advantage of this “lack of clarity” in attempts to avoid their obligations. It is therefore up to the ethics committees to be firm on this point and to demand compliance. Drs Téaldi and Gonorazky assured us, however, that not all do. What is more, in the article that Dr Gonorazky devoted to the analysis of around 30 protocols authorised by private ethics committees, he noted that “24% of the protocols made no mention of any kind of obligation towards patients following the end of a trial”.

When asked about Novartis’s policy on the issue, Jorge Cuneo assured us that they guaranteed that patients who had participated in one of their clinical trials obtained the best treatments possible for their particular pathology after the trial ended: “We use several methods for that. In particular, we create ‘extended protocols’, so that patients continue to receive the drug in question until they have access to it. And let me be clear about this: they do get access. It’s not a question of the drug being marketed, because in Argentina, the fact that a drug is authorised for sale does not guarantee that all patients have access to it.”

For its part, Roche claims to be exemplary on this point: “The well-being of patients in general, and in particular those who voluntarily participate in trials that enable the development of (our) products, is a top priority. Starting from this principle, and over and above the required conditions defined by various regulations, Roche ensures that patients who participate in clinical trials can continue to receive the benefits of the products once the trial is over. This requires meticulous evaluation on the part of the researcher and attending physician.” Roche therefore claims that it does what is “necessary in order that the patient, still under the supervision and the monitoring of the attending physician and the researcher, receives the appropriate treatment for as long as is necessary.” Roche also says that “the cost of this type of support varies, but Roche doesn’t evaluate or decide these questions on the basis of cost, but of the interests of patients.”

Despite these reassurances, we note that the consent form for a trial conducted by Roche in Argentina between 2007 and 2010 (17) that is analysed in greater depth in section 3 makes no mention of this commitment.

The female patient who gave us the form currently has no access to the drug she received during the trial in question, which her attending physician identified as being beneficial to her.

This woman’s case is special. The drug that her attending physician judged to be effective for her, in fact, was not the one officially being studied in the clinical trial. It was given as a “standard treatment” that was supposed to serve as a basis for the clinical trial, which was of another product. The latter ultimately turned out to be a danger to the health of participants of both sexes.

It should also be noted that Paragraph 33 of the Declaration of Helsinki (version 2008) stipulates that: “At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and 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.” Sub-clause 4.11. (f) of ANMAT Regulation 6677 also requires that the protocol “provide for access at the end of the trial to the intervention

identified as beneficial during the trial or to an appropriate alternative or to an adequate benefit.”

In the case of this patient, the “support” drug for the trial happened to prove effective for her. But because the woman has no health insurance and this drug is not officially authorised for her pathology in Argentina, she no longer has access to it. But Roche does in fact market this drug, which is currently prescribed for “off label” (other than officially approved) use in the treatment of her pathology.

A former Roche employee also told us that when he worked for the company – not long ago – it was Roche’s policy not to commit to supplying drugs tested in trials once they had been marketed, because it would “cost too much”.

Our exchange on the subject with Dr Iannantuono, well-known member of an independent ethics committee, is also interesting: “Continuity of treatments after the end of trials is a very controversial subject, which deserves serious debate and positions to be taken all round, as it cannot remain bound by the opinion of just a few people – especially because even members of the committee to which I belong sometimes have conflicting opinions.”

It should be remembered, however, that sub-clause 2.6.4 of Resolution 1480/2011 of the National Ministry of Health states that “the research ethics committee must review and approve the following precautions for the care and protection of participants in research: (...) (e) guaranteed access to the treatment being studied when the research is complete”.

In his response, Dr Iannantuono also raised another problem: “On that question, I would separate the protocols of which the sponsor is physically in Argentina from those of which the sponsor is represented by a CRO. In the first case, the problems regarding continuity of treatment are *a priori* less important than in the second, in which nobody can guarantee that the new drug will be marketed in Argentina.” This comment leads us to the conclusion that the protocols of clinical trials are approved in Argentina even when “no-one can guarantee that the new drug will be marketed” in the country. This totally contravenes a basic rule of clinical trials. Resolution 1480/2011 of the National Ministry of Health actually stipulates that “studies must be planned in such a way that the knowledge being researched benefits the group represented by the participants” – a principle that is clearly not respected if marketing of the drug being tested is not planned in the country where the participants live.

Also, Paragraph 17 of the Declaration of Helsinki (version 2008) stipulates that “Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research”. On this point, Jorge Cuneo likes to think he is quite clear: “Novartis would never conduct a trial in Argentina if we weren’t counting on marketing the drug being studied there.”

3. Case studies

Trial conducted on schizophrenic adolescents

Although kept secret, the problems associated with the protocol relating to Asenapine for schizophrenic adolescents caused something of an earthquake in the world of clinical trials in Argentina. Although it highlights the serious shortcomings in the analysis of protocols by ANMAT, this case has never been made public. No information whatsoever has filtered down to the media, even though all the specialists who know about it consider it nothing short of scandalous.

In spite of strict instructions to keep the affair quiet, we managed to reconstruct the case and its history by piecing together and analysing the various scraps of information we were able to obtain.

In 2010, management at the office for the assistance of vulnerable groups at Argentina's National Human Rights Secretariat received an anonymous tip regarding an ongoing clinical trial in Argentina that seemed "problematic". The bioethics team at the Secretariat of Human Rights told us: "We investigated this clinical trial that was being conducted on adolescents and discovered numerous irregularities, particularly regarding the use of placebo. After studying the case we informed ANMAT of our findings and they suspended the trial." They refused to go into further detail, and Victoria Martinez, head of the office for the assistance of vulnerable groups at the National Human Rights Secretariat, explained that they "did not want to discuss specific cases. We prefer to work on more general problems."

Research on ANMAT's website using the keyword "adolescents" yields 24 results, only one of which shows the status "suspended": it was a clinical trial conducted by the CRO Latin America Argentina S.A., for Schering Plough Research (18). Its title in Spanish is "Estudio de 26 semanas, multicentrico, abierto, de dosis flexibles y a largo plazo para evaluar la seguridad de la asenapina en sujetos adolescentes con esquizofrenia", and in English: "A 26-week, Multi-center, Open-label, Flexible Dose, Long-term Safety Study of Asenapine in Adolescent Subjects with Schizophrenia" (19). Looking through the website of the United States' clinical trials registry (www.clinicaltrials.gov), we learned that the trial, which is global, is being conducted by Merck, and that it (P05897) is an extension of Protocol P05896, the shorter title of which is "Fixed Dose Efficacy and Safety Study of Asenapine for the Treatment of Schizophrenia in Adolescents". Its official title is "An 8-week, Placebo-controlled, Double-blind, Randomized, Fixed-dose Efficacy and Safety Trial of Asenapine in Adolescent Subjects with Schizophrenia".

Although only one of these protocols is listed on the ANMAT site, we were able to verify that both were indeed authorised and implemented in Argentina before being suspended. Protocol P05896 was the subject of an in-depth

analysis in connection with violations of basic ethical rules. It was these violations that resulted in the suspension of both trials.

This protocol for an "8-week, placebo-controlled" trial stipulated that the participants would have all their treatments withdrawn before their first dose of the experimental medication (antipsychotics, antidepressants and mood stabilisers). The subjects were also not allowed to start receiving any psychotherapy during the trial.

At this point it should be remembered that minors and people suffering from mental disorders are deemed vulnerable subjects. Particular attention should therefore be paid to respect for their basic rights. Adolescents suffering from schizophrenia are deemed an at-risk group on two counts.

It should also be noted that, according to specialists, continuity of treatment is particularly important to avoid relapses in schizophrenics. As the subjects in question were adolescents, they had probably experienced few crises associated with their illness, which means that each new episode could potentially be very traumatic.

The specialists who analysed Protocol P05896 estimated that the assessment of potential risks and benefits had been conducted only in relation to the group of participants who were to receive the experimental medication, totally leaving the "control" group aside. In fact, the adolescents receiving placebo not only had no chance of receiving any benefit from participating in the trial, but also risked experiencing a deterioration in their condition once their usual medication was discontinued.

All the evidence shows that this case violated the basic principles of the Declaration of Helsinki, in particular: "The health of my patient will be my first consideration" (Paragraph 4 of the version 2008 of the Declaration). Paragraph 6 of the same version then stipulates: "In medical research involving human beings the wellbeing of the individual research subject should take precedence over all other interests". Also, sub-clause 4.1 of ANMAT Regulation 6677/2010 stipulates: "The interests and wellbeing of every participant of the study shall prevail over the interests of science and society in all clinical pharmacology studies."

In addition, Paragraph 32 of the Declaration of Helsinki (version 2008) stipulates: “The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:

- The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
- 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.”

The review of the protocol also revealed several problems in the informed consent form intended for the adolescents’ parents. The description of the risks associated with placebo use was in fact deemed totally insufficient.

To summarise: this clinical trial violates several important rules of the reference texts on respect for ethics and/or the regulations in force in Argentina. All the evidence shows that the protocol in question did not meet the obligation to conduct an in-depth analysis of the risks/benefits for patients taking part in the trial. It clearly did not respect the

principle that the risks for participants should not outweigh the expected benefits; it flouted the fact that the wellbeing of every individual involved in research must take precedence over all other interests and, most importantly: it was a breach of the duty to afford the special protection to which vulnerable populations are entitled.

Despite these deficiencies, the protocol in question was approved by an ethics committee and authorised by ANMAT. It is worth noting that the “private institution” ethics committee that approved it – the Comité de ética del instituto nacional de psicopatología (ethics committee of the national psychopathology institute) (18) – is accused of having been created on an “ad hoc” basis to approve all the trials of the principal researcher, Dr Luis Daniel Mosca (18). But the protocol was apparently also reviewed in advance by Dr Zieher’s committee, mentioned above.

It was only after the National Human Rights Secretariat received an anonymous complaint and conducted a review of the protocol that ANMAT itself reviewed it, before suspending the clinical trial. According to information we have received, the person at the drug regulatory agency who had initially approved the protocol has been removed from the post – again, very discreetly.

The Glaxo COMPAS scandal

The topic of clinical trials is not often discussed in Argentina. The COMPAS study conducted by GlaxoSmithKline (GSK or Glaxo) between 2007 and 2011 appears to be an exception. The violations of ethical rules that were committed during this clinical trial of Synflorix – a vaccine against pneumonia, otitis and meningitis – received a great deal of media coverage after December 2007 (20).

The COMPAS study, conducted in some of the country's poorest provinces, involved thousands of new-borns. 14 babies died during the trial. GSK and ANMAT claim that the vaccine played no role in the death of those babies, but in fact, both the pharmaceutical company and the regulatory authorities stress that the babies were part of a control group and that they had therefore only received placebo. ANMAT approved the vaccine Synflorix for Argentina in 2009 (21), following its authorisation by the European authorities. Research carried out by journalists and accusations from health professionals, however, led to the discovery of a large number of ethical violations, which were confirmed by an in-depth investigation by ANMAT.

For the first time ever, Argentina's drug regulatory agency imposed fines on a multinational company for violating ethical rules during a clinical trial. The fines were imposed in three separate cases, one for each province in which the COMPAS trial had been conducted.

In June 2009, ANMAT imposed fines of 400,000 pesos (US\$ 105,000 at the then exchange rate) on GlaxoSmithKline, 300,000 pesos (US\$ 80,000) on Dr Tregnaghi, the principal investigator and the coordinator for Argentina of this huge clinical trial, and 300,000 pesos on Dr Henrique Smith, the investigator in charge for the trial in Santiago del Estero (22). ANMAT did in fact find that during the COMPAS part of the trial, conducted in this extremely poor province in the north of the country, numerous irregularities in the inclusion of patients had been committed. Babies presenting with antecedents of acute respiratory infections had been recruited, as well as HIV-positive new-borns. In addition, a number of problems in the process for obtaining informed consent were identified.

After having made enquiries in the provinces of Mendoza and San Juan, ANMAT imposed new fines in April 2011 (23 and 24) of 400,000 pesos on GlaxoSmithKline (in two separate cases), 300,000 pesos on Dr Tregnaghi (in each of those two cases also), 300,000 pesos on Dr Héctor Abate, principal researcher in Mendoza, and 300 000 pesos on Drs Ana Ceballos and Adriana Posleman, principal researcher and researcher responsible for the province of San Juan respectively. Several problems associated with the enrolment of patients and obtaining informed consent were actually identified in those provinces. In Mendoza in particular, a baby received the vaccine even though its

mother had expressly refused to have it participate in the trial.

Defending themselves against the criticisms, people in responsible positions at GSK declared to the press on several occasions – most notably, Roxana Felice, Medical Director at GSK, to the magazine *Veintitres* (25) – that the fines imposed by ANMAT were “obviously civil penalties”, while Miguel Tregnaghi complained of a “political campaign” against clinical research (25).

Argentinian courts (26 and 27) in fact confirmed the fines imposed by ANMAT, despite various appeals GSK filed in a number of courts. In April 2012, GSK finally decided not to challenge the last court decision pronounced against it in December 2011 by Judge Marcelo Aginsky before the Supreme Court. That decision confirmed the fine relating to the COMPAS part of the trial, conducted in the province of Mendoza (28). GSK had previously appealed to the country's highest court in relation to the Santiago del Estero part of the trial, but that appeal had been thrown out (29 and 30).

It should be emphasised that the COMPAS trial is the largest clinical trial ever to have been organised in Argentina. Initially, some 17,000 babies were to be recruited, but eventually only 13,981 participated in the trial, recruitment of new babies having been suspended following the ANMAT investigation.

“The manner in which this clinical trial was conducted was particularly offensive”, says Dr Jorge Yabkowski, President of FESPROSA, Argentina health professionals' union. “To start with, it should be remembered that Dr Miguel Tregnaghi was supposed to start the trial several years earlier, in the province of Cordoba, where he was head of the Department of Paediatrics at the children's hospital financed by the municipality of Córdoba and the CeDEPAP foundation (Centre for the Development of Advanced Projects) in Cordoba. But the municipal authorities blamed him for a series of ethical deficiencies and operational problems within his department. They accused him of the improper use of the public hospital for conducting private research. He also was forced to announce retirement to escape sanctions, fines and prosecution” – which twelve of his co-workers could not do (31).

But, despite everything, all Dr Tregnaghi had to do to conduct this vast and lucrative trial was go to other provinces within the country – which happened to be Santiago del Estero, Mendoza and San Juan. Dr Yabkowski

also told us that in Santiago del Estero, Dr Tregnaghi came to an arrangement with the province's minister of health at the time, Juan Carlos Smith. When the paediatric hospital's ethics committee raised objections against COMPAS, they closed it down and recreated it as a new "custom-made" one. When the hospital manager complained about this, she was dismissed. Dr Tregnaghi was thus able to appoint Dr Henrique Smith, the health minister's brother, as principal researcher for the province."

The witness accounts gathered by journalists and health professionals in Santiago del Estero, the case that received the most media attention, are particularly revealing of the conditions in which patients were recruited. Numerous complaints showed that the researchers took advantage of the low level of education of the babies' parents in order to recruit them.

As Dr Ana María Marchese, of the Hospital de Niños Eva Perón, the children's hospital in Santiago del Estero where the trial was conducted, told us: "Not one of those parents can make sense of a thirteen-page informed consent form. Also, a number of them didn't receive the form, to read at home, until after their children had been vaccinated." (32).

One inhabitant of Santiago del Estero told the journalist from *Clarín*, Pablo Calvo, that a paediatrician had scared her neighbour into having her child participate in the COMPAS study (20). "They read her the thirteen pages, because she can't read, and they repeated words that scared her, like "deafness", "mental retardation" and "death", twice. She thought that if she didn't have her son vaccinated she would be exposing him to those evils."

Another account, given by Julieta Ovejero, the great aunt of one of the six babies who died in Santiago del Estero, can be found in an article in the journal *Critica de la Argentina*, which is now defunct. According to Ms. Ovejero, "Many people wanted to leave the protocol (Editor's note: the clinical trial), but they weren't allowed to, and they were threatened that their children would receive no other vaccine (33)." The weekly magazine *El Guardian* gathered a statement from the mother of another child who died in the province, little Sofia Gioria (34). The doctors from COMPAS assured her that the vaccine was soon to become compulsory and would cost 300 pesos (about US\$ 100 at that time). They apparently asked her: "Have you got the 300 pesos to pay for it?" Knowing she would not be able to find such a sum, she signed the informed consent form.

It should be pointed out that Argentina has a schedule of mandatory vaccines, and that under that programme all children are vaccinated free of charge.

The weekly *Veintitres* questioned María Esther Robles, the mother of a little girl called Micaela, who died during the trial. She tells how the nurse who persuaded her to vaccinate her daughter did not explain what it was all about,

but simply assured her that there was no risk (25). She also states that when the people working on the trial came to fetch her, to administer a second injection on her daughter, they threatened her, saying that if she didn't bring her little girl in they would denounce her and her child would be taken away from her.

Elsewhere, journalists who investigated this affair have revealed that Glaxo paid 350 US dollars to the researchers for each baby included in the study (20), initially providing for an amount of 5.9 million dollars – a colossal amount for Argentina.

El Guardian, which had access to the pay slips of doctors working on the COMPAS trial, reported that they were paid 4500 pesos a month (about US\$ 1,500) while working on the study. This was at a time when the salary of a doctor in Santiago del Estero was around 1800 pesos (US\$ 600) a month (34).

As part of its investigation in the provinces of San Juan and Mendoza, the drug regulatory agency ANMAT set up a pilot experiment. In parallel with the "technical" enquiry, two sociologists carried out their own research from a human sciences perspective. We were able to track down the results of their work – which has gone totally unrecognised – on the internet (35). Although COMPAS is not directly named in the document, it is clear that it is referring to that clinical trial when it mentions a trial of a vaccine.

The witnesses' accounts contained in this document show that certain improper practices observed in Santiago del Estero were reproduced in other provinces in which the COMPAS trial was conducted. This particularly applies in cases of incorrect information given to parents, taking advantage of their very low socio-cultural level, or of abuse of the structures and data of the public health system.

One mother explained to the sociologist researchers the factors that pushed her to agree to participate: "I was afraid that if I refused this vaccine, my baby wouldn't receive the others". Another mother told them she had wondered whether "the vaccine was for sale". She also expressed regret: "Sometimes I blame myself for not asking the doctor those questions at the time, but whenever I see him again I still don't dare ask. I know that I ought to ask questions, but I'm ashamed because I don't understand. Perhaps that is why we don't ask questions when it (the protocol) is explained to us –because if you haven't understood anything you don't ask any questions."

The sociologists asked another mother if she had understood the informed consent form when she read it. She replied: "I understood certain things and not others; it was in medical language." Another mother said: "I don't understand anything! I forget everything!"

The staff who had worked on the trial also told the researchers how they had used the public hospital's register

of births to find mothers who might include their babies in the COMPAS trial, adding: “They also came to fetch milk, through the Nacer (“being born”) Plan, and we took the opportunity to talk to them about the vaccine.” Sometimes, they also told parents that “receiving this vaccine was a favour granted by the hospital”.

This document also shows that certain parents of babies participating in the trial enrolled their children to have access to better medical care. For example, as the father of a baby explained to the researchers: “Here, you arrive and they see you. Otherwise, you have to come at four in the morning (...) and you are treated like a rat.”

In his pronouncement regarding GSK’s appeal against ANMAT’s fine for the Santiago del Estero part of their study (26), Judge Alejandro Catania stressed the fact that the population on which the trial had been conducted was “doubly vulnerable”: not only were the subjects new-borns, but the trial had been conducted on a group “belonging to a stratum of the population that is clearly disadvantaged due to their socioeconomic situation”. In his view, “need is the main factor that would induce a father to include his healthy child of only a few months in the pharmacological trial of a vaccine that was still at the experimental stage”.

It should also be noted that Dr Tregnaghi, in addition to being the principal investigator and the coordinator for Argentina of the largest clinical trial ever conducted in the country, was working on another clinical trial, also of a vaccine. It also involved new-borns in various hospitals in the province of Cordoba. That trial was conducted on behalf of Novartis (36 and 37).

And was Novartis worried about the conditions under which this trial was being conducted, having learned that its principal researcher had been fined for ethical violations committed in another trial with major similarities and conducted in parallel with it? Dr Jorge Cuneo, Medical Director at Novartis’s Argentine subsidiary told us that it was not: “We carry out our own monitoring on all our clinical trials. As our monitoring of this trial didn’t show up any problems, we left it at that.”

Dr Cuneo also explained to us that Novartis hadn’t hesitated to hire Dr Ana Ceballos to conduct a new clinical trial after the COMPAS affair (38 and 39), saying: “There is no black list in Argentina. The fact that a researcher encountered some problems during a previous trial doesn’t mean that we can’t hire her for another study.”

Roche's ocrelizumab trial

The case of Maria (borrowed name) is particularly interesting because it concretely illustrates a number of ethical deficiencies singled out by observers of the clinical trials – here, offences committed by the Swiss company Roche.

The first thing that should be stressed here is the astonishing contrast between what Maria and her husband – who was at her side throughout the process, and who signed the informed consent form as a witness – remember of the clinical trial, and the way it is presented in the consent form in question (17).

Maria, who is in her thirties and the mother of two children, explained to us that she had participated in a clinical trial conducted by Roche between 2008 and 2010. Some months earlier, she had been diagnosed with systemic lupus erythematosus (SLE), which was attacking her kidneys. Having no medical insurance, she went to a public hospital in the city of Buenos Aires. After she had followed a “standard” treatment for the illness, which had no effect, her doctor suggested she participate in a “protocol” conducted by the company Roche, which was to last for three years. She explained to us that the clinical trial in question consisted of an intravenous treatment with an experimental drug, as well as taking pills “authorised for other illnesses in Argentina, but not for lupus, unlike in other countries”. Desperate in the face of this serious illness, Maria agreed. She assured us that everything was clearly explained, both by her doctor and by “the Roche people”, who treated her extremely well; and what is more, she is extremely grateful to them.

She then explained to us that she had very soon understood that she had been lucky to be part of the group of patients to receive the drug and not the placebo, as she quickly started to feel better (it was confirmed to her later that she was). She also lost some of the weight that she had put on, and stopped losing hair. At the end of a year and a half, the intravenous treatment was suspended, but she continued to take the pills of the standard treatment for another year and a half. The people from Roche “had been very clear from the start” telling her that they were “only committing to giving her the drugs being tested during the three years of the trial”. In her view, they “had been kind” because they gave the pills for an additional year. Maria says she is very grateful, considering the effectiveness and price of the treatment (almost 3000 pesos or US\$ 1,000 per month, as she recalls, i.e. much more than the minimum monthly wage at the time). But also – and most importantly – “the treatment was not commercially authorised” for her illness, so she had no other means of procuring it.

When Roche stopped supplying her with the drug, her doctor managed to find her some for a certain amount of time, “until the time when different problems arose for the

hospital”. Once that channel was exhausted, Maria turned to the state to see if it could supply her with the drug. She wrote and explained about her illness, attaching prescriptions from her doctor. Her request was refused because “the drug in question is not authorised for lupus”. Still, with her doctor’s support, she then asked for “a similar drug”, but was also refused that, for the same reasons.

When we spoke to her, Maria was feeling very well. She told us that her illness is “dormant”, which means that it could “wake up” at any time. She would then not have access to an authorised drug – and one that has been shown to be effective – because she has no medical insurance and “it still isn’t authorised in Argentina”.

At the time of our conversation, this patient provided us various documents, including the final version of the informed consent form. Reading it, one notices several differences between what this lady and her husband remember of the “protocol” and the way the clinical trial is presented in the informed consent form.

From this document, entitled “Information for the patient and informed consent form, Version 3, final, 10 Feb. 2010” (17), signed by Maria, her husband and her doctor in mid-2010, one learns first of all that the study being presented is only of an experimental drug called ocrelizumab. The scientific title in English of clinical trial number WA20500/ACT4072g is in fact: “A randomized, double-blind study of the effect of ocrelizumab on renal response in patients with class III or IV nephritis due to systemic lupus erythematosus” (40). This trial was suspended on 19 October 2009, while the experiment was still ongoing, due to negative results that were putting the health of patients in danger.

The second drug that Maria took – mycophenolate mofetil (marketed by Roche under the name of CellCept) – which is the one the patient describes as effective in the treatment of her illness, is not mentioned in the official presentation of the actual trial.

It is in fact mentioned in the form, but as a “standard” support treatment given to certain groups of patients participating in the clinical trial testing the efficacy and safety of ocrelizumab. In the chapter “Treatment with an immunosuppressant regimen of drugs”, we learn, for example, that in addition to the experimental treatment, “the doctor had to start one of the following two standard treatments for LN (lupus nephritis) – mycophenolate mofetil or a regimen called EuroLupus (...)”.

Research of this case and careful reading of the informed consent form thus reveal several problems – in particular, how difficult it is to understand a clinical trial protocol when one is ill and desperate. Maria and her husband – both middle class and with a good basic education – did not notice the significant differences between the doctor’s verbal explanation and the information in the informed consent form.

According to several ethicists and professionals consulted on this case, the false presentation of mycophenolate mofetil as a standard treatment for lupus nephritis in Protocol WA20500/ACT4072g should have resulted in a rejection of the trial. Mycophenolate mofetil, a drug used all over the world to prevent rejection in organ transplants, is not actually authorised in Argentina for pathologies associated with lupus, as ANMAT confirms (1). It is also not authorised for use in Switzerland, the country where the pharmaceutical company Roche has its headquarters, or in the United States – as the FDA specifies (41) – which is where Genentech, initially “associated” with Roche on this study, and Quintiles, the CRO responsible for organising the trial in Argentina, are based.

It should also be noted that Roche was conducting another, very similar, trial at that time, entitled “A Study of Mycophenolate Mofetil (CellCept) in Management of Patients With Lupus Nephritis” (42). It is thus astonishing that a pharmaceutical company, officially conducting a clinical trial to “evaluate the efficacy and safety” of a drug in the treatment of a specific pathology, almost simultaneously presents that same drug as a “standard treatment” for the same illness in another protocol produced – especially as, in a press release dated 3 June 2010 (43) presenting the “positive results” obtained during the trial of CellCept for lupus nephritis, Roche itself acknowledges that the FDA “has not authorised CellCept for any auto-immune disease, not even lupus nephritis”.

It can be seen, however, that several doctors confirmed that the “off label” use of mycophenolate mofetil for serious cases of lupus is common.

Whatever the case may be, to Dr Juan Carlos Téaldi, presenting a drug that is not authorised for the treatment of a certain disease (even though it is authorised for another

use) as a standard treatment for that same disease is a serious ethical violation. Other specialists consulted also thought that such a protocol should never have been approved by the clinical trials monitoring body.

Also to be noted is the fact that, when Roche explained good practice in the use of placebo to us, it specified that one group of patients received “the most effective approved treatment PLUS the new drug being studied and the control group was given the most effective approved treatment PLUS placebo”.

Questioned regarding the false presentation of mycophenolate mofetil in the protocol approved by Dr Zieher’s committee and authorised by ANMAT, Dr Iannantuono said that he could not comment on this case due to medical confidentiality. ANMAT simply did not respond to the question, even though it responded to around thirty others. Roche refused to comment on “either hypothetical or specific cases without knowing all the details of them”, although we had quite clearly set out the problems raised, and had given the precise number of the protocol in question.

Not only does the informed consent form provide interesting reading because of its false presentation of mycophenolate mofetil, but also because of several other points. One notices, for example, that not a single paragraph in that document makes reference to access for patients participating in the trial to the drugs tested once the trial is over. This goes against both the principles of the Declaration of Helsinki and the regulations in force in Argentina.

The trial in question thus tends to show that Roche’s policy is to try to avoid committing itself to supplying drugs to trial participants once trials have ended, which confirms what the former employee we questioned had said. This appears to be a far cry from the official policy on the issue communicated by Roche’s Argentine subsidiary.

The informed consent form makes no mention of any commitment to pay compensation if problems associated with the trial arise, but only “all medical costs” for the harm caused.

The trial was, however, approved by Dr Zieher’s ethics committee and validated by ANMAT.

The “BAY 11.643” case

The trial conducted by the German company Bayer to test the efficacy and safety of “moxifloxacin on children suffering from complicated intra-abdominal infection” sheds light on numerous shortcomings in the monitoring of clinical trials, compounded by the lack of transparency prevailing in the field.

Even without a detailed analysis of the methodological and ethical flaws in the above trial (a critical analysis of the protocol can be found in documents 44 and 45 listed in Annex II), the case of this trial conducted by Bayer to verify the safety and efficacy of “moxifloxacin on children suffering from complicated intra-abdominal infection” raises numerous problems regarding monitoring of trials generally – primarily, but not solely, in Argentina.

On ANMAT’s website, one learns that this trial (ref no: BAY 12-8039/11643) was authorised by Argentina’s regulatory body, after having been approved by Dr Zieher’s ethics committee for two centres and by a second committee for a third centre. Moreover, the clinicaltrials.gov website lists 101 centres in the world for this trial, six of which are in Argentina (46).

The Hospital Privado de Comunidad (HPC), the private community hospital in Mar del Plata, a city in Buenos Aires province 410 kilometres from the capital, is supposed to be one of the centres in which this trial is being conducted. But apparently the hospital never agreed to conduct it. In fact, its institutional ethics committee (EC) and Institutional Review Board (IRB) for the review of research trials rejected implementation of the protocol, stating that it contained important methodological flaws and serious ethical deficiencies. They also found fault with the informed consent form.

The EC and IRB were of the opinion that the “methodological design” of the protocol BAY 11643 that had been submitted to them did “not provide for the establishment of formal statistical evidence to confront the results of the group receiving the experimental drug with the results of the control group, an omission that would prevent the establishment of the compared safety and efficacy (superiority, equivalence or non-inferiority) – which were the two objectives, primary and secondary respectively, of this study.”

In an article on the case published on the Mar del Plata private community hospital’s website (44), both its EC and its IRB press for an explanation for the rejection, stating that “further review of the protocol led (them) to the conclusion” that it “lacked methodological coherence”, and did “not meet basic ethical requirements.”

After carrying out a detailed critical analysis of the problems encountered, and highlighting the errors contained in the informed consent form, the EC and the IRB concluded: “We would like to emphasise the fact that this

study exposes vulnerable people (children) to uncertain risks, without justifying any hope of benefit for them, given the way the protocol is designed.” According to the specialists, conducting the trial in the manner presented would amount to “not respecting the precautionary principle, which requires that caution be exercised toward any action which one believes could cause harm” – in other words, to conduct “on a vulnerable population, a trial that carries risks and no foreseeable benefits (to that population) goes against the principle of justice.”

Following this rejection, the HPC’s ethics authorities were surprised to receive no response whatsoever from Bayer. They then contacted other ethics committees and wrote to ANMAT to find out if other institutions had received any response from the company. According to Antonio Ugalde and Nuria Homedes, who researched the case, ANMAT’s response to IRB was that the evaluations of other ethics committees did not concern them. Members of the IRB subsequently learned that Dr Zieher had approved that protocol. By visiting the clinicaltrials.gov website, they also realised that their hospital was on the list of centres at which the trial had been conducted. It was listed as “terminated”, which implied that it had been approved. The website’s glossary in fact defines the term as follows: “The study has stopped recruiting or enrolling participants early and will not start again. Participants are no longer being examined or treated.” But in this particular case the protocol had never been approved, which meant that the HPC had never started recruiting patients.

Specialists Ugalde and Homedes point out that, as frequently happens in this type of case, the problem was not limited to Argentina. This trial, conducted by Bayer in four British hospitals, was also listed as “terminated”. Ugalde and Homedes explain in their article that “after several exchanges with the ethics advisor at the National Research Ethics Service in the UK, it became apparent that the organisation had not reviewed that protocol. Subsequently, the advisor contacted the research and development department of one of the hospitals involved and confirmed that the hospital had no record of the trial.”

While carrying out their research, these professors from the University of Texas were able to establish that the three Belgian and three Indian sites for which the trial was also listed as “terminated” on clinicaltrials.gov had also decided not to participate in it, and that a hospital in Madrid had also terminated the trial in 2011.

Conclusion

The number of clinical trials conducted in Argentina has continued to rise over the last ten years, and with the government's support. Swiss pharmaceutical companies play an important role in this growth. Novartis in fact has conducted the most clinical research in the country, and Roche the sixth most. Argentina's system for regulating clinical trials however, by no means guarantees respect for international ethical standards.

Argentina may have no law governing clinical trials, but the activity is regulated by the Ministry of Health and by certain provincial authorities. Also, ANMAT, the clinical research regulatory agency, is considered a reference body at the regional level. Major players in clinical research thus judge standards of monitoring and observance of ethical rules as "mostly good". But the system has numerous flaws – flaws that allow abuses to occur.

To begin with, the way that certain ethics committees responsible for approving clinical trials operate is highly problematic. The committees are in fact supposed to be the guarantors of patients' rights. But private committees approve trials and informed consent forms that pose major ethical problems or do not meet some of the companies' obligations towards trial participants.

Our research also revealed a lack of rigour on the part of ANMAT in the monitoring of certain protocols, mainly in a serious case of abuse of placebo during a clinical trial conducted on schizophrenic adolescents. Several cases also reveal a serious problem regarding the discontinuation of treatment at the end of trials and the absence of any

commitment to provide compensation if problems arise from the research. These last two obligations in particular are not mentioned in the informed consent form of a trial conducted by Roche which we were able to read.

The scandal of the GSK COMPAS affair also highlighted several problems associated with recruitment from the population's poorest and most vulnerable segments. A number of people who participated in the trial did not really understand the experimental nature of the research, and many patients were easily recruited on the promise that they would receive better medical care if they participated in research. Numerous players in clinical research single out this fact.

One can thus conclude that the poorer the population of a country or region in which a trial is conducted, and the more limited the access to a health care system, the easier it is to recruit volunteers. It therefore would appear that the offshoring of clinical trials is clearly a response to the pharmaceutical companies' desire to speed up the process of recruitment.

Appendix I: List of people questioned

- Jorge Cuneo, Medical Director at Novartis Argentina: interviewed at Novartis' headquarters.
- Laura de la Fuente, spokesperson for Novartis Argentina: telephone contact.
- Andrea Rodriguez, head of communications at CAEMe (Camara argentina de especialidades medicinales), the umbrella organisation of the multinational pharmaceutical companies with a presence in Argentina.
- Patricia Blanco, managing director of Paradigma PEL Comunicación, the company in charge of communications for Roche Argentina: exchange of e-mails.
- Maria Martinez, spokesperson for ANMAT: telephone conversation and exchanges of e-mails.
- Dr Sergio Gonorazky, neurologist, member of the IRB (Institutional Review Board) for the review of research trials at the Hospital Privado de Comunidad (HPC), the private community hospital in Mar del Plata: telephone interview.
- Dr Jorge Yabkowski, President of the Federación Sindical de Profesionales de la Salud de la República Argentina (FESPROSA, Argentina health professionals' union): interview at FESPROSA's headquarters.
- Dr Juan-Carlos Téaldi, head of the ethics division of the Hospital de Clinicas de Buenos Aires: interview at the hospital de Clinicas José de San Martín.
- Victoria Martinez, head of the office for the assistance of vulnerable groups at Argentina National Human Rights Secretariat: interview at the offices of the Secretariat, in the presence of several members of her organisation's bioethics team.
- Pablo Liuboschitz, director at the CRO Research & Development RA SA: telephone interview.
- Dr Rubén Iannantuono, Professor of Pharmacology at the Faculty of Medicine at the University of Buenos Aires and a vice president of the Comité independiente de etica para ensayos en farmacologia clinica of the FEFyM (Foundation for Pharmacological Research and Drugs): exchange of e-mails.
- Doctors Antonio Ugalde and Núria Homedes, President and Vice President respectively of the NGO Salud y Farmacos: exchange of e-mails.

Others who collaborated with us in the course of this research have requested that we respect their wish to remain anonymous.

Appendix II: Notes

- 1) ANMAT (División Prensa y Difusión (press and communications division)'s response to a questionnaire on clinical trials in Argentina (March and May 2013, available on request in electronic form)
- 2) Information put out by CAEME (March 2013, available on request in electronic form)
- 3) Resultados del Censo Investigación Clínica Farmacológica 2010 – Foro Argentino de Investigación Clínica (F.A.I.C): <http://www.faic.org.ar/pacientesxprov.php> (consulted 12/6/2013)
- 4) ANMAT's website: http://www.anmat.gov.ar/aplicaciones_net/applications/consultas/ensayos_clinicos/principal.asp (consulted 20/5/2013)
- 5) Exchanges of correspondence with Roche Argentina (March to May 2013, available on request in electronic form)
- 6) Gonorazky S. E., Comentarios al artículo «Ética e Investigación», Rev Peru Med Exp Salud Publica 2012; 29(1): 153-154: <http://www.scielo.org.pe/pdf/rins/v29n1/a25v29n1.pdf> (consulted 20/5/2013)
- 7) ANMAT's website: http://www.anmat.gov.ar/webanmat/institucional/ANMAT_referencia OPS.asp (consulted 20/5/2013)
- 8) ANMAT Regulation 6677/2010: http://www.anmat.gov.ar/Comunicados/Dispo_6677-10.pdf (consulted 20/5/2013)
- 9) Ministry of Health Resolution 1480/2011: http://www.anmat.gov.ar/webanmat/legislacion/medicamentos/Resolucion_1480-2011.pdf (consulted 20/5/2013)
- 10) Letters from CILFA and COOPERALA (May 2011, available on request in electronic form)
- 11) Letter from UIA (May 2011, available on request in electronic form)
- 12) ANMAT's website: <http://www.anmat.gov.ar/webanmat/institucional/institucional.asp> (consulted 20/5/2013)
- 13) Gonorazky S. E., Comités de ética independientes para la investigación clínica en la Argentina : Evaluación y sistema para garantizar su independencia, Medicina (Buenos Aires) 2008; 68:113-119: <http://www.scielo.org.ar/pdf/medba/v68n2/v68n2a01.pdf> (consulted 20/5/2013)
- 14) Iannantuono R., Visión de los pacientes participantes en ensayos clínicos en Argentina, Rev Fed Arg Cardiol 2012; 41(2): 141-145 : http://www.fac.org.ar/1/revista/12v41n2/art_espe/art_especial01/ianantuono.pdf (consulted 20/5/2013)
- 15) Website of the City of Buenos Aires: http://www.buenosaires.gov.ar/areas/salud/dircap/investigacion/cceiautor.php?menu_id=29732 (consulted 20/5/2013)
- 16) Website of the Comité de Ética Central (central ethics committee): <http://www.ms.gba.gov.ar/sitios/cec/funciones/> (consulted 20/5/2013)
- 17) Consentimiento informado – Estudio Ocrelizumab Roche ARG (informed consent form for the Roche ARG ocrelizumab study) (February 2010, available on request in electronic form)
- 18) ANMAT's website: – Announcement of the suspension in Argentina of the Asenapine clinical trial (June 2011, available on request in electronic form)
- 19) Website of ClinicalTrials.gov –Asenapine clinical trial (P05897 AM2 EXT): <http://clinicaltrials.gov/ct2/show/NCT01190267?term=NCT01190267&rank=1> (consulted 20/5/2013)
- 20) Clarín article (December 2007): <http://edant.clarin.com/suplementos/zona/2007/12/23/z-04015.htm> (consulted 20/5/2013)
- 21) <http://archivo.lavoz.com.ar/09/09/26/Aprueban-nueva-vacuna-meningitis-otitis.html> (consulted 20/5/2013)
- 22) Clarín article (July 2009): <http://edant.clarin.com/suplementos/zona/2009/07/12/z-01956901.htm> (consulted 20/5/2013)
- 23) Disposición 2626 Ministerio de Salud_COMPAS Mendoza (April 2011, available on request in electronic form)
- 24) Disposición 2708 Ministerio de Salud_COMPAS San Juan (April 2011, available on request in electronic form)
- 25) Veintitres article (January 2012): <http://veintitres.infonews.com/nota-4016-portada-Cobayos-involuntarios.html> (consulted 20/5/2013)
- 26) Court decision –GSK Compas trial, Santiago del Estero (December 2011, available on request in electronic form)
- 27) Court decision –GSK Compas trial, Mendoza (December 2011, available on request in electronic form)
- 28) perfil.com article –GSK Compas trial(April 2012):

- http://www.perfil.com/contenidos/2012/04/12/noticia_0037.html (consulted 20/5/2013)
- 29) La Nación article – GSK Compas trial (January 2012):
<http://www.lanacion.com.ar/1437654-un-laboratorio-fue-multado-por-ensayos-irregulares-con-ninos>
(consulted 20/5/2013)
- 30) Homedes N., Ugalde A., La contribución de las revistas clínicas de alto impacto a la ciencia: the Lancet case, Salud Colectiva, Buenos Aires, 9(1):5 - 10, January - April, 2013:
http://www.scielo.org.ar/scielo.php?script=sci_arttext&pid=S1851-82652013000100001&lng=es&nrm=iso#ref
(consulted 20/5/2013)
- 31) Clarín article– GSK Compas trial (July 2009):
<http://edant.clarin.com/diario/2009/07/14/sociedad/s-01957869.htm> (consulted 20/5/2013)
- 32) IPS Noticias article– GSK Compas trial (August 2008): <http://ipsnoticias.net/wap/news.asp?idnews=89557>
(consulted 20/5/2013)
- 33) Critica de la Argentina article – GSK Compas trial (July 2008, available on request in electronic form)
- 34) Article El Guardián – GSK Compas trial (January 2012):
<http://elguardian.com.ar/nota/revista/394/experimentos-con-pibes-pobres> (consulted 20/5/2013)
- 35) Report on sociological research into clinical trials in Argentina (2008-2010):
http://www.iigg.sociales.uba.ar/saludypoblacion/ixjornadas/ponencias/ponencia_zuleta_ixisyp.doc
(consulted 20/5/2013)
- 36) ClinicalTrials.gov register–Novartis & Tregnaghi trial:
http://clinicaltrials.gov/ct2/show/study?term=V59P14&rank=2&show_locs=Y
- 37) ANMAT register – Novartis & Tregnaghi trial (December 2010, available on request in electronic form)
- 38) ANMAT register – Novartis & Ceballos trial (January 2012, available on request in electronic form)
- 39) ClinicalTrials.gov register – Novartis & Ceballos trial:
<http://clinicaltrials.gov/ct2/show?term=AGRIFLU++children+Novartis+72&rank=1>
- 40) Roche register – ocrelizumab trial: <http://www.roche-trials.com/trialDetailsGet.action?studyNumber=WA20500>
(consulted 20/5/2013)
- 41) FDA communication regarding CellCept and Myfortic:
<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHealthcareProfessionals/ucm072438.htm> (consulted 20/5/2013)
- 42) ClinicalTrials.gov register – Roche mycophenolate mofetil/lupus trial:
<http://www.clinicaltrials.gov/show/NCT00377637> (consulted 20/5/2013)
- 43) Roche news release: http://www.roche.com/investors/ir_update/inv-update-2010-06-03a.htm
- 44) Critical analysis of BAY 11.643 protocol (January 2012):
<http://www.hpc.org.ar/images/adjuntos/842-BAY11643.pdf> (consulted 20/5/2013)
- 45) Homedes N., Ugalde A. The evaluation of complex clinical trial protocols: resources available to research ethics committees and the use of clinical trial registries. A case study, 2013 (as yet unpublished, available on request in electronic form)
- 46) ClinicalTrials.gov register – Bayer moxifloxacin trial: <http://www.clinicaltrials.gov/ct2/show/NCT01069900>
(consulted 20/5/2013)