

Putting Contract Research Organisations on the Radar

An exploratory study on the outsourcing of clinical trials by pharmaceutical companies to contract research organisations in non-traditional trial regions



Mariëtte van Huijstee & Irene Schipper (editors)

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It is a trend for pharmaceutical companies to contract third parties to conduct their clinical trials in order to test their drugs. This trend is referred to as 'outsourcing', and the companies that carry out the work are called 'contract research organisations' (CROs). In addition, clinical trials are increasingly conducted in non-traditional trial regions, which are mainly low- and middle-income countries. This trend is called 'offshoring'. It is widely agreed that the offshoring of clinical trials to these regions should be scrutinised from an ethical perspective because of the vulnerability of the trial population. What happens when offshoring is combined with outsourcing? Do additional ethical risks arise when clinical trials are contracted out? Virtually all pharmaceutical companies publicly declare that they test their drugs in accordance with the highest ethical guidelines, such as the Declaration of Helsinki. But how do pharmaceutical companies safeguard their commitments when they outsource clinical trial activities to CROs in poor regions? These are the central questions that are addressed in this report.

The report is based on research conducted in India, Argentina, Brazil and Peru, and combined with interviews with pharmaceutical companies and clinical trial experts. The research experiences demonstrate that the pharmaceutical sector is generally not transparent, which hinders the definitive answering of the research questions. Nevertheless, the secondary and interview data collected in India, Argentina, Brazil and Peru provides some valuable insights into the way the CRO sector is developing in these countries. Furthermore, the report demonstrates that pharmaceutical companies have elaborate systems in place to manage their supply chain responsibility, although their functioning can not be independently verified. In addition, experts, authorities and clinical trial practitioners in the selected non-traditional trial regions still expressed grave concerns about the implementation of clinical trials in these countries.



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Colophon

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Glossary¹

Adverse Event (AE)

In the clinical trial setting, an adverse event (AE) can be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease that is associated in time with the use of a medicinal (investigational) product, whether or not this is related to the medicinal (investigational) product.

Audit

A systematic and independent examination of trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analysed and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

Clinical trial/study

Any investigation involving human subjects that is intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy. The terms 'clinical trial' and 'clinical study' are synonymous.

Contract Research Organisation (CRO)

A CRO can be described as an organisation/person that is contracted by a sponsor to manage various steps in the drug development process, including conduct of preclinical studies, clinical study design and execution, data management, analysis, medical writing, and regulatory submission.²

Data and Safety Monitoring Board (DSMB)

Synonyms: Independent Data-Monitoring Committee, Monitoring Committee, Data-Monitoring Committee

An independent data-monitoring committee that may be established by the sponsor to assess at intervals the progress of a clinical trial, the safety data and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify or stop a trial. Some policy documents require DSMBs for multi-centre trials and all Phase III clinical (interventional) trials (for an explanation of clinical trial research phases, see 'Phase I-IV' below). Sometimes a DSMB is required when a trial involves vulnerable populations, is blinded (ie. participants are unaware on whether they are in the experimental or control arm of the study), or is considered to be of high or significant risk.

¹ This Glossary is based on the Glossary of the International Conference on Harmonisation – Good Clinical Practice, available at http://ichgcp.net/?page_id=106 (accessed 30 December 2010). When additional or different sources are used, this is specified in footnotes.

² Tufts Center for the Study of Drug Development. "Tufts CSDD Outlook 2010". <http://csdd.tufts.edu/documents/www/Outlook2010.pdf> (accessed 30 December 2010).

Declaration of Helsinki

The Declaration of Helsinki of the World Medical Association sets global ethical standards that each clinical trial should comply with. European regulations specify that the trials providing the underlying data for marketing applications of new drugs need to comply with the Declaration of Helsinki.³

Due diligence

Due diligence is a term used for a number of concepts, but here it refers to an investigation/evaluation of a CRO prior to signing a contract. This evaluation will include a whole range of aspects, including price, quality, and according to the pharmaceutical companies, also ethical compliance.⁴

Ethics Committee (EC)

Ethics Committees go by various names around the world including: Institutional Review Boards (or IRBs in the US); Research Ethics Boards (REBs, Canada); Research Ethics Committees (RECs, many Western European countries); Helsinki Committees (Israel); Bioethics Committees (Poland); and Committees for Ethical Protection (CEPs, Brazil).⁵ An EC can be defined as a review board or a committee (institutional, regional, national or supranational), constituted of medical professionals and non-medical members. It is their responsibility to ensure the protection of the rights, safety and well-being of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, reviewing and approving/providing favourable opinion on the trial protocol, the suitability of the investigator(s), facilities and the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

Good Clinical Practice (GCP)

A standard for the design, conduct, performance, monitoring, auditing, recording, analysis and reporting of clinical trials that provide assurance that the data and reported results are credible and accurate, and that the rights, integrity and confidentiality of trial subjects are protected.

ICH-GCP (International Conference on Harmonisation – Good Clinical Practice) Guidelines

Good Clinical Practice (GCP) guidelines issued by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The ICH-GCP are the most commonly used GCP guidelines in practice as this facilitates the mutual acceptance of clinical trial data by the regulatory authorities of the EU, Japan and the US. The ICH-GCP guidelines have also been written into the laws of many emerging research countries. The ICH-GCP guidelines are weaker than the Declaration of Helsinki in some respects.⁶

³ Irene Schipper & Francis Weyzig. "Ethics for drug testing in low and middle income countries: Considerations for the European Market Authorisation", SOMO, February 2008.

⁴ Based on authors' knowledge.

⁵ Value of Insight Consulting, Inc. "The Case for Globalization: Ethical and Business Considerations in Clinical Research", 21 July 2009. Available online at: <http://www.voiconsulting.com/freereports/Clinical%20Trials%20Globalization%20-%20ACRO.pdf>

⁶ For instance, the ICH-GCP do not make reference to insurance policies for the volunteers. For further information see: Irene Schipper & Francis Weyzig. "Ethics for drug testing in low and middle income countries: Considerations for the European Market Authorisation", SOMO, February 2008.

Informed consent

A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.

Inspection

The act by a regulatory authority(ies) of conducting an official review of documents, facilities, records and any other resources that are deemed by the authority(ies) to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or CRO's facilities, or at other establishments deemed appropriate by the regulatory authority(ies).

Institutional Review Board (IRB)

See 'Ethics Committee'.

Monitoring

The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded and reported in accordance with the clinical trial protocol, standard operating procedures (Detailed, written instructions to achieve uniformity of the performance of a specific function), Good Clinical Practice (GCP) and the relevant regulatory requirement(s).

Offshoring

Offshoring describes the relocation by a company of a business process from one country to another – typically an operational process, such as manufacturing or supporting processes such as accounting. The economic logic is to reduce costs; therefore the relocation is to countries with more favourable economic conditions, such as lower labour costs or tax advantages.

Outsourcing

Outsourcing can be defined as “the strategic use of outside resources to perform activities traditionally handled by internal staff and resources”.⁷ The basic rationale behind outsourcing is the recognition that, in some cases, other companies can perform a service more effectively and at lower costs.

Phase I-IV

Clinical trials are conducted in phases. The trials at each phase have a different purpose and help scientists answer different questions:

In Phase I trials, researchers test an experimental drug or treatment in a small group of people (20-80 healthy participants and/ or patients) for the first time to evaluate its safety, determine a safe dosage range, and identify side effects.

In Phase II trials, the experimental study drug or treatment is given to a larger group of people (100-300 patients) to see if it is effective and to further evaluate its safety.

In Phase III trials, the experimental study drug or treatment is given to large groups of people

⁷ Dave Griffiths. “The Theory and Practice of Outsourcing”. Date unknown. Available from: <http://www.c-trade.org/files/clusters/ICT/The%20Theory%20and%20Practice%20of%20Outsourcing.pdf> (accessed 2 December 2010).

(1,000-3,000 patients) to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow the experimental drug or treatment to be used safely.

In Phase IV trials, post marketing studies delineate additional information including the drug's risks, benefits, and optimal use.

Pivotal trial

Pivotal trials are the clinical trials that are used as the basis for filing with drug authorities for marketing approval of the drug.⁸

Principal investigator

A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.

Protocol

A document that describes the objective(s), design, methodology, statistical considerations and organisation of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents.

Regulatory Authorities

Bodies with the power to regulate. In the ICH-GCP guidelines, the expression 'Regulatory Authorities' includes the authorities that review submitted clinical data and those that conduct inspections. These bodies are sometimes referred to as 'competent authorities'.

Sponsor

"Sponsor" means a person who takes responsibility for and initiates a clinical investigation. The sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organisation, or other organisation.⁹

Supply chain responsibility

Supply chain responsibility implies that a company does all it can to enable, promote and implement responsible business practices throughout its supply chain.¹⁰

Trial participant/subject/trial subject

An individual who participates in a clinical trial, either as a recipient of the investigational product(s) or as a control.

Trial site

The location(s) where trial-related activities are actually conducted.

⁸ American Association of Cancer Research. "Glossary of Cancer Research". <http://www.aacr.org/home/survivors--advocates/glossary-of-cancer-terms-k-z.aspx> (accessed 31 December 2010)

⁹ U.S. Food and Drug Administration. Code of Federal Regulations. <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=312.3> (accessed 1 February 2011)

¹⁰ MVO Platform. CSR Frame of Reference 2007. <http://mvoplatform.nl/wat-is-mvo/mvo-referentiekader-engels> (accessed 2 February 2011)

Vulnerable subjects/participants

Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate. Examples are members of a group with a hierarchical structure, such as [...] members of the armed forces and persons kept in detention. Other vulnerable subjects include patients with incurable diseases, people in nursing homes, unemployed or impoverished people, patients in emergency situations, ethnic minority groups, homeless people, nomads, refugees, minors and those incapable of giving consent.

Acronyms

AAHRPP	Association for the Accreditation of Human Research Protection Programs
ABRACRO	Brazilian Association of CROs
ACRO	Association of Clinical Research Organisations
AE	Adverse event
ANMAT	National Administration of Drugs, Food and Medical Technology of Argentina
ANVISA	National Health Surveillance Agency Brazil
BMJ	British Medical Journal
CAOIC	Argentinean Association of CROs
CDSCO	Central Drugs Standard Control Organisation (India)
CEP	Committees for Ethical Protection
CIOMS	Council for International Organisations of Medical Sciences
CONEP	National Commission of Research Ethics (Brazil)
CRO	Contract Research Organisation
CSER	Centre for Studies in Ethics and Rights
CSR	Corporate Social Responsibility
CTRI	Clinical Trials Registry of India
DCGI	Drug Controller General of India
DSMB	Data Safety and Monitoring Board
EC	Ethics Committee
EMA	European Medicines Agency
EU	European Union
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
ICMR	Indian Council of Medical Research
ICH-GCP	International Conference on Harmonisation – Good Clinical Practice
IEC	Institutional Ethics Committee
INS	Instituto Nacional de Salud (regulatory agency responsible for authorizing and monitoring clinical trials in Peru)
IRB	Institutional Review Board
KPO	Knowledge Process Outsourcing
MAA	Marketing Authorisation Application
PPD	Pharmaceutical Product Development
R&D	Research and Development
REC	Research Ethics Committees
SAE	Serious adverse event
SMO	Site Management Organisation
SOMO	Stichting Onderzoek Multinationale Ondernemingen (Centre for Research on Multinational Corporations)
SOP	Standard Operating Procedures
SUS	Sistema Único de Saúde (Brazil)
TRIPS	Trade Related Intellectual Property Rights
US	United States of America
WHO	World Health Organisation
WTO	World Trade Organisation

Executive Summary

Outsourcing and offshoring are popular trends in the pharmaceutical industry. *Outsourcing* can be defined as “the strategic use of outside resources to perform activities traditionally handled by internal staff and resources”. In the pharmaceutical sector, the outsourcing of clinical trials offers the greatest advantages, as the clinical trial phase is the most labour intensive, time consuming and costly part of the drug development process. Nearly 70% of the total research and development (R&D) costs are spent on clinical trials. Clinical trials are a key factor in the rising R&D costs because today’s drug trials are larger and more complicated on average and require more participants than ever before. In addition, recruiting participants is becoming more difficult in western countries. In 2008, US pharma companies spent \$32.2 billion on trials. Pharmaceutical companies are under pressure to bring more new drugs to the market while at the same time they have to cut their R&D budgets. As a result, companies are increasingly outsourcing their R&D to Contract Research Organisations (CROs), which offer services that can increase R&D effectiveness and at lower costs. Currently, about half of the clinical trial activities are outsourced to CROs. The CRO market is estimated to account for \$24 billion in 2010. Objections expressed by pharmaceutical companies against outsourcing to CROs include the fact that the supervising costs of outsourcing contracts are so high compared to other industries that the cost advantages largely disappear; secondly, some companies cannot accept the loss of control.

The increased outsourcing of clinical trials goes along with the *offshoring* of clinical trials to non-traditional research areas. The combination of push and pull factors for outsourcing and offshoring results in the fact that certain middle- and low-income countries and regions are increasingly popular locations for clinical trials with a booming CRO industry. These regions are Latin America, India, China, Eastern Europe and Russia. They are popular for their fast recruitment of trial participants, the presence of a broad spectrum of diseases, the availability of human resources and technical skills, differing ethnic responses to drugs, and the availability of a “treatment naïve population”. Currently, between 40% and 50% of the new drug applications submitted in the EU and US are tested in these regions. Compared to Western Europe and North America – the traditional trial regions – these regions are often less regulated (or offer a regulatory maze), have a less developed healthcare system and a relatively vulnerable population.

It is widely agreed that the offshoring of clinical trials to non-traditional trial regions should be scrutinised from an ethical point of view. But what happens when offshoring is combined with outsourcing to CROs? In India, as well as in Brazil, the regulatory process has recently been modified to expedite the approval of clinical trials, which is a decisive factor to attract CROs. CROs can operate without registration or accreditation; a registration at the chamber of commerce is enough to start testing drugs on humans. Currently, all the major CROs are present in the popular trial locations. In Peru, 70% of all trials are conducted by CROs.

The ultimate goal of this study is to persuade all the actors (e.g. regulatory authorities, pharmaceutical companies, CROs, principal investigators, ethics committees) to take responsibility to protect the human rights of clinical trial participants in non-traditional trial regions. To reach this, insight into the current practice of outsourcing in offshoring countries is required. The present research goal is to provide such insight.

The research questions and expectations are as follows:

1. What are the characteristics of the CRO sector in general, and in offshoring countries in particular?¹¹
2. What ethical risks are associated with the outsourcing of clinical research to CROs in non-traditional trial regions?

Expectation: The problems with outsourcing that have been observed in other industries – i.e. lowering of labour and environmental standards because of cost and competition pressures and scattered responsibilities amongst value chain actors (especially when subcontracting takes place) – are also present in the R&D of pharmaceuticals.

3. How do pharmaceutical companies safeguard the upholding of the ethical standards they are committed to when they outsource clinical research to CROs in non-traditional trial regions?

Expectations:

- Notwithstanding the widespread practice of outsourcing to CROs in non-traditional trial regions, pharmaceutical companies do not yet fully recognise and implement their supply chain responsibility.
- Because the outsourcing trend in the pharmaceutical sector is relatively new, the liability distribution between sponsor and CRO is not fully crystallised yet.

The research process and methods used to answer these questions involved a preliminary literature study, country level studies in Argentina, Brazil, India and Peru, and interviews with clinical trial experts and pharmaceutical companies.

The realisation of the research ambition proved much harder than anticipated, because of the extreme lack of transparency of CROs in particular and of the pharmaceutical sector in general. As a result, the empirical research conducted for this study delivered diverse and not necessarily comparable information. This means that some findings remain anecdotal, and thus any generalisations from these findings should be avoided. Nevertheless, the collected data does provide valuable insights that help to validate the expectations that were formulated.

The expectation that the problems with outsourcing that have been observed in other industries would also be present in the pharmaceutical supply chain is confirmed. Interviews and secondary data revealed concerns over trade-offs between speed and costs of the clinical trial managed by CROs on the one hand, and the ethical quality of these trials on the other. The suggestion is that sponsors expect CROs to conduct the trial as quickly as possible, which might put pressure on the CROs to be lax on the ethics (e.g. by circumventing informed consent procedures, not reporting adverse events etc.). The interviews also point to subcontracting by CROs. This fragments clinical trial-related tasks further and squeezes budgets even more. Cost and time pressures combined with the fragmentation of clinical trials can easily lead to a lack of oversight over and comprehension of the full trial process.

Sponsors confirmed the concerns over CRO performance. Because of this, they have developed mechanisms to select, monitor and evaluate CROs in order to guarantee compliance with relevant laws and ethical standards. In fact, these mechanisms greatly increase the costs of CRO-sponsor contracts, which affect the business case for working with CROs, and makes some sponsors wary

¹¹ No expectation formulated; descriptive research question; results described in chapter 3 and 4.

of outsourcing clinical trial management altogether. Notwithstanding these claims of sponsors, interviews with CROs indicate that the stringency of monitoring mechanisms varies widely among sponsors, which obviously creates opportunities for under-performing CROs. Organisations that may not effectively ensure the quality of the trial and the ethical protection of trial participants might slip through these control mechanisms. Whether these risks actually materialise into more harm for clinical trial participants cannot be assessed with this study. However, since our data reveal that independent oversight of CROs and clinical trial sites by authorities and ethics committees is perceived to be insufficient in at least India, Brazil and Argentina, the concerns remain justified.

The second expectation – that pharmaceutical companies might not yet fully recognise and control their responsibility for all the actors in the research and development process – is not confirmed: according to international regulations, pharmaceutical companies remain formally responsible for the ethical conduct of the trial they sponsor. This is in sharp contrast to other sectors where supply chain responsibility is not enforceable but instead is characterised as a moral responsibility. Pharmaceutical companies claim they have several mechanisms in place to control the research and development process: due diligence in CRO selection, contractual arrangements, auditing and training of CROs, clinical investigators and trial sites are the most important means in this regard.

At the policy level, the protection of participants in clinical trials managed by CROs in non-traditional trial regions seems to be in order, but what happens in practice is hard to verify. The design of the current research could not verify whether pharmaceutical companies indeed do what they claim to do and whether their monitoring of CROs is adequate. And as the study indicates, independent oversight by authorities in India and Brazil and by ECs in India, Brazil and Argentina leaves a lot to be desired. Furthermore, European Marketing Authorisation Application (MAA) procedures for drugs that have involved testing outside Europe do not include independent verification of the ethical conduct of the trials. This situation obviously leaves a lot of room for improvement in the protection of clinical trial participants in non-traditional trial regions.

The expectation that the liability distribution in outsourcing relationships within the pharmaceutical industry would not be fully crystallised is not fully confirmed: responsibilities are fairly clear on paper, as according to drug laws and ethical guidelines, the sponsor remains responsible for the ethical conduct of the clinical trial. However, there are exceptions (e.g. negligence and misconduct by CROs or principal investigators), and the conditions for these exceptions are not strictly outlined. Furthermore, it remains unclear how responsibility will shift when sponsors and CROs enter into partnerships. And since such partnerships seem to be a trend, this leaves an important area unexplored.

The research experiences and findings have possibly resulted in more questions than answers. In this regard, the current study might be interpreted more as a discussion document than as a concluding document. In fact, possibly the largest contribution of this study is that it highlights the lack of transparency of the pharmaceutical sector, which inherently implies that ethical concerns over the safety of clinical trial participants in non-traditional trial regions are justified.

From the problems we experienced in conducting this study, it is apparent that the transparency of the sector needs to be greatly improved, along with independent oversight of clinical trial conduct. It remains an area of grave concern that the parties that earn most money with the trials – CROs and sponsors – seem to be the most important monitors in non-traditional trial regions.

To improve transparency and independent oversight of clinical trials in non-traditional trial regions, several measures could be taken:

- Set up a worldwide, compulsory trial register in which all parties involved in the trial, including contractors and subcontractors, are disclosed.
- Increase the number of inspections of trial sites in non-traditional trial regions.
- Include in MAA procedures independent verifications that the drugs have been tested in accordance with the Declaration of Helsinki.
- Involve independent organisations that promote the interest of clinical trial participants in (CRO and sponsor) audits of trial sites.
- Involve clinical trial participants in inspections and audits, so that their perspective on the ethical conduct of the trial is included.
- Make audit and inspection results publicly available.

1 Introduction

“The average American income is \$47,000 a year – 16 times what the average Indian takes home, according to the CIA World Factbook. There is one doctor for every 384 Americans, while there are 1,667 patients for each Indian doctor, the World Health Organization says. The average American patient consumes nearly \$7,000 in medical care each year; the average Indian’s annual health care tally is \$39. Nearly every American adult can read, but 39% of Indians are illiterate... What does it mean for research subjects around the world to give informed consent when the playing field is so uneven?”¹²

1.1 Study rationale

Outsourcing and offshoring are popular trends in many industries, including the pharmaceutical industry. *Outsourcing* can be defined as “the strategic use of outside resources to perform activities traditionally handled by internal staff and resources”.¹³ The basic rationale behind outsourcing is the recognition that, in some cases, other companies can perform a service more effectively and at a lower cost.

In the pharmaceutical sector, the outsourcing of Research & Development (R&D) activities offer the greatest advantages; pharmaceutical companies face extreme rising costs to develop new medicines, capacity constraints and longer R&D timelines. Contract research organisations (CROs, see Glossary) offer services that can help to alleviate these constraints and increase efficiency and R&D effectiveness.¹⁴ In the past decade, the global spending on new drug development has been growing at an annual rate of 9.1%. However, the spending on contract clinical services has been growing nearly 50% faster – at an annual rate of 13.4%.¹⁵

Alongside the increased outsourcing of clinical trials (see Glossary), another trend is that clinical trials are increasingly *offshored* to non-traditional research areas, which are mainly low- and middle-income countries. In general, offshoring describes the relocation by a company of a business process from one country to another – typically an operational process, such as manufacturing, or supporting processes, such as accounting. The economic logic here is to reduce costs; therefore the relocation is to countries with more favourable economic conditions, such as lower labour costs or tax advantages.

The drivers for the offshoring of clinical trials are more complex than in other industries; one of the most important drivers for offshoring to developing countries is the high patient enrolment rate compared to North America and Europe. High enrolment rates imply that clinical trials can be finished sooner, meaning that the profits of patent exclusivity can be enjoyed for longer.¹⁶ Other factors that determine the attractiveness of a country for the conduct of clinical trials include a

¹² K. B. O'Reilly. “Outsourcing clinical trials: Is it ethical to take drug studies abroad?” Amednews, 7 September 2009, <http://www.ama-assn.org/amednews/2009/09/07/prsa0907.htm> (22 December 2010)

¹³ Dave Griffiths. The Theory and Practice of Outsourcing. Date unknown. Available from: <http://www.c-trade.org/files/clusters/ICT/The%20Theory%20and%20Practice%20of%20Outsourcing.pdf> (accessed 2 December 2010)

¹⁴ Tufts Center for the Study of Drug Development. “Tufts CSDD Outlook 2009”. http://csdd.tufts.edu/reports/description/tufts_outlook (accessed August 2010); K.A. Getz & J. R. Vogel. “Successful Outsourcing: Tracking Global CRO Usage”. Applied Clinical Trials, 17 August 2009, <http://appliedclinicaltrials.findpharma.com/appliedclinicaltrials/Online+Extras/Successful-Outsourcing-Tracking-Global-CRO-Usage/ArticleStandard/Article/detail/619120> (accessed 2 December 2010)

¹⁵ Tufts Center for the Study of Drug Development. “Tufts CSDD Outlook 2010”.

¹⁶ D. Normile. The Promise and Pitfalls of Clinical Trials Overseas, Science, 10 October 2008

broad spectrum of diseases, a more rapid approval of trials, availability of human resources and technical skills, differing ethnic responses to drugs and cost advantages. Another important factor is the availability of a “treatment naïve population”, a term that refers to populations that (apparently) have not been diagnosed or treated for a particular condition. This condition minimises the number of variables affecting clinical trial results.¹⁷

The combination of push and pull factors for outsourcing and offshoring described above means that certain middle- and low-income countries and regions are increasingly popular locations for clinical trials with a booming CRO industry. These regions are Latin America, India, China, Eastern Europe and Russia.¹⁸

There is growing concern among regulators and the general public about how well trials in non-traditional regions are conducted from an ethical and a scientific/organisational point of view. This includes compliance with good clinical practice (GCP, see Glossary) guidelines, as well as adherence to the available framework for the supervision of these trials.¹⁹ Compared to Western Europe and North America – the traditional trial regions – these regions are often less regulated, have a less developed healthcare system and a relatively vulnerable population (less economic and educational development, see Glossary). Many people in these regions would not have access to pharmaceuticals if they were not enrolled in a clinical trial.

It is widely agreed that the offshoring of clinical trials to non-traditional trial regions should be scrutinised from an ethical point of view. However, what happens when offshoring is combined with outsourcing? If the ethical conduct of clinical trials in non-traditional trial regions is already raising concerns, how is the ethical conduct of clinical trials guaranteed when CROs are in charge of conducting the trial in offshoring countries? In line with drug regulations, all pharmaceutical companies declare that they test their drugs in accordance with GCP guidelines, and some explicitly commit to the Declaration of Helsinki (see Glossary). But how do pharmaceutical companies safeguard their commitments when they outsource clinical trial management to CROs? These are the central questions in this report.

As Shuchman notes: “Contract research organizations (CROs) have gradually taken over much of academia’s traditional role in drug development over the past decade. They’ve been able to do so by offering greater speed and efficiency in conducting clinical trials than academic groups can, but questions have been raised about their qualifications, ethics, accountability, and degree of independence from their pharmaceutical-industry clients”.²⁰ This study aims to contribute to this debate by putting CROs on the radar.

¹⁷ A Petryna. Clinical trials offshored. *Biosocieties* 2, 2007, p.28; B. Davin Stengel, Therapeutic Benefits and Risks, <http://www.sas.upenn.edu/home/SASFrontiers/petryna.html>, 3 August 2010; Irene Schipper & Francis Weyzig, Ethics for drug testing in low and middle income countries: Considerations for the European Market Authorisation, SOMO, February 2008.

¹⁸ K. Jakovic Business Insights, “The CRO Market Outlook: Emerging markets, leading players and future trends”, 2007, <http://www.globalbusinessinsights.com/content/rbcr0001t.pdf> (11 June 2010).

¹⁹ European Medicines Agency. Reflection paper on ethical and GCP aspects of clinical trials of medicinal products for human use conducted in third countries and submitted in marketing authorisation applications to the EMA. May 2010. http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2010/06/WC500091530.pdf (accessed 31 December 2010)

²⁰ M. Shuchman. Commercializing clinical trials—risks and benefits of the CRO boom, *New England Journal of Medicine*, 4 October 2007

1.2 Research goal and target groups

SOMO research experience in other industries demonstrates that outsourcing and offshoring practices are often associated with trade-offs in human rights, labour rights and environmental norms. For instance, in the electronics industry, contracting of production to third parties (i.e. outsourcing) in developing countries (offshoring) is common practice. In the electronics supply chain, several social and environmental problems have been documented. For example, research has demonstrated that terrible labour conditions are no exception at electronics suppliers.²¹ And labour conditions in the mines that supply metals for electronics are possibly worse, while the environmental effects of such mining are also detrimental.²² When these problems were first documented in 2005, electronics companies denied their responsibility for conditions in their supply chain. And due to an extreme lack of transparency of supply chain relations, it was hard to attribute accountability. Nevertheless, research efforts have come a long way in moving companies to accept their supply chain responsibility (see Glossary), even though supply chain responsibility beyond first tier suppliers remains contested.

Expecting a parallel development in the pharmaceutical sector, the ultimate goal to which this study aims to contribute is to persuade all the actors (e.g. regulatory authorities, pharmaceutical companies, CROs, principal investigators, ethics committees – see Glossary) to take responsibility to protect the human rights of clinical trial participants (see Glossary) in non-traditional trial regions. To reach this, insight into the current practice of outsourcing in offshoring countries is required. The present research goal is to provide such insight.

1.3 Research questions and expectations

To provide insight into the current practice of outsourcing in offshoring countries, three research questions were formulated, the first one descriptive, the second and third more analytical. For research questions 2 and 3, some expectations were articulated at the start of the study. These expectations are examined in the report.

The research questions and expectations are as follows:

1. What are the characteristics of the CRO sector in general, and in offshoring countries in particular?
2. What ethical risks are associated with the outsourcing of clinical research to CROs in non-traditional trial regions?

Expectation: The expectation is that the problems with outsourcing that have been observed in other industries – i.e. lowering of labour and environmental standards because of cost and competition pressures and scattered responsibilities amongst value chain actors (especially when subcontracting takes place) – are also present in the R&D of pharmaceuticals.

3. How do pharmaceutical companies safeguard the upholding of the ethical standards they commit to, when they outsource clinical research to CROs in non-traditional trial regions?

²¹ I. Schipper & E. de Haan, *CSR Issues in the ICT Hardware Manufacturing Sector* (Amsterdam: SOMO, September 2005).

²² T. Steinweg & E. de Haan, *Capacitating Electronics. The corrosive effects of platinum and palladium mining on labour rights and communities* (Amsterdam: SOMO, November 2007).

Expectations:

- Notwithstanding the widespread practice of outsourcing to CROs in non-traditional trial regions, pharmaceutical companies do not yet fully recognise and implement their supply chain responsibility.
- Because the outsourcing trend in the pharmaceutical sector is relatively new, the liability distribution between sponsor and CRO is not fully crystallized yet.

1.4 Study outline

The report is organised as follows:

- Chapter 2 describes the research process and methods used to produce this report.
- Chapter 3 mainly deals with the first research question. It describes the CRO sector in general and provides more insight into the characteristics of the outsourcing and offshoring trends in the pharmaceutical sector.
- Chapter 4 also deals with the first research question, but focuses on the CRO sector in the selected offshoring countries.
- Chapter 5 mainly deals with the second research question, and analyses the ethical risks that are associated with the outsourcing of clinical research to CROs in non-traditional trial regions, based on interview data.
- Chapter 6 deals with the third research question and analyses the formal responsibility of pharmaceutical companies for clinical trial participants in CRO-conducted trials, as well as the way they address this responsibility.
- Chapter 7 contains the conclusions and provides suggestions for follow-up research.

2 Research process and methods

2.1 Research process

This research project was started in August 2009 in collaboration with Wemos. The main research questions were as follows:

1. What are the characteristics of the CRO sector in general, and in offshoring countries in particular?
2. What ethical risks are associated with the outsourcing of clinical research to CROs in non-traditional trial regions?
3. How do pharmaceutical companies safeguard the upholding of the ethical standards they commit to, when they outsource clinical research to CROs in offshoring countries?

To address these questions, the research was conducted in several phases. Phase one was an exploratory phase to assess the existing knowledge base on CROs and to identify prevailing knowledge gaps. It drew on desk research of secondary sources combined with three expert interviews.

After this first phase, the research questions were narrowed down, and partners were sought to conduct 'on the ground' research in two major emerging non-traditional trial regions: India and Latin America. SOMO coordinated the research in India and partnered with Centre for Studies in Ethics and Rights, while Salud y Fármacos joined the research project at this point and coordinated the study in Argentina, Brazil and Peru. The protocol for the Latin American component was prepared at a meeting in San Jose (Costa Rica) in November 2009. Originally, Costa Rica was to be included in the study. However, a January 2010 Supreme Court decision prohibited the implementation of clinical trials until the government approved a law regulating biomedical research on humans, therefore the Costa Rica team decided not to participate. In March, the researchers from Peru were incorporated and the protocol was adjusted to fit the Peruvian context.

The full references of the country studies are the following:

- Divya Bhagianadh, "Contract Research Organisation (CRO) sector in India", 9 August 2010
- Evangelina Martich, "Estudios de las Organizaciones de Investigación Clínica por Contrato (CRO) en Argentina", 13 August 2010
- Corina Bontempo Duca de Freitas, Rachelle Amália Agostini Balbinot, and Sueli Gandolfi Dallari, "Estudo de Organizações Responsáveis por Pesquisas Clínicas – ORPC (CROs) no Brasil", 23 September 2010
- Gabriela Minaya and Duilio Fuentes, "Organización de Investigación por Contrato (OIC)", 15 September 2010.

The three Latin American studies were subsequently summarised in a report and supplemented with a case study on Costa Rica.²³ The full reference of this report is as follows:

- Núria Homedes and Antonio Ugalde, "Contract Research Organizations in Argentina, Brazil, Costa Rica, and Peru", 30 September 2010.

²³ The case study of Costa Rica is not included in this report, because it did not include fieldwork.

Chapter 4 and 5 of the current report integrate the data from the country-level studies.

The purpose of the studies was the same for each country: to gain an overview of the CRO sector at a country level and to understand how it works. The original set up for each country case study was to interview the top ten market-leading CROs in each country, but this ambition soon appeared unrealistic. The CRO sector was characterised by an extreme lack of transparency, and only a small number of CROs was willing to provide an interview. This meant that researchers had to rely on the information they could find. Since the researchers were confronted with a different set of constraints and opportunities in each country, each research report includes unique information, but they are not necessarily comparable across the full range of data. The consequence is that we do not have the same type of information for each country, and are thus not able to provide the comparison that we anticipated. Nevertheless, the secondary and interview data collected in India, Argentina, Brazil and Peru provides some valuable insights into the way the CRO sector is developing in these countries, and is indicative of the concerns about the implementation of clinical trials that are held by experts, authorities and clinical trial practitioners in these non-traditional trial regions.

It should be noted that there are several expensive market research reports available for download on the internet, which could have formed an alternative for our country research with regard to the descriptive market information. However, we purposely chose not to follow this route and instead we worked with local researchers for the following reasons: 1. as a form of capacity/knowledge building for researchers in the non-traditional trial regions; 2. to experience the (un)transparency of the pharmaceutical sector.

Since the country-level research delivered insufficient insight into the way ethical trial conduct is guaranteed when clinical trials are managed by CROs, it was decided to involve the clients of the CROs – pharmaceutical companies – to see how they ensure the ethical conduct of the trials they sponsor (see Glossary). The major global pharmaceutical companies were invited to participate in a research on the ethical risks associated with outsourcing and offshoring. This included Abbot, AstraZeneca, Bristol Meyers Squibb, Eli Lilly, GlaxoSmithKline (GSK), Janssen (the pharmaceutical division of Johnson & Johnson), Merck/MSD, Novartis, Pfizer-Wyeth, Roche and Sanofi-Aventis. After a lot of persuasion, six companies finally agreed to participate. Four of these participated in a full interview (by telephone or by email), two others provided a written statement regarding their offshoring and outsourcing policies and practices. In Table 1, the participation level of all the companies approached is described.

Table 1: Participation of pharmaceutical companies in present research

No participation, despite request	Bristol Meyers Squibb, Eli Lilly, Merck/MSD Pfizer-Wyeth, Roche
Written statement	Janssen, Sanofi-Aventis
Full interview (by telephone or email)	Abbott, AstraZeneca, GSK, Novartis

As a last step in the research process, a review of a draft of this report was organised, involving the partners Wemos, Salud y Fármacos (reviewing on behalf of the Latin American researchers) and CSER, the experts interviewed in phase one and the pharmaceutical companies that participated in the research. Their comments have been integrated in the final version of this report.

The subsequent research phases are summarised in Table 2. A full list of 43 interviewees is included in Annex 1.

Table 2: Methods and purpose of each research phase

Phase	Purpose	Methods
1. Preliminary, exploratory study	Assess existing knowledge base on CROs, identify prevailing knowledge gaps	Literature research, web research, expert interviews
2. Country-level studies	Understand characteristics of the CRO sector in respective countries, analyse ethical risks associated with outsourcing of clinical research to CROs in respective countries	Literature research, web research, expert interviews
3. Analysis and integration country studies	Draft research report	Categorising and grouping results
4. Interviews with pharmaceutical companies	Understand how pharmaceutical companies safeguard the upholding of the ethical standards they commit to, when they outsource clinical research to CROs in offshoring countries	Interviews, written and by telephone
5. Review by partners and companies	Correct factual mistakes in concept report	Sending out draft, receive and integrate written comments.

The information presented in this report is based on all the data gathered throughout the process: literature, expert interviews, country-level interviews and interviews with pharmaceutical companies. Throughout the report, reference will be made to the sources of information and statements.

2.2 Research partners

SOMO

SOMO's activities and research on corporations and their international context focus on sustainable economic and social development and are aimed at promoting sustainable development and the structural eradication of poverty, exploitation, and inequality. SOMO has the following primary goals:

- Change through knowledge building: The research SOMO carries out is aimed at stimulating change. This means that on the one hand, SOMO fulfils a 'watch dog' function; SOMO collects the necessary information and carries out analyses to reveal unsustainable corporate conduct and contradictions in economic and political systems. On the other hand, with its analyses and its alternative proposals, SOMO contributes to the policy development of governments, international organisations, NGOs and corporations.
- Strengthening of civil society in the global North and South: By providing information and facilitating cooperation, SOMO helps to strengthen civil society in the global North and South. SOMO's activities focus on the disclosure of previously fragmented information, the building of networks of NGOs and the training of NGOs. SOMO concentrates its efforts on NGOs that work with Multinational Enterprises and international trade, such as labour unions and human rights, consumer, environmental, gender and development organisations.
- Increasing the impact of civil society organisations: Through its research as well as cooperation with partners from the South, and joint initiatives with other NGOs, SOMO contributes to the debate on CSR. SOMO targets its policy influence, workshops, and public meetings at opinion leaders and decision makers from governments, civil society

organisations and the media. SOMO promotes the interests of the global South when participating in policy dialogues, lobby activities, conferences, expert meetings, and other fora.

Salud y Fármacos

Salud y Fármacos is an organisation committed to promote access and the appropriate use of pharmaceuticals, through education and research projects, among Spanish-speaking populations, that has been incorporated in the USA, Argentina and Peru. Salud y Fármacos has created and coordinates the Latin-American Network of Ethics and Pharmaceuticals (RELEM) and achieves its goals through education, research and services.

Salud y Fármacos maintains a webpage in Spanish that contains all the issues of Boletín Fármacos that have been published since 1998. The webpage also includes hundreds of links to major institutions, documents and programs of interest for those who advocate and search for better strategies to improve the use of pharmaceuticals around the world. The repository is frequently updated to ensure that all the electronic addresses are current.

Salud y Fármacos has carried out and published research on:

- patient-physician communication
- strategies to improve the use of medicines at the community level
- patient's compliance with physician's advice
- the transformation of the pharmaceutical industry
- evaluations of programs to improve access to pharmaceuticals
- pharmaceutical policies of international organisations
- the role of pharmacies in promoting the adequate use of pharmaceuticals
- clinical trials and ethics in Latin America.

Salud y Fármacos has organised workshops and gave presentations in the U.S., Spain, England, and different countries in Latin America at the request of universities, medical societies, and organisations engaged in the promotion of the appropriate use of pharmaceuticals among Spanish-speaking populations.

Centre for Studies in Ethics and Rights (CSER)

CSER, established in the year 2005, is a research and training institute of the Anusandhan Trust. CSER endeavours to promote ethics, human rights and social relevance in the different aspects of public life. CSER intends to develop the understanding of ethics in both the conceptual and practical realm, drawing on diverse historical and cultural traditions and social and political visions. CSER's mission is:

- To undertake research and writing in ethics and rights in various disciplines;
- To encourage, educate and mentor students, academics and professionals through bioethics training programmes, fellowships and internships;
- To foster collaborations among multidisciplinary organisations and institutions in the field of bioethics.

3 Outsourcing and offshoring in the pharmaceutical industry

3.1 Outsourcing

In this chapter, we describe the outsourcing and offshoring of Research & Development (R&D) activities by pharmaceutical companies. This chapter is based on desk research and focuses on the clinical trial-related activities. Of the several R&D activities within drug development (see Table 3), the clinical trial phase is the most labour intensive, time consuming and costly part of the drug development process.

Table 3: Phases in the research and development process

Research	Pre-discovery: Understand the disease and choose a target molecule. Starting with 5,000–10,000 compounds. ²⁴	
	Drug discovery: Find a drug candidate.	3 to 6 years
	Preclinical: Test extensively to determine if the drug is safe enough for human testing. In this phase about 250 compounds are left.	
Development	Investigational New Drug Application: Obtain FDA approval to test the drug in humans.	6 to 7 years
	Clinical Trials: Test in humans to determine if the drug is safe and effective (Phase I, Phase II and Phase III trials). In this phase about 5 remaining compounds will be tested.	
	New Drug Application: Regulatory authorities like the FDA review the results of all tests to determine if the drug can be approved for patients to use. Leading to one approved drug.	0.5 to 2 years
	Manufacturing: To make the new medicine ready for production.	
Ongoing studies	Phase 4 Clinical Testing: Post-marketing testing.	

Source: Pharmaceutical Industry Profile 2010, Pharmaceutical Research and Manufacturers of America (PhRMA), based on Figure 9: The Drug Discovery and Development Process.²⁵

Another way to present pharmaceutical R&D is a division into three categories:

- Basic research: to discover new compounds for treating a disorder.
- Applied research: to develop a discovery into a specific practical application, including research on manufacturing processes and preclinical or clinical studies.
- Other research: research for drug regulation submissions, bioavailability studies and post-marketing trials.

According to some critical scientists, only a fraction of overall industry expenditure is on basic research that leads to important therapeutic breakthroughs; only 18% of the amount spent on R&D is invested on such basic research. They also argue that only 10-15% of newly approved drugs provide important benefits over existing drugs.²⁶ This implies that a lot of R&D effort is spent on 'me-too' (drugs that largely duplicate the action of existing drugs of competitors), as well as on

²⁴ Compounds refer to the molecules researched to see if they can be developed into active ingredients for medicines.

²⁵ Pharmaceutical Research and Manufacturers of America. Pharmaceutical Industry Profile 2010, Washington, DC: PhRMA, March 2010. Available at http://www.phrma.org/sites/phrma.org/files/attachments/Profile_2010_FINAL.pdf

²⁶ Donald W. Light, Joel Lexchin. Foreign free riders and the high price of US medicines, BMJ, 2005; 331: 958 doi: 10.1136/bmj.331.7522.958 (published 20 October 2005).

generics and on line extensions.²⁷ This information is included, as it is important to notice that the number of trial participants (who are taking risks) is increasing while minority of all clinical trials are conducted to develop new drugs. The selling of drugs is an even more important driver to set up clinical trials. In this respect, Professor Trudy Dehue concluded in a presentation that drug-marketing is an inherent aspect of drug-testing and vice versa.²⁸

Exactly how much the development of a new medicine costs is heavily disputed among the industry and independent researchers. At present, according to the US industry association PhRMA, it takes an average of 10 to 15 years and an estimated \$1.2 billion to \$1.3 billion to create a successful new medicine. This amount has raised considerably since the 1980s. In 2009, the estimated total costs spent on R&D worldwide by (bio)pharmaceutical companies was \$65.3 billion.²⁹ Critics argue that the industry includes marketing costs in the development costs and that the real development costs are much lower. Whatever the exact costs are, it is evident that the clinical trials are responsible for the majority of the costs and are a key factor in the rising R&D costs. Today's drug trials are larger and more complicated on average and require more participants than ever before. At the same time, recruitment of trial participants in western countries has become more difficult and thus, more expensive.³⁰ In 2008, US-based pharmaceutical companies spent \$47.4 billion on R&D, of which 54% (\$25.4 billion) was spent on Phase I, Phase II and Phase III clinical trials (of which \$15.4 billion or 32.5% was spent on Phase III trials alone). By including the Phase IV trials, which account for another \$ 6.8 billion, all clinical trials account for \$32.2 billion of the \$ 47.4 billion R&D spending in total or 68% of R&D costs.³¹ This confirms that the clinical trials, and in particular the Phase III trials, are the most expensive R&D activity and therefore presumably offers the greatest potential for cost savings related to outsourcing.

Historically, outsourcing in the pharmaceutical sector started out in the 1980s concerning non-core activities like IT, finance, HR and payroll, sales etc. It only moved up to core functions like drug manufacturing and R&D in the second half of the 1990s and the latter gave rise to a whole new contract research industry.³² CROs are the companies that execute most of the outsourced R&D activities.³³ They can take on several tasks in the drug development process, which are not explicitly limited to the conduct of clinical trials. CROs are generally recognised as performing clinical trial management. This includes activities such as: design of study protocol, case report form design, trial site and investigator recruitment, patient enrolment, study monitoring and data collection, data management, report writing and medical services (see Glossary for definitions). But many CROs provide their clients with additional specialised services, such as preclinical services, laboratory services, filing of Investigational New Drugs (INDs), formulation, manufacturing and

²⁷ A line extension is a variation of an existing drug of the same brand. The variation can be a new formulation of an existing product or a new modification of an existing molecular entity. It can be defined as a marketing strategy: if a company can introduce an extension, such as an extended release version for the drug, six months or a year before an existing drug's patent expires, it has the chance to shift patients to the new, patent-protected drug. If this strategy is successful, the company can retain market share, even after generic copies of the original drug reach market.
<http://ipbiz.blogspot.com/2005/02/pharma-strategies-of-line-extension.html>

²⁸ Trudy Dehue, (University of Groningen), presentation "Merging trials and publicity", at the Conference 'Selling Sickness', Amsterdam 8-10-2010

²⁹ \$63.7 billion in 2008; \$63.2 billion in 2007 and \$56.1 billion in 2006. Data from the PhRMA Pharmaceutical Industry Profile 2010.

³⁰ FORM 10-K Charles River Laboratories International, INC. For the fiscal year ended 26 December 2009
http://thomson.mobular.net/thomson/7/3069/4180/document_0/CRL_AR09.pdf

³¹ Pharmaceutical Research and Manufacturers of America. Pharmaceutical Industry Profile 2010, Washington, DC: PhRMA, March 2010. Available at http://www.phrma.org/sites/phrma.org/files/attachments/Profile_2010_FINAL.pdf

³² V. Roychowdhury, "CROs Evolve to a New level", Express Pharma, 1 April 2010.

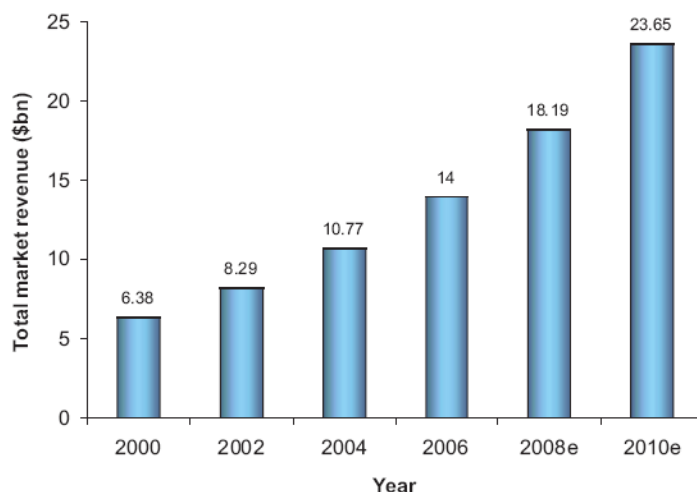
³³ Site Management Organisations (SMOs) are another type of contractor. They provide clinical trial-related services to a CRO, a pharmaceutical company, a biotechnology or a medical device company. The site is usually a hospital or a similar healthcare institution. The scope of an SMO's responsibility is limited to the 'site'.
http://en.wikipedia.org/wiki/Site_management_organization. There has also been an emergence of the so-called Medical Knowledge Process Outsourcing (KPO) organisations, which offer niche services like medical writing, coding, diagnostic services, testing services, pharmacovigilance etc.

packaging services, regulatory affairs services, medical and safety reviews and post-marketing studies. Some also provide back office services to clients, including processing the payments of investigators and patients. And coming back to the statement of Dehue that drug-marketing is an inherent aspect of drug-testing marketing; CROs increasingly play a role in the marketing of the drugs they test. The advantage of CROs compared with ordinary marketing bureaus is that they can entwine marketing and clinical trials. According to Dehue, the methodological handbooks of CROs explain how the four phases of clinical trials are connected to four phases of drug-marketing³⁴. For this purpose, the CRO Quintiles has its own capital group “to help clients to optimize the commercial value of their R&D”. Through their ‘Co-promotion investments’ they invest with cash and/or services in a customer’s commercialization programs in a customer’s drug in exchange for a return from that specific product in the form of royalties.³⁵

Contract research is a multi-billion dollar industry and has seen an explosive growth over the past decade. Figures and estimations vary among sources, but the following figures provide a snapshot:

- In the past decade, the global spending on contract clinical services has been growing at an annual rate of 13.4% on average.³⁶
- The global CRO market was worth \$16.5 billion in 2007.³⁷
- The CRO market will grow at an annual rate of 14-16% to reach \$24 billion through 2010.^{38,39}
- In 2010, CROs constitute approximately half of the research workforce involved in drug and medical product development.⁴⁰

Figure 1: Estimated CRO total market revenues, 2000-2010



Source: Business Insights, The CRO Market Outlook, Emerging markets, leading players and future trends, 2008.⁴¹

³⁴ Trudy Dehue, (University of Groningen), presentation “Merging trials and publicity”, at the ‘Conference Selling Sickness’, Amsterdam 8-10-2010

³⁵ Quintiles website “About our capital group” <http://www.quintiles.com/locations/asia/japan/japan-capital>, assessed 1 February, 2011.

³⁶ Tufts Center for the Study of Drug Development. Tufts CSDD Outlook 2010. <http://csdd.tufts.edu/documents/www/Outlook2010.pdf>

³⁷ CROs Evolve to a New level, Express Pharma, 1 April 2010.

³⁸ Health Insurance Week, Officials from Research and Markets Ltd. provide details of new developments, 23 September 2007.

³⁹ http://www.evotec.com/uploads/cms_article/192/Evotec_Initial_coverage_2010-07-30.pdf

⁴⁰ Quote from Simon Higginbotham, senior vice president and chief marketing officer of CRO ‘Kendle’ in CRO industry update: riding the R&D recession wave, by Kristin Brooks, Contract Pharma, p. 56(4) Vol. 12 No. 5, 1 June 2010.

The CRO sector is highly fragmented with over 1,100 CROs worldwide, although more than two-thirds of all CROs are based in the US.⁴² CROs come in many shapes and sizes: some are specialised in certain services in certain areas (the small specialty CROs), and some offer the whole spectrum of services in a drug development process around the world. This latter group comprises the global full service CROs, which have a presence in all emerging markets. Of the major global CROs, Quintiles is the market leader, with 14% of the global market share; followed by Covance and Pharmaceutical Product Development (PPD), which hold 10% each of the market share (see Table 4). The five largest CROs hold 45% of the total market between them.⁴³

Table 4: Presentation of the top global CROs, based on corporate information

<p>Quintiles Transnational Corporation (North Carolina, USA) Offers full-service contract research operations in more than 60 countries. It provides clinical, commercial, consulting and capital solutions. The company employs about 23,000 people. Quintiles is a private company, and does not publish annual reports; therefore, the company's financial details are not available. The estimated revenue was \$2.7 billion in 2007.⁴⁴</p> <p>Profiling quotes: "More efficient clinical trials. The result of having more experience in Phase II/III trials than anyone – even the top five global pharma companies." "Patient recruitment in diverse countries, which speeds up your trial" "Almost 80% of all clinical trials run behind schedule, and patient recruitment is the leading cause of delay. In fact, recruitment delays account for up to 95% of all days lost. To keep trials on schedule – or even ahead of schedule – Quintiles is increasingly leveraging its global reach." "For faster clinical trials, start farther from home."⁴⁵</p>
<p>Covance, Inc. (New Jersey, USA) A global full service CRO with net revenues in 2009 of \$1.9 billion, operations in more than 25 countries, and more than 10,000 employees worldwide.</p> <p>Quotes: "We believe that it is important to provide a broad range of drug research and development services on a global basis." "Our proven record of implementing well-crafted strategic agreements will help our clients reduce time and cost of drug development and help us secure committed volume contracts."⁴⁶</p>
<p>Pharmaceutical Product Development, Inc. (PPD, North Carolina, USA) A global full service CRO with net revenues of \$1.42 billion; operations in 45 countries and more than 10,500 employees worldwide.</p> <p>Quotes: "In high-growth emerging regions, pharmaceutical companies increasingly look to a CRO partner that understands drug discovery and development from target identification to new drug approval. PPD offers clients robust global experience, plus a local understanding of clinical research in Asia Pacific, Central and Eastern Europe, and Latin America." "We expanded our footprint in 2009 and strengthened our operations to continue offering our clients the services they want in the geographic locations they need."</p>

⁴² <http://www.cipher-sys.com/Global%20Contract%20Research%20Organizations.pdf>, 2008.

⁴³ http://www.evotec.com/uploads/cms_article/192/Evotec_Initial_coverage_2010-07-30.pdf

⁴⁴ Business Insights. The Top 10 Contract Research Organizations. Positioning, performance and SWOT analyses, 2009. <http://www.bharatbook.com/detail.asp?id=126596&rt=The-Top-10-Contract-Research-Organizations-Positioning-performance-and-SWOT-analyses.html>

⁴⁵ Quintiles Transnational Corporation website: <http://www.quintiles.com/clinical-services/patient-investigator-nontraditional-regions>

⁴⁶ Covance annual report 2009: http://www.covance.com/docs/investors/CVD_Annual_Report_2009.pdf

"We have the experience and ability to conduct clinical trials in more than 100 countries."⁴⁷

Charles River Laboratories (USA)

A global service provider that focuses on laboratory and pre-clinical services. With (a declined) revenue in 2009 of \$1.2 billion. Operating approximately 70 facilities in 16 countries worldwide.

"Core competencies in vivo biology and regulatory-compliant preclinical services in an efficient and cost-effective way to aid our customers in bringing their drugs to market faster."

"In order to convert largely fixed costs into variable expenses and to facilitate and speed their research, our pharmaceutical and biotechnology customers are making strategic decisions to outsource a portfolio of services to [...] service providers like us."⁴⁸

ICON, plc. (Ireland)

A global full service CRO supporting Clinical Development – from compound selection to Phase I-IV clinical studies. ICON operates offices in 69 locations in 39 countries worldwide. 2009 revenue was \$887.6 million, of which 8.6% was earned outside the US and Europe. The average number of employees in 2009 was 7,052.⁴⁹

Quote:

"We have the operational flexibility to provide development services on a stand-alone basis or as part of an integrated 'full service' solution."

PAREXEL (Massachusetts, USA)

A global full service CRO. PAREXEL operates in 70 locations throughout 54 countries and has 9,720 employees worldwide. Total revenue in 2010 was \$1,1billion, of which \$870.7 million was for clinical research services. Net income in 2010 was \$41.5 million. 12% of total 2010 revenue was earned in the Asia/Pacific region.

Quotes:

"We have broadened our extensive global presence across emerging markets in Latin America, Eastern Europe, Africa, and the Asia/Pacific region, so that customers can access diverse patient populations, reduce study costs, and conduct high-quality clinical research worldwide."

"As the needs of our customers evolve, PAREXEL continues to develop new partnership models that blend sponsor and service provider resources for maximum efficiency."⁵⁰

Kendle International Inc. (Ohio, USA)

A global CRO that provides a broad range of Phase I-IV global clinical development services to the biopharmaceutical industry, offering services spanning more than 100 countries. Revenue in 2009 was \$551.9 million. (Net service revenues were \$416.7 million). The company employed approximately 3,640 associates, about 61% of whom were located outside the United States.

Quote:

"At Kendle, we focus on creating long-term strategic partnerships based on transparency, efficiency and consistent value."

PharmaNet Development Group Inc. (Princeton, NJ, USA)

A global full service provider: early and late stage consulting, Phase I clinical studies and bioanalytical analyses, and Phase II, III and IV clinical development programmes. The company has approximately 2,300 employees in 41 facilities in North America, Latin America, Europe, Asia, Australia and Africa.

In 2009, it signed a merger agreement with the private equity investment firm JLL Partners, Inc. No financial information is available on the website or on 10-K forms.⁵¹ The last 10-K report dates back to 2006⁵² and reports a revenue of \$ 302.4 million.

⁴⁷ PPD annual report 2009,

<http://www.biotechprofiles.com/companyfiles/madisonnetwork/4f1f0c817c01480a8a0c47ca784182aa.pdf>

⁴⁸ Form 10-K, Charles River Laboratories International, Inc. For the fiscal year ended 26 December 2009:

http://thomson.mobular.net/thomson/7/3069/4180/document_0/CRL_AR09.pdf

⁴⁹ ICON annual report 2009: http://files.shareholder.com/downloads/ICLR/1109533893x0x370716/3BFE9EC9-2913-4DF0-96AD-90D797B6A017/ICON_plc_Annual_Report_2009.pdf

⁵⁰ PAREXEL annual report 2010: <http://investor.parexel.com/phoenix.zhtml?c=94569&p=irol-reportsannual>

PRA International Inc. (North Carolina, USA)

A full service provider with 35 offices conducting clinical trials in more than 85 countries across six continents. PRA provides outsourced clinical services across all phases of pharmaceutical and biotech drug development. PRA has conducted over 2,100 studies in the past five years.⁵³ In 2007, PRA had approximately 2,700 employees located in North America, Europe, Africa, South America, Australia and Asia.⁵⁴ Revenue was \$338.2 million in 2006. In 2007, PRA International entered into a merger agreement to be acquired by Genstar Capital, a private equity firm. Since then, no annual reports have been published.

Quotes:

“Our global scale enables us to select locations that produce more cost-effective and efficient clinical drug development. In addition, our global platform facilitates access to strategic locations and timely patient recruitment for complex clinical trials, which tends to be one of the most significant challenges for our clients during the clinical trials process.”

The worldwide business association for CROs is the Association of Clinical Research Organisations (ACRO). ACRO members employ more than 66,000 people worldwide, of whom 43% are in North America, 36% in Europe and 21% are in Asia, Latin America, Africa and Australia. In 2008, ACRO member companies conducted more than 9,000 clinical trials globally, involving nearly 2 million participants, with research carried out in 115 countries.⁵⁵

So far, the only independent accreditation in the field of clinical research can be obtained at the Association for the Accreditation of Human Research Protection Programs (AAHRPP). AAHRPP was set up because compliance with existing regulations proved to be insufficient.⁵⁶ Currently, AAHRPP has accredited mostly research sites in the US, primarily at universities and hospitals, but there are also seven AAHRPP-accredited independent IRBs and one CRO: Ethica Clinical Research based in Montreal, Canada.⁵⁷

CRO market growth explained

In recent years, pharmaceutical companies have faced pressures from rising R&D costs while the number of new drug applications is declining. In fact, the US Food and Drug Administration (FDA) expect a record low number of drug applications for 2010.⁵⁸ As has already been indicated, key factors in rising costs are related to clinical trials, but also technological advances increased R&D investment costs.⁵⁹ Additional pressures come from increased regulatory scrutiny, impending regulatory measures to reduce drug prices, and competition from generic drugs, which are

⁵¹ A Form 10-K is an annual report required by the U.S. Securities and Exchange Commission (SEC) that gives a comprehensive summary of a public company's performance.

⁵² Pharmanet 10 K form 2006, <http://www.secinfo.com/dsVsf.u2fr.1.htm>

⁵³ Website accessed December 2010:

<http://www.prainternational.com/About%20PRA/Global%20Reach%20and%20Locations>

⁵⁴ 10k Form for 2007: <http://www.secinfo.com/dsvRq.u123.htm>

⁵⁵ Website of Association of Clinical Research Organizations – ACRO (accessed 15 December 2010)

<http://www.acrohealth.org/cro-market1.html>

⁵⁶ Government reports and inspections showed that IRBs (institutional review boards) were dysfunctional and that clinical research wasn't being conducted to high ethical standards. Seeking The AAHRPP Seal, 19 May 2008

http://www.clinpage.com/article/seeking_the_aahrpp_seal

⁵⁷ AAHRP website <http://www.aahrpp.org/www.aspx?PageID=11>

⁵⁸ The agency expects to receive about 118 applications by the end of 2010, compared with about 140 in 2009, which was also the average number for the previous four years, with the lowest number of 134 in 2007. FDA expects record low drug applications in 2010, Kansas City Business Journal, by Aly Van Dyke

http://www.bizjournals.com/kansascity/blog/2010/08/fda_expects_record_low_drug_applications_this_year.html

⁵⁹ Charles River Corporation, annual report 2009.

expected to affect a large percentage of pharmaceutical companies' existing revenues in the intermediate future.⁶⁰

In dealing with these challenges, the companies are pressured to improve the management of their R&D costs while at the same time maintaining or developing a strong pipeline of innovative new drugs and shortening the timelines to bring these to the market. Time is money: the faster a drug is brought to market, the longer the company can enjoy the profits of patent exclusivity. The pharmaceutical industry is responding to these challenges by pursuing consolidations in the form of mergers and acquisitions, reducing head counts in R&D, and by increasing the outsourcing of R&D to CROs.

The CRO PRA International formulates the advantages of using CROs as follows: *“CROs have the therapeutic expertise and manpower to help drug companies improve and potentially shorten the drug development process by up to six months, thereby lengthening the product’s marketing life within its patent exclusivity period. Furthermore, outsourcing eliminates the pharmaceutical company’s need to invest in information systems, infrastructure, hire development researchers, or ramp up operations, thereby avoiding unnecessary fixed costs.”*⁶¹

The CRO Kendle says: *“The CRO industry, by specializing in clinical trial management, often performs the needed services with a higher level of expertise or specialization at a faster pace and at a lower cost than a biopharmaceutical company could perform such services internally.”*⁶²

In summary, the key driver of outsourcing is to enhance the performance of R&D investments by achieving greater R&D effectiveness, reducing costs and expediting time to market for new medications.⁶³ Other drivers, which are mentioned in literature, are as follows:

- Access to extra capacity/global capacity
- Access to medical and clinical knowledge in specific therapeutic areas
- Ability to shift large fixed costs to variable costs
- Expanding reach into emerging markets (globalisation of R&D)⁶⁴
- Access to knowledge of regulatory affairs in a particular country of interest⁶⁵
- Ability to increase flexibility to handle the highs and lows and fluctuating pipelines
- Lower personnel costs^{66,67}
- Access to innovative enabling technology without making huge investments.

It is clear that the globalisation of R&D has increased the outsourcing of clinical trials to CROs. All major CROs are currently working hard on their global presence so they can serve their clients with the services they want in the geographic locations they need.

⁶⁰ Related to the expiring patents, about \$128 billion of branded revenues are losing patent protection in the period from 2009-2014. Industry developments in US bio-contract services: opportunities and challenges for the CSP sector, by Brian Stemme, Contract Pharma, 1 June 2010.

⁶¹ Form 10-K 2007, PRA international, <http://www.secinfo.com/dsvRq.u123.htm>

⁶² Kendle International, Inc., Form 10-K, For the Fiscal Year Ended December 31, 2009.

<http://www.sec.gov/Archives/edgar/data/1039151/000095012310025149/l39024e10vk.htm>

⁶³ CRO industry update: riding the R&D recession wave, by Kristin Brooks, Contract Pharma, Pg. 56(4) Vol. 12 No. 5, 1 June 2010, also accessible at: <http://www.contractpharma.com/articles/2010/06/cro-industry-update>

⁶⁴ Outlook 2009, Tufts Center for the Study of Drug Development, Tufts University, Boston, USA.

⁶⁵ The Top 100 Contract Research Organisations in Europe, Research Facts Ltd, April 2009.

http://www.researchandmarkets.com/reportinfo.asp?cat_id=0&report_id=835791&q=top%20Contract%20research&p=1

⁶⁶ Outlook 2009, Tufts Center for the Study of Drug Development, Tufts University, Boston, USA.

⁶⁷ M. Shuchman. Commercializing Clinical Trials – risks and benefits of the CRO boom, New England Journal of Medicine, 4 October 2007.

Box 1: R&D cost reductions by pharmaceutical companies

The drastic cuts in head counts by pharmaceutical companies in their R&D divisions have limited internal capacity, which results in more outsourcing of R&D activities to CROs.

Accelerated by the 2008 recession, most of the leading pharmaceutical companies have recently undertaken or are currently in the midst of broad R&D cost-cutting programmes. The *Wall Street Journal* reported that the pharmaceutical industry reduced its head count by 40,000 workers in 2009.⁶⁸

For example, on 2 December 2010, Roche announced that it was cutting about 4,800 workers overall with several thousand more workers facing transfers to new locations. Roche said that “certain product development activities are expected to be discontinued or transferred—most of them from the US—to other Roche sites or third parties to improve overall productivity”.⁶⁹ This will probably mean being outsourced to CROs in low-cost offshore venues like India, China, Latin America or Russia.

At the beginning of 2010, more cuts to internal research operations were announced by the major pharmaceutical companies GlaxoSmithKline, AstraZeneca and Pfizer. GSK has proposed ending R&D activities across several sites to carve \$400 million from its R&D budget. The British drug firm also plans to develop more drugs outside its own labs; GSK already ‘farms out’ 30% of its research activities, or more than 80 projects, to some 47 partners.

AstraZeneca is cutting another 8,000 jobs on top of the 15,000 positions previously targeted for elimination between 2007 and 2009. The company says some R&D sites could be closed. AstraZeneca has also dropped 20 compounds from development.⁷⁰ Pfizer, meanwhile, says it will spend far less on research in coming years. Pfizer has also weeded out 100 of its 600 drug candidate programmes.⁷¹

In September 2010, Bristol-Myers Squibb said that it will cut three per cent of its global workforce – a total of roughly 840 jobs – during the next six months. The company earlier eliminated 7,000 jobs. In September 2009, Lilly announced a company-wide reorganisation and restructuring aimed at lowering its cost structure and accelerating the development of new products. The plan targets \$1 billion in cost savings by the end of 2011 and accelerates Lilly’s existing strategy of moving from a fully integrated pharmaceutical company to a fully integrated pharmaceutical ‘network’ of internal capabilities and external companies partnering to discover and develop new therapies.⁷² Abbott Laboratories is going to take the axe to its R&D operations as part of a broad plan to trim 3,000 workers in a restructuring inspired by its merger with Solvay.⁷³ Other big pharma mega-mergers that mark this period are that of Pfizer with Wyeth and Merck with Schering-Plough.

Outsourcing trend reversed?

Almost all literature points to increased outsourcing of R&D to CROs. However, a study conducted by Cutting Edge Information in 2009 indicated that outsourcing represented a smaller portion of clinical trial budgets than it did in 2006. Surveyed pharmaceutical companies in 2009 outsourced an average of 46% of their Phase III clinical trial budgets compared to 59% in 2006. Clinical operations executives revealed to Cutting Edge Information that a few factors have sparked a declining trend in outsourcing spending in the current market. For one reason, many experts assert

⁶⁸ Brian Stemme. Industry developments in US bio-contract services: opportunities and challenges for the CSP sector, Contract Pharma, 1 June 2010.

⁶⁹ Roche to cut 4,800 jobs in global restructuring plan, 2 December 2010: <http://www.centerwatch.com/news-resources/clinical-trials-today/headline-details.aspx?HeadlineID=1015>

⁷⁰ Pharmaceutical companies are narrowing their pipeline focus on a smaller number, [...] in high-potential therapeutic areas where they may yield the greatest returns (with particular focus and competition in oncology, metabolism/obesity, autoimmune/inflammatory, central nervous system and infectious disease).

⁷¹ <http://pubs.acs.org/cen/news/88/i06/8806notw4.html>

⁷² Brian Stemme. Industry developments in US bio-contract services: opportunities and challenges for the CSP sector, Contract Pharma, 1 June 2010.

⁷³ <http://www.fiercebiotech.com/story/bms-cut-3-workforce/2010-09-23#ixzz17MicGPF1>

that outsourcing does not present the cost savings that were once promised. And secondly, many companies simply cannot accept the loss of control when outsourcing certain aspects of trials. Thirdly, the risks involved can be costly; if they are poorly managed, trials could derail and cost much more to restart.⁷⁴

Opinions differ over whether outsourcing of clinical trial management is cheaper for sponsors than doing the work in-house. One study indicates that the management costs of outsourcing contracts in the pharmaceutical companies are high compared to other industries, and that sponsors actually pay double when they outsource to CROs: once for the contract, and once for supervising the contract.⁷⁵ However, the cost advantages might be indirect via the shortening of the duration of trial projects. According to one source, clinical trials conducted by CROs are completed up to 30% more quickly than those conducted in-house by pharma companies.⁷⁶

It remains to be seen how the trend will develop in the future. However, even when outsourcing of R&D has reached its peak, it is clear that CROs currently play a major role in clinical trial management.

Outsourcing models

Two basic types of sponsor-CRO outsourcing models are used:

1. Functional outsourcing: fee-for-service model.
2. The full-service model, where CROs functions as a 'one-stop shop' across the development cycle.

Functional outsourcing refers to the model in which individual clinical operations functions are outsourced to multiple firms, rather than outsourcing a complete trial to a single firm. Functions are outsourced to specialised vendors that are functional experts rather than drug development experts. The most common areas to be outsourced are study monitoring, data management, statistical programming, medical writing and statistics.⁷⁷ In the full service model, a sponsor engages with global CROs to complete the services of a full clinical trial. A study under both sponsors and CROs showed that currently 9% of sponsor respondents use a purely functional service outsourcing model, 11% use a purely full-service model, and 80% use a combination.⁷⁸

Not tied to one of the models in particular is the trend that pharmaceutical companies want CROs to take greater risks and responsibility in outcomes-based agreements. In those outcomes-based agreements the specific goals and milestones are outlined and compensation is tied to delivery against those goals. For example outcomes-based contracting is popular around patient access and delivery and site selection.⁷⁹

⁷⁴ Companies Outsourcing a Lower Percentage of Their Total Clinical Budgets, Says Cutting Edge Information, Marketwire, 6 August 2009.

⁷⁵ B. Anderson. How we fail to use CROs effectively. 2008, <http://appliedclinicaltrialsonline.findpharma.com/appliedclinicaltrials/Project+Management/How-We-Fail-to-Use-CROs-Effectively/ArticleStandard/Article/detail/534160> (accessed 16 December 2010).

⁷⁶ Health Insurance Week, 23 September 2007, Officials from Research and Markets Ltd. provide details of new developments.

⁷⁷ Kim Oliver. Functional Outsourcing: how to implement a new model? <http://www.contractpharma.com/articles/2005/05/feature3>

⁷⁸ The State of Clinical Outsourcing: In-depth survey reveals trends, outlooks, and future plans of both sponsors and service providers. 1 March 2010 <http://appliedclinicaltrialsonline.findpharma.com/appliedclinicaltrials/article/articleDetail.jsp?id=660743&sk=&date=&pageID=4>

⁷⁹ Kristin Brooks. CRO industry update: riding the R&D recession wave, Contract Pharma, p. 56(4) Vol. 12 No. 5, 1 June 2010, also accessible at: <http://www.contractpharma.com/articles/2010/06/cro-industry-update>

Next to these two basic models, there are different levels of supplier relationships that can be viewed as a step-wise progression: starting with a transactional relationship, to a preferred relationship, to a partnering relationship, to an alliance and this can end in integration with the supplier. The increasing closeness of relationships can be characterised with the following descriptions in Table 5.

Table 5: Increasing closeness of relationships between sponsors and CROs

	Transactional	Preferred	Partnering	Alliances	Integration
Description	'Fee for service'	'Reduced fee for service'	'Risk sharing and shared milestones'	'Sharing both profits and risk'	'One profit/loss'
Features	Tenders tactical negotiation	Pre-conditions Pre-qualifications	Mutual development	Joint ventures	Mergers and acquisitions

Source: J.E. Winter & J. Baguley, 2006⁸⁰

Experts and practitioners signal a shift from transactional relationships to strategic partnerships and alliances in which risk-sharing plays an important role. In a risk-sharing situation, it is eventually possible that the molecule or the project is jointly funded by both parties, Quintiles is offering such 'Co-Development investments' but this is still quite exceptional.⁸¹ Another example of the increased closeness of relationship between sponsors and CROs is the asset transfer agreement that is currently much more popular. Under this agreement, the CRO buys a pharma company's research facility below value. This is typically combined with a long-term service contract. Some high-profile agreements of this type were recently formed (see Box 2).

Box 2: Some high-profile agreements typical for asset transfer models

- In 2009, Covance acquired Merck's Gene Expression Labs for \$145 million. As part of the transaction, Merck transferred the facility's employees to Covance and signed a five-year contract to provide genomic analysis services.
- Covance and Eli Lilly and Co. formed a similar type of strategic partnership in 2008 when Covance acquired Lilly's toxicology and preclinical facility in Greenfield, IN, and entered into a ten-year contract to provide such services to Lilly.
- PPD acquired a vaccine-testing laboratory in Chester County from Merck, and PPD received a contract to supply testing services to Merck for five years. According to PPD's 2008 annual report, it paid \$25.2 million for Merck's lab.⁸²

In these examples, the pharmaceutical company reduces its operating expense and head count associated with these activities, while benefiting from additional operational flexibility through a long-term outsourcing contract.⁸³

⁸⁰ J.E. Winter & J. Baguley. Outsourcing clinical development: strategies for working with CROs and other partners, Gower, Hampshire, 2006.

⁸¹ Quintiles has its own capital group for Co-Development Investments in which Quintiles invests with cash and/or Quintiles services, in a customer's drug in exchange for a return from that specific product. This return may be, in the form of milestones or royalties, or other approved products. Source: Quintiles website "About our capital group" <http://www.quintiles.com/locations/asia/japan/japan-capital>, assessed 1 February, 2011.

⁸² http://www.philly.com/philly/blogs/phillyinc/PPD_to_expand_former_Merck_vaccine-testing_lab_in_Wayne.html Wednesday, PPD to expand former Merck vaccine-testing lab in Wayne, 3 November 2010.

⁸³ Brian Stemme. Industry developments in US bio-contract services: opportunities and challenges for the CSP sector, Contract Pharma, 1 June 2010.

3.2 Offshoring

Alongside the increased outsourcing of clinical trials, a second trend is that clinical trials are increasingly *offshored*. This means they are conducted in non-traditional trial regions that are mainly middle- and low-income countries. Pharmaceutical companies are eager to develop, test and market greater numbers of new drugs in less time, but recruiting and retaining patients is a major cause of clinical trial delays in traditional trial regions. Non-traditional trial locations with large populations can offer faster recruitment. Another important reason for pharmaceutical companies to increase the number of clinical trials in these countries is that they are potentially very large and interesting pharma markets. However, to market medicines in these countries, the regulations for marketing approval often require the conduct of local trials.

Other factors that determine the attractiveness of a country for carrying out clinical trials is the presence of a broad spectrum of diseases, the availability of human resources and technical skills, differing ethnic responses to drugs, compliance with international regulations and standards, cost advantages, reliable data quality and data management, and a functioning infrastructure.⁸⁴ An important factor is the availability of a “treatment naïve population”, a term that refers to populations that (apparently) have not been diagnosed or treated for a particular condition. This condition minimises the number of variables affecting clinical trial results.⁸⁵

Another factor that feeds the offshoring trend, according to Jeff Thomis and Smita Desai from Quintiles Ltd., is the ethical climate in Western Europe, North America and Japan, the traditional clinical trial regions, which makes the conduct of placebo controlled and treatment naïve studies much more difficult.⁸⁶ This statement indicates the importance of scrutinising the offshoring trend: if part of the rationale for offshoring is escaping tighter regulations in the developed world, the question arises what ethical standards are raised in these developing regions. In this respect, we also refer to a previous SOMO report, *Ethics for Drug testing in Low and Middle Income Countries* (2008). In the report, AstraZeneca explains that the reasons for conducting placebo controlled trials with schizophrenic patients exclusively in low- and middle incomes countries is because “almost all Western ethics committees do not approve this kind of trials anymore because of ethical concerns and therefore AstraZeneca is compelled to look for destinations outside Western Europe as these placebo controlled studies are still required by the EMEA and the FDA for market authorisation”.⁸⁷

The combination of push and pull factors for offshoring described above mean that certain middle- and low-income countries and regions are increasingly popular locations for clinical trials and have a booming CRO industry. These regions are Latin America, Eastern Europe and Asia.⁸⁸ Especially the so-called ‘BRIC’-countries with large populations and large market potential: Brazil (191 million), Russia (142 million), India (1,136 million) and China (1,331 million) - have strongly improved their relative growth in the number study sites over the past year.⁸⁹ The background, make-up and functioning of the CRO sector in two of these regions – India and Latin America – will be examined in depth in the following chapter.

⁸⁴ R. Maiti and M. Raghavendra. Clinical Trials in India. *Pharmacological Research* 56. 2007 (1-10).

⁸⁵ A. Petryna. Clinical trials offshored. *Biosocieties* 2, 2007, p.28.

⁸⁶ Jeff Thomis and Smita Desai. Outsourcing strategies. 2006 in: *Outsourcing clinical development*. Eds J.E. Winter and J. Baguley, p. 14.

⁸⁷ Schipper & Weyzig. Ethics for drug testing in low and middle income countries: considerations for European market authorization, SOMO, 2008.

⁸⁸ K. Jakovcic. Business Insights, The CRO Market Outlook: Emerging Markets, leading players and future trends, 2007, <http://www.globalbusinessinsights.com/content/rbcr0001t.pdf> (11 June 2010).

⁸⁹ Clinical Trial Magnifier, Feb 2008 Sponsored Clinical Trial Globalization Trends, By Johan PE Karlberg, MD, PhD Clinical Trials Centre, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, PR China.

All in all, there is a growing demand for clinical development services in non-traditional trial regions; in the last five years, 37.3 %⁹⁰ of the participants in pivotal trials⁹¹ used for Marketing Authorisation Applications (MAAs) submitted in the EU were recruited in non-traditional research countries.⁹² However, due to the time lag (there are often several years between the time of the trial and the time of the application), this percentage actually reflects the situation of a number of years ago. It is expected that at least 60% of FDA-regulated clinical trials will be conducted offshore by 2012.⁹³ A survey by Jeffersy from 2008 concluded that the share of R&D budgets spent outside North America and Europe was 29% in 2007. This is expected to almost double to 54% by 2011.⁹⁴ It is not possible to obtain exact figures on the current offshoring, especially of the clinical trials, but it is suggested that the percentage lies between the 40 and 50%.

There is a growing concern among regulators and the general public about how well these trials are conducted from an ethical and scientific/organisational standpoint. This includes good clinical practice (GCP) compliance and adherence to the available framework for the supervision of these trials.⁹⁵

Because of their nature – exposing humans to health risks for the health benefits of other humans in the future – clinical trials inherently involve the consideration of many ethical issues, irrespective of where the trials are conducted or who is conducting them. In response to this inherent ethical minefield, multiple ethical guidelines have been developed. When it comes to the conduct of clinical trials in developing countries, the basic international document in the field of ethics in biomedical research and the leading standard is the Declaration of Helsinki, first issued by the World Medical Association in 1964 and last revised in 2008,⁹⁶ together with the Council for International Organizations of Medical Sciences (CIOMS) Guidelines.⁹⁷ However, in practice when the regulatory agencies review the market applications for new drugs they only verify that the trial has been conducted in accordance to the guidelines for Good Clinical Practice (GCP) of the International Conference on Harmonisation (ICH),⁹⁸ as this facilitates the mutual acceptance of clinical trial data by the regulatory authorities of the EU, Japan and the US. The ICH-GCP guidelines (see Glossary) have been written into the laws of many emerging research countries and are followed uniformly by CROs throughout the world.⁹⁹ The FDA has formally stated that they will not longer confirm that trials conducted outside the USA comply with the Declaration of Helsinki. As we explain in the following paragraphs, EMA is in the process of developing a

⁹⁰ Clinical trials submitted in marketing authorisation applications to the EMA, Overview of patient recruitment and the geographical location of investigator sites, updated with data from marketing authorisation applications submitted in 2009, EMA, 5 November 2010.

http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/12/WC500016819.pdf

⁹¹ Pivotal trials are only a fraction of the total numbers. It is a possible scenario that a drug development process includes 50 trials, of which in the end only five are identified as pivotal and those are used for the marketing application, meaning that in this case only 10% of the trials are included in the collected data. Supportive trials are not included, which means Phase I, most Phase II, and some Phase III trials.

⁹² This figure includes the new EU accession countries of 2004 (Cyprus, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Malta, Poland, Slovakia and Slovenia) and the new EU countries of 2007 (Bulgaria and Romania). At the time of the MAAs, these countries were EU member states, but at the time of the recruitment of the pivotal trials they were very likely not. http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/12/WC500016819.pdf

⁹³ Frost & Sullivan, Contract Research Organization (CRO) Markets in Europe. August 2006.

⁹⁴ Jim Miller. Clinical Outsourcing Steams Ahead, Pharmaceutical Technology, August 2008.

⁹⁵ Clinical trials submitted in marketing authorisation applications to the EMA, Overview of patient recruitment and the geographical location of investigator sites, updated with data from marketing authorisation applications submitted in 2009, EMA, 5 November 2010.

http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/12/WC500016819.pdf

⁹⁶ The 2008 version has replaced all earlier versions and is the only official one:

<http://www.wma.net/en/30publications/10policies/b3/17c.pdf>

⁹⁷ See CIOMS Guidelines: http://www.cioms.ch/publications/layout_guide2002.pdf

⁹⁸ The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). See for the GCP guidelines <http://www.ich.org/LOB/media/MEDIA482.pdf>

⁹⁹ The Case for Globalization: Ethical and Business Considerations in Clinical Research, Value of Insight Consulting, Inc. 21 July 2009.

mechanism to monitor compliance with ethical standards for clinical trials conducted outside of Europe.

The 2004 revisions to the European pharmaceutical legislation increased emphasis on the ethical standards required of clinical trials conducted outside Europe and included in Marketing Authorisation Applications (MAAs) submitted in the EU.¹⁰⁰ This was relevant as the number of patients recruited in countries outside Europe for European applications grew substantial.

Since 2001, European legislation states very clearly that: *“In particular, with respect to clinical trials conducted outside the Community on medicinal products destined to be authorised within the Community, at the time of the evaluation of the application for authorisation, it should be verified that these trials were conducted in accordance with the principles of good clinical practice and the ethical requirements equivalent to the provisions of the said Directive.”*¹⁰¹ And these principles *“are equivalent to the provisions of Directive 2001/20/EC. They shall be carried out in accordance with the ethical principles that are reflected, for example, in the Declaration of Helsinki.”*¹⁰²

However, in an earlier SOMO report,¹⁰³ three cases studies showed that medicines that were clearly not tested in accordance with the Declaration of Helsinki were approved by the European regulatory authorities based on these trials. The truth is that the regulatory authorities in Europe are not equipped yet to check clinical trials outside Europe on compliance with GCP and international ethical standards like the Declaration of Helsinki; the EMA is currently working on procedures to verify that pivotal clinical trials (ie. those that are included in MAAs), conform with ethical standards.¹⁰⁴ The legislation seems in order, but it is simply not fully implemented yet. Medicines tested in non-traditional research regions are finding their way to the European market relying on the statements made by the pharmaceutical companies that they are conducted according to GCP, and relying on the local frameworks for ethical review and the local frameworks for regulatory oversight. In Chapter 5, the ethical risks associated with offshoring of clinical trials are further addressed.

¹⁰⁰ The European pharmaceutical legislation sets out the ethical requirements for the conduct of clinical trials in Directive 2001/20/EC, Directive 2005/28/EC and Directive 2001/83/EC.

¹⁰¹ Regulation (EC) No EC/726/2004 states in recital 16.

¹⁰² Paragraph §8 of the Preamble – Introduction and General Principles of Annex 1 to Directive 2001/83/EC.

¹⁰³ Irene Schipper & Francis Weyzig. Ethics for drug testing in low and middle income countries: Considerations for the European Market Authorisation, SOMO, February 2008.

¹⁰⁴ Reflection paper on ethical and GCP aspects of clinical trials of medicinal products for human use conducted in third countries and submitted in marketing authorisation applications to the EMA (draft), EMA, London, 26 May 2010: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/12/WC500016819.pdf.

4 CROs in case study countries

4.1 Introduction

This chapter characterises the role of CROs in the implementation of clinical trials in selected Latin American countries and India. The studies in India, Argentina, Brazil and Peru all reported on the scarcity of available information and on the reluctance of the selected key informants to participate in the study. The planned interviews with the international CROs were particularly difficult to realise. Eventually, a total of ten CROs were interviewed, while eight to ten interviews were planned per country. As the availability of information varies for each country, the presented information per country is not uniform. For example, the Peruvian study delivered very valuable and precise information about clinical trials conducted by CROs in Peru. This was due to the fact that two staff members of the Instituto Nacional de Salud (INS), the Peruvian regulatory agency responsible for authorising and monitoring clinical trials, were involved in this study. At the same time, due to their position as staff of the INS, they could not approach CROs for interviews. In Table 6, the presence of the top ten multinational CROs in the case study countries is listed. It is clear that all the major CROs have local branches in the non-traditional trial countries that were selected for this report, with the exception of Charles River Laboratories. This may be explained by the fact that this company offers specialised services in various types of laboratory testing like animal testing and preclinical and clinical support services, and no clinical trials services.

Table 6: Operations of top ten multinational CROs in Argentina, Brazil, Peru and India

	Argentina	Brazil	Peru	India
Top ten multinational CROs with headquarters in industrialised countries (ranking based on 2008 revenues)				
Quintiles (USA)	x	x	x (2003)	x
Covance (USA)	x	x ¹⁰⁵	x (2007)	x
Pharmaceutical Product Development (PPD) (USA)	x	x	x (2006 registered in 2008)	x
Charles River Laboratories (CRL) (USA)				x ¹⁰⁶
ICON Clinical Research (Ireland)	x	x	x (2007)	x
PAREXEL (USA)	x	x	x (2008)	x
MDS ¹⁰⁷ /INC Research* (USA)	x	x ¹⁰⁸	x (2004)	x ¹⁰⁹
Kendle (USA)	x	x	x (2007)	x
Pharmanet (USA)	x	x	x (2009)	x
Pharmaceuticals Research Associates (USA)	x	x	x (2008)	x

Note: Country of origin between brackets. Source: the company websites accessed in December 2010, and Regulatory Agency of Peru.

*This refers to the 2008 position of MDS; INC Research has now acquired all MDS clinical trial operations.

¹⁰⁵ On 9 September 2009, Covance Inc. announced the opening of new clinical development offices in Sao Paolo, Brazil and Mexico City, Mexico.

¹⁰⁶ CRL has its presence in India through its BPS agents, Zelle Biotechnology Private Limited. see <http://www.criver.com/en-us/prodserv/bytype/biopharm/Pages/home2.aspx>

¹⁰⁷ In June 2009, INC Research has acquired MDS Pharma Services' Phase II-IV operations, which includes approximately 800 employees who conduct clinical trials in more than 25 countries. http://www.pharmaceutical-business-review.com/news/inc_research_acquires_mds_pharma_services_phase_iiiv_operations_090701

¹⁰⁸ According to website of INC Research: <http://www.incresearch.com/Global/Clinical-Trials-in-Latin-America.aspx>

¹⁰⁹ INC Research is present in India through its 50:50 joint venture with GVK Biosciences.

Table 7 presents a non-exhaustive list of other CROs operating in the Latin America case study countries (minus the top ten CROs already listed above). This list is compiled by the Latin America researchers. Later on, we added the CROs headquartered in industrialised countries that are present in India. It has been very difficult to identify the exact number of CROs operating in Argentina, Brazil and Peru. Only the regulatory agency of Peru requires CROs to register with the agency; in Argentina, CROs are not required to register until they present the first clinical trial regulatory package for approval and the same is the case in Brazil. The names of CROs included in this table were obtained from the regulatory agencies, company websites, and the national associations of CROs. Each source provided a different list of CROs, and in this report we have included all the CROs that were listed at least once in any of the three lists. For India, more listings of CROs are available on the internet; therefore a more extensive list of CROs that are active in India is included in Annex 3.

Table 7: Names and country of origin of multinational CROs operating in Argentina, Brazil, Peru and India

	Argentina	Brazil	Peru	India
Multinational CROs headquartered in industrialised countries (minus the top ten CROs)	(14)	(8)	(9)	(7)
AAIPharma (USA) ¹¹⁰ /ZeeCRO Inc.	x	x	x (2009)	x
ACLIREs International Ltd. (USA)	x			
Chiltern (UK)	x			x
Eurotrials (Portugal)		x		
Genexion (Switzerland)	x	x	x (2008/9)	
i3 Latin America (antes Latin Trials) (USA)	x	x	x (2004) registered in 2008	
INC Research (bought MSD Pharma Services) (USA)	x		x (2004)	
Ingenix (USA) also known as i3 Research	x			x ¹¹¹
MedPace (USA)	x			x
Omnicare (USA)	x	x		x
Oncopartners (specialised in cancer studies) (USA)		x		
Pharm-Olam Serviços Clínicos (USA)	x	x		x
Progenitor (Germany)	x		x	x
PSI (in Argentina purchased Thywill - Russia) (Swiss)	x		x (2009)	
RPS (USA)	x	x	x	
Siplas Research Organisation (Latam clinical Trials – USA)			x (2009)	
World Wide Clinical Research (USA)	x		x (2008)	
Multinationals headquartered in Latin America	(1)	(4)	(0)	(not relevant)
ECLA (Argentina)	x	x		
HRPC (Brazil)		x		

¹¹⁰ AAIPharma Inc. has changed its name to ZeeCRO Inc.

¹¹¹ In India, operating under the name of i3 research (located in Gurgaon, Mumbai and Pune). i3 is a business unit of Ingenix, a wholly-owned subsidiary of UnitedHealth Group.

Intrials (Brazil)		x		
Vigium (Brazil)		x		
National CROs	(12)	(6)	(6)	(not relevant)
Abel Santos	x			
Activa CRO	x			
Blancahrd y Asociados	x			
DS Consult			x (1995)	
EGCP	x			
Gonzalez Asociados Pharma Consulting	x			
Gotuzzo Asociados			x (2004)	
Grupo Jasovich	x			
HMED – Distributor of medical supplies		x		
INMENSA			x (2007)	
IMPACTA			x (2000)	
Investigación Clínica Asociada	x			
IPCSP (linked to the Federal University of Sao Paulo)		x		
Klixar	x			
Latinamerican Research			x (2008)	
Latinclin	x			
M Matiss	x			
Newco Trials		x		
Panamerican Medical Supply		x		
Peruvian Clinical Research			x (2007)	
PHC Pharma Consulting		x		
PGS Medical Statistics		x		
QUID consultora	x			
RD Lantam	x			

Latin America as attractive clinical trial region

Many of the pull factors mentioned in section 3.2 certainly account for the popularity of Latin America with its large populations, offering a broad spectrum of diseases, differing ethnic groups and treatment naïve patients. The population is concentrated in the major cities, and thus makes recruitment even faster. For instance, Brazil has a population of 192.09 million people, of which 19.88 million live in Sao Paulo. Argentina has a population of 40.48 million people, of which 13.35

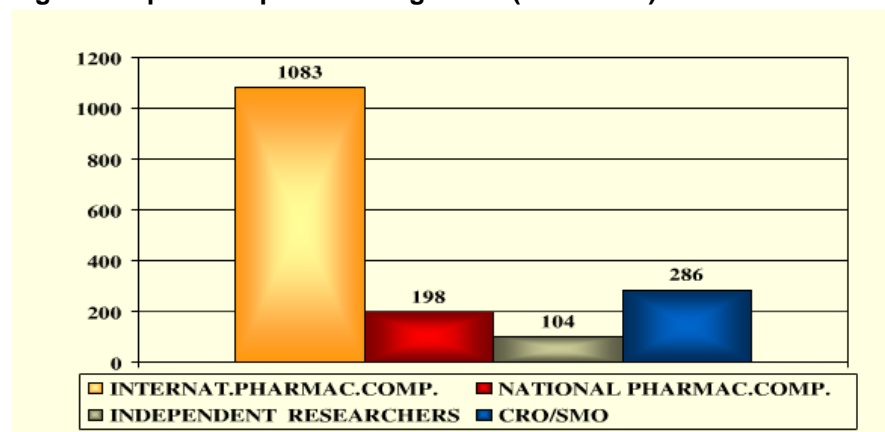
million live in Buenos Aires alone. The Latin American market for drugs is already large, but it still has enormous growth potential: in 2008 the medicines market accounted for \$50 billion and this is estimated to rise to \$80 billion in 2013. The three top markets are Argentina, Brazil and Mexico. On top of the pull factors that account for all emerging clinical trial locations, Latin America has the advantage of having only two major official languages: Spanish and Portuguese. It is also known for strong patient-doctor relationships, and low retention rates (minimal dropout rates).¹¹²

4.2 Argentina

CRO market in Argentina

The first CRO that established offices in Argentina was COROMED in 1995, which was a CRO specialising in cardiovascular diseases and was later purchased by OMNICARE.¹¹³ Very few statistics are available about CROs in Argentina, but the fact that more and more CROs include Argentina in their geographical coverage suggests that their role in conducting clinical trials is increasing. According to information provided by executives of three large pharmaceutical firms in Argentina,¹¹⁴ currently about 30% of clinical trials are conducted by CROs. The percentage of trials submitted to ANMAT (National Administration of Drugs, Food and Medical Technology) as part of a regulatory package by CROs/SMO, was 26% in the period between 1994 and 2006 (see Figure 2).

Figure 2: Sponsors profile in Argentina (1994-2006)



Source: ANMAT, 2008¹¹⁵

CAOIC is the acronym for the Argentinean Association of CROs¹¹⁶ (see Table 8). It was established in 2008. At present the CAOIC has 15 CRO members, which are primarily large multinational CROs, predominantly from the US (see Table 8). According to a top officer of CAOIC, for a CRO to become a member it has to have presented a clinical trial protocol by the regulatory agency ANMAT.¹¹⁷ The CROs that have no membership of the CAOIC tend to be small and do not conduct many clinical trials, but instead provide supporting services such as training of

¹¹² World Pharmaceutical Frontiers. 'Latin Fever', March 2008, www.worldpharmaceuticals.net/editorials/013_march08/013_latin.pdf (accessed 7 February 2011); S. Bandyopadhyay. 'Towards Global Access to Health', 30 August 2006, <http://www.ghf06.org/reports/35> (accessed 7 February 2011)

¹¹³ Interview with a top officer of the Argentinean Association of CROs (CAOIC), Buenos Aires 17 May 2010.

¹¹⁴ According to the information provided in interviews with executives of three major international pharmaceutical companies on 28 May 2010, 4 February 2010, and 27 May 2010, respectively.

¹¹⁵ The source of this graph is Analia Pérez. Clinical Trials in Argentina: 10 years of experience, 2008, Buenos Aires: ANMAT.

¹¹⁶ Cámara Argentina de Organizaciones de Investigación Clínica (CAOIC): <http://www.caoic.org.ar/>

¹¹⁷ Interview, Buenos Aires, 17 May 2010.

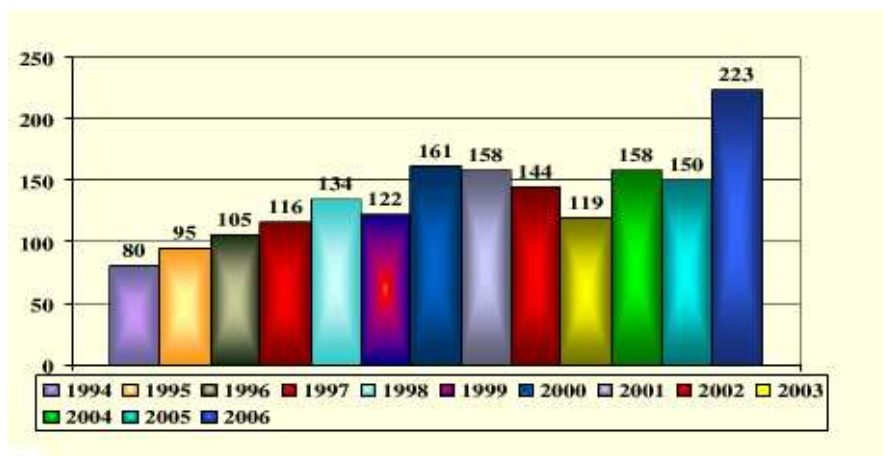
researchers, quality control, planning and logistics, support and consulting for ethics, recruiting personnel and identifying research centres.

Table 8: CRO members of the CAOIC, 2010

PAREXEL	Omnicare Clinical Research
PPD	Quintiles
PSI (CH)	ICON
PRA International	ECLA
Pharmanet Development Group	EGCP
Ingenix/i3 Research	Kendle
INC Research	Research & Dev (RD LATAM)
	Covance

In 2008 the Argentinean Regulatory Agency (ANMAT) approved 180 protocols of clinical trials. The 2009 figures are not yet available. There has been a steady increase in protocol approval since 1994 (see Figure 3), with the largest number of approvals in 2006: 223 protocols. The cause for the decrease between 2006 and 2008 is unclear.

Figure 3: Pharmaceuticals protocols assessed and approved between 1994-2006 in Argentina.



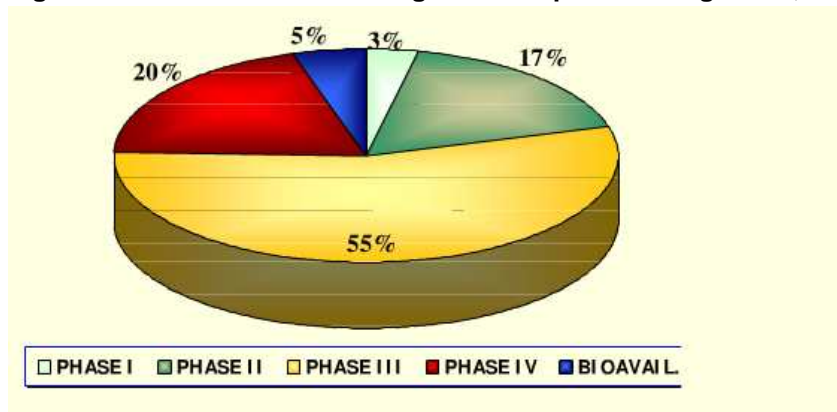
Source: ANMAT, 2008¹¹⁸

In decreasing order these protocols concern drug tests to treat the following disease groups: cardiology, oncology, metabolism/endocrinology, infectious diseases, gastroenterology, respiratory system, nervous system and dermatology.

In Figure 4, the distribution of clinical trials according to research phase is shown. Phase III is the most common type of trial, accounting for 55% between 1994-2006. Second place with 20% are the Phase IV trials, closely followed by Phase II trials with 17%. 3% of the trials concerned Phase I trials.

¹¹⁸ This graph is made by Pérez, Analía. Clinical Trials in Argentina: 10 years of experience, 2008, Buenos Aires: ANMAT.

Figure 4: Clinical trials according research phase in Argentina, 1994-2006.



Source: ANMAT, 2008¹¹⁹

The total number of clinical trials from 1994-2006 is 1,894.

The overviews in Table 6 and 7 show 36 CROs operating in Argentina:

- nine of the top ten multinational CROs
- fourteen other foreign multinational CROs
- one Argentinean multinational CRO
- twelve national CROs.

Regulatory framework

ANMAT (National Administration of Drugs, Food and Medical Technology), the regulatory agency equivalent to the FDA, was created in 1992. It is responsible for approving the clinical trial protocols and authorising the marketing of drugs. In addition to ANMAT, since 2000 the National Direction for the Protection of Personal Data of the National Ministry of Justice has been responsible for protecting personal data in all public and private archives, registries and data bases, and consequently of all personal information gathered during the clinical trials.

In Table 9, the most important clinical trial-related Argentinean legislation is listed. We want to highlight three pieces of important legislation that were introduced in the past years.

- In 2009, the Ministry of Health of the Nation issued a resolution creating the Registry of Clinical Trials on Humans. At present, the Registry is being made available to the public.
- In 2008, ANMAT established a new process for reporting the unexpected and serious adverse reactions to medications occurring during the trials. The adverse reactions have to be reported to ANMAT immediately. This has to be followed by a detailed explanation and the subject has to be identified by a unique code number. The researcher also has to inform the ethics committee of the adverse reaction.
- In 2007, a resolution approved the Guidelines for the Good Practice of Clinical Research in Humans based on the international ICH-GCP standard. It requires that all trials should be approved by an Ethics Committee. When the institution does not have an Institutional Ethics Committee that is GCP-compliant the project can be approved by a private Independent Ethics Committee. Both are financially compensated for this work.

For an overview of the main legislation regarding clinical trials, see Table 9.

¹¹⁹ This graph is made by Pérez, Analia. Clinical Trials in Argentina: 10 years of experience, 2008, Buenos Aires: ANMAT.

Table 9: Main legislation regarding clinical trials

Institution and year	Content
ANMAT 1997 Disposition 5330/97	Approves Good Clinical Research Practices in Clinical Pharmacology http://www.mimdes.gob.pe/files/PROGRAMAS%20NACIONALES/PNCVFS/capacitacion_facso/Disposiciones_Argentina/Disposicion_ANMAT_5330_1997.pdf
ANMAT 2005 Disposition 690/05	Approves Guidelines to conduct inspections of clinical investigations http://www.hospitalaleman.com/joomla/images/Nuevacarpeta/anmat-4-690-2005.pdf
Ministry of Health 2007 Resolution 1490/07	Approves Guidelines of Good Clinical Practices for Research in Humans http://www.anmat.gov.ar/webanmat/Legislacion/Medicamentos/Resolucion_1490-2007.pdf
ANMAT 2008 Disposition 6550/08	Requires additional documentation to be presented before receiving approval for clinical trials such as: coordination with ethics committees, verification that the necessary information has been submitted (duties and rights and safeguards of the parties including economic arrangements), authorisation from the head of the institution where the research will take place. It also requires that the consent form includes in big capital red letters in the page of signatures the phone number of ANMAT, so that the participant can call to ask any questions regarding the trial. http://www.reumatologia.org.ar/userfiles/file/investigacion-farmaco-clinica/ANMAT-6550-08.pdf
ANMAT 2008 Disposition 1067/08	Has a new system of reporting all serious and unexpected adverse drug reactions to ANMAT and the ethics committees http://www.infoleg.gov.ar/infolegInternet/anexos/135000-139999/138239/norma.htm
Ministry of Health of the Nation 2009 Resolution 102/09	Creates the Clinical Trials Registry http://www.anmat.gov.ar/webanmat/Legislacion/Medicamentos/Resolucion_102-2009.pdf
National Congress 2000 Law 25.326 / 00	Determines that the Ministry of Justice of the Nation, through its National Directorship for Personal Data Protection, is responsible for maintaining the confidentiality of personal data collected in all public and private registries, data bases and archives, including those in clinical trials. http://www.infoleg.gov.ar/infolegInternet/anexos/60000-64999/64790/norma.htm

In Argentina, there are no regulations specifically for CROs, which are not required to register themselves with ANMAT until they present the first clinical trial regulatory package for approval.¹²⁰ They have to comply with the ICH-GCP guidelines and they have to obtain a license to operate, like any other company at the chamber of commerce. Formally, ethics committees are in the position to analyse some of the financial agreements between the sponsor, CROs, and the researchers, since from 2009 onwards (according to Disposición 6550/08 ANMAT), Argentina's ethics committees are required to evaluate the contracts of the sponsoring agencies with the different entities responsible for the implementation of the trials. These evaluations should be submitted to ANMAT. However, it is doubted whether these evaluations occur in practice, as in interviews, ethics committee members have complained they do not have the technical capacity and/ or guidelines to perform these evaluations.

The legislation that is in place shows that the government of Argentina and ANMAT seem to be willing to improve the quality of clinical trials and the protection of participants' human rights. The problem is that there are many laws, presidential decrees, regulations, norms, dispositions, etc. many of which are not observed, and/ or are replaced by new ones, which turns the situation into a legislative/regulatory maze.

¹²⁰ Interview with president CRO business association, Buenos Aires, May 17 2010.

4.3 Brazil

The advantages of Brazil as a clinical trial location as promoted by CROs:

- Eurotrials: *“Sponsors have discovered that Brazil provides unique advantages during the clinical trial process. Brazil’s large and highly concentrated patient populations, its low per-patient cost, and its world-class healthcare facilities combine to make Brazil an ideal site for studies in many therapeutic areas.”*¹²¹
- Oncopartners: *“there are 150 million uninsured people, [...] and there is a high degree of motivation to participate in clinical research.”*¹²²

CRO market in Brazil

The first CROs in Latin America were established in Brazil in the 1980s as initiatives of research centres (IPCSP, Vigium), health professionals (Newco Trials, Oncopartners) or professionals in the pharmaceutical industry (PHC). The surge of CROs in Brazil occurred in the late 1990s, and was led by national groups who were later purchased by multinational CROs. As indicated in the introduction of this chapter, it has been very difficult to identify all CROs operating in Brazil based on public secondary sources and the overview of CROs operating in Brazil is expected to be incomplete. The overviews in Table 6 and 7 show 26 CROs operating in Brazil, most located in Sao Paulo:

- nine of the top ten multinational CROs
- eight other foreign multinational CROs
- three Brazilian multinational CROs
- six national CROs.

ABRACRO, the Brazilian Association of CROs, was founded in 2006 and includes 23 CROs.¹²³ ABRACO’s role is to represent its members, contribute to the improvement of clinical trial regulations in Brazil, and stimulate the development of educational activities linked to the sector. An example of ABRACO’s activities is its intervention in the recent modification to the Brazilian regulation that expedites the regulatory approval of multicentre clinical trials.¹²⁴

Regulatory framework

In July 2009, the Brazilian regulatory agency ANVISA introduced some changes to the regulatory process to expedite the regulatory approval of multicentre clinical trials. Before these changes, the sponsor or CRO had to approach and get approval from local ethics committee(s) that have jurisdiction over each investigator site involved, then get approval from Brazil’s national central ethics committee, and subsequently get approval from ANVISA and then go through the importation process that is necessary for any unapproved drug coming into the country. After the changes, only the local ethics committee of the ‘coordinator site’ (also called the ‘coordination centre’) has to approve the study instead of all the sites; then approach the National Ethics Committee (CONEP) and ANVISA, simultaneously instead of sequentially. Subsequently, ANVISA is the agency that arranges for importation (see Figure 5).

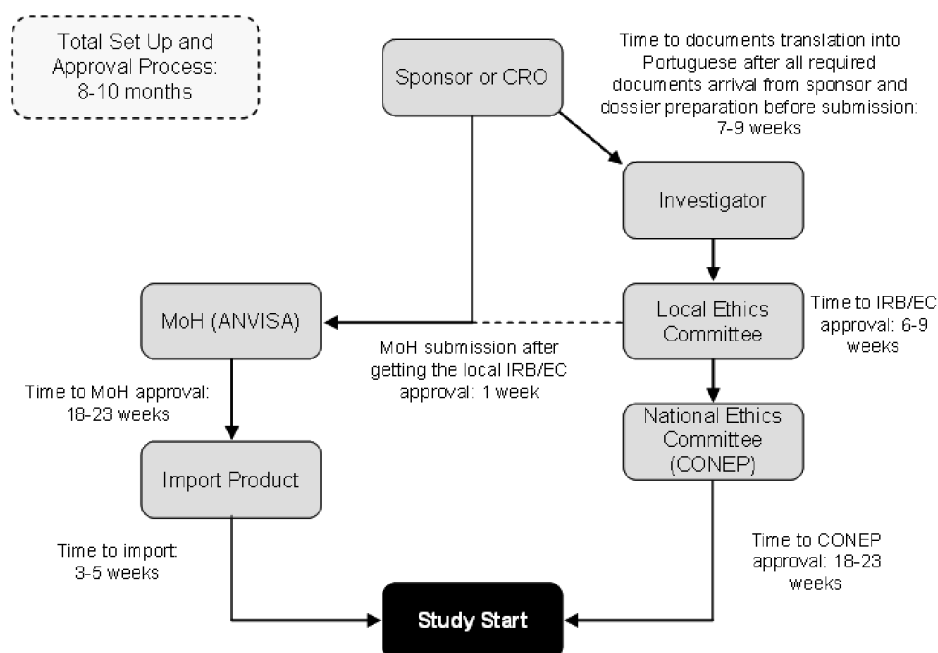
¹²¹ Website Eurotrials: <http://www.eurotrials.com/index.php?m=100&idioma=2>

¹²² States News Service, 16 March 2009, Outsourcing, Offshoring and New Value Propositions Key to BigPharma’s Future? <http://www.abracro.org.br/>.

¹²⁴ S. Readfearn. “Trials thriving in Brasil: a quickening process”. ClinPage. December 2008 http://www.clinpage.com/article/trials_thriving_in_brazil/ (accessed September 23, 2010)

The choice of the coordinator site is now crucial as the approval for all investigators sites is now in the hands of one local ethics committee. If used appropriately, the new legislation should not weaken the protection of clinical trial participants. However, in an interview, a member of the National Ethics Commission expressed concern and emphasised the need to monitor the implementation of the new process.¹²⁵ The interviews with CROs indicate that the speed of proposal approval by the ethics committees is an important decisive factor in selecting the coordinating centre.¹²⁶

Figure 5: Regulatory flowchart – Brazil¹²⁷



Source: Business Insights.

The first Brazilian regulation that mentions the word CRO (known as ORCP in Brazil) is the *RDC number 39*, which was approved on 5 July 2008. This regulation defines the concept of CRO and its obligations. Like in Argentina, the only requirement is that the CROs obtain a license to operate, as any other health provider. ANVISA does not register a CRO until they present a project to the regulatory agency.

Contrary to the situation in Argentina, there is no obligation to disclose the conditions of the contracts between the sponsors of the study and the CROs, or between the sponsors and the principal investigators, to the ethics committees. This means that ECs cannot include the lines of responsibility in their judgement when deciding whether to allow a clinical trial to proceed. ANVISA has access to this information, but it is not used to evaluate whether the contractual arrangements protect the rights of the research participants.

For an overview of the main legislation regarding clinical trials in Brazil, see Table 10.

¹²⁵ Brasília, 9 September 2010.

¹²⁶ Interview clinical investigator, Sao Paulo, 17 August 2010.

¹²⁷ Emerging Clinical Trial Locations. Market dynamics and the changing healthcare and regulatory environment, Business Insights, July 2009.

Table 10: Main legislation regarding clinical trials

Regulations of the National Health Council (CNS)	
Res. CNS 196/96	Deals with the ethical requirements of research involving humans, and creates the system of CEPs and CONEP, assigning responsibilities for approval of various types of projects.
Res. CNS 251/ 97	Deals with ethical requirements specific to research into new drugs, vaccines and diagnostic tests.
Res. CNS 292/98	Deals with research that involves foreign cooperation, including multicenter clinical trials, with and without external sponsorship, and drug imports.
Res. CNS 301/2000	CNS opposes the proposed changes to the Declaration of Helsinki, especially regarding the use of placebo.
Res. CNS 346/ 2005	Deals with storage and use of biological materials in research.
Res. CNS 347/2005	Establishes procedures for submission of multicenter studies, eg defining a center coordinator.
Res. CNS 370/2007	Sets up requirements on registration and accreditation of ECs.
Res. CNS 404/2008	Describes the position taken by the participants in a Forum for the preparatory meeting of the World Medical Association on the amendments to the Declaration of Helsinki, with regard to placebo use (only in case there is no approved drug for the disease or condition) and ensuring access to the studied drug.
Res. CNS 421/2009	Modifies the composition of CONEP to include representatives of health workers to the CNS.
NPCNS 006	Detailed aspects of evaluation and accreditation of research Ethics Committees
ANVISA regulations	
RDC 39/2008	Regulation for the authorization of clinical research, including prior approval requirements and ANVISA responsibility: eg monitoring the development of research in accordance with Good Clinical Practice, accreditation of CROs, monitoring adverse drug reactions, and imposition of sanctions as determined by health legislation.
IN n°4 2009	Contains the Inspection Guidelines for Good Clinical Practice.

4.4 Peru

CRO market in Peru

In Peru, the first CRO was registered in 2003, but there were national CROs that were conducting trials in the country prior to that date. The overview in Table 6 and 7 shows a total of 24 CROs operating in Peru:

- nine of the top ten multinational CROs
- nine other foreign multinational CROs
- six national CROs.

The name of the Peruvian Association of CROs is Asociación Peruana de Organizaciones de Investigación Clínica por Contrato, abbreviated as APOICC. It was established in May 2010. It has no website yet and the members are not known.

Peru is the only country in our selection of which we could access precise information on the number of clinical trials that have been subcontracted to CROs. In 2009, 94 out of the total of 134 trials conducted in Peru were executed by CROs which is 70% of the total (74 by international

CROs and 20 by national CROs). In Table 11, the number of trials conducted by multinational CROs is listed. Only four CROs (PPD, Quintiles, ICON and PAREXEL) together carry out 70% of all clinical trials conducted by multinational CROs.

Table 11: Number of clinical trials executed by multinational CROs, Peru 2009

CROs	No. of clinical trials
PPD Peru S.A.C.	19
Quintiles Perú S.R.L.	14
ICON Clinical Research Perú S.A.	10
PAREXEL International Perú S.A.	10
Kendle Perú S.R.L.	6
INC Research (previously MDS Pharma Services)	5
I3 Latin America Perú S.A.	2
World Wide Clinical Research del Perú S.A.C.	2
Covance Perú Services S.A.	1
Genexion S.A.C.	1
Pharmaceutical Research Associates Perú S.A.C.	1
Pharmanet Perú S.A.C.	1
Rps Perú S.A.C.	1
Psi cro Perú S.A.C.	1
Aaipharma S.A.C.	1
Worldwide clinical trials Perú SRL-W.C.T. Perú SRL	1
Total	76

In Table 12, the number of clinical trials conducted by national CROs is listed. IMPACTA is responsible for half of the clinical trials that involve a national CRO. Gotuzzo and Associates is only responsible for recruiting the principal investigators and communicating with the regulatory agency, which could indicate that the sponsors or the CRO is subcontracting other activities.

Table 12: Number of clinical trials executed by national CROs in Peru, 2009

CROs	No. of clinical trials
Asociación Civil IMPACTA, Salud y Educación	10
Gotuzzo Asociados S.A.C.	6
Investigaciones Médicas en Salud (INMENSA)	2
Consultores Asociados para el Desarrollo de la Salud. Ds-Consult S.A.C.	1
Peruvian Clinical Research S.A.C.	1
Total	20

Four of these national CROs have acquired considerable influence in the clinical trial industry by creating ties to authorities, universities and the pharmaceutical industries. These CROs are described in Box 3.

Box 3: Peruvian CROs with influential ties

DS-Consult. This CRO was established in 1995 and its executive director is a prominent pediatrician, Dr. Eduardo Salazar Lindo. Dr. Salazar is also a researcher and advisor to the Panamerican Health Organisation on pediatric diarrhea. He occupied high administrative positions at a prestigious private university, Universidad Peruana Cayetano Heredia, and in government, as director of the regulatory agency (INS).

IMPACTA. This NGO¹²⁸ was created in 2000 to conduct clinical, biomedical and public health research. It specialises in studies of HIV and AIDS and other sexually transmitted diseases. It collaborates with the Universidad Peruana Cayetano Heredia and with the Peruvian branch of the US Naval Academy Research Institute on Tropical Medicines (NMRCD). Its executive director, Dr. Jorge Sánchez, occupied leadership positions at the national programme for HIV and AIDs and has a great deal of influence among associations of patients with HIV and AIDs.

Gotuzzo Asociados. This company was created in 2004 and it is the legal representative for the pharmaceutical company Takeda Global Research. The director is D. Eduardo Gotuzzo Herencia, a recognised physician at national and international levels, with multiple publications on infectious diseases published in both national and international literature. Since 1995 he has been the director of the Tropical Disease Research Center 'Alexandre von Humbolt' at the Universidad Peruana Cayetano Heredia. He has been part of national commissions, including the commissions on tuberculosis and on AIDs. He was also medical research director at Pharmacia & Upjohn.

INMENSA. Created in 2007, it is an NGO very similar to IMPACTA.

Table 13 presents the clinical trials in Peru implemented by phase crossed by types of CRO. All Phase IV trials are implemented by national CROs and national CROs are also implementing Phase I and Phase II studies.

Table 13: Phases of clinical trials implemented by international and national CROs in Peru, 2009

Clinical Trial Phases	International CRO	National CRO	Total
I	1	2	3
II	17	3	20
III	58	9	67
IV	0	6	6
Total	76	20	96

The original data collection plan for the current study included an analysis of preferred working relationships between pharmaceutical companies and CROs. We could only access this information for the case of Peru (see Table 14). Most pharmaceutical companies work through one CRO or a maximum of two, except Boehringer, which had used four CROs, but CROs are contracted by several pharmaceuticals; Quintiles works with nine different companies, PPD with five, and ICON with four.

¹²⁸ This organisation is registered as not-for profit, which enables them to apply for certain grants and avoid taxes. However, they function as a commercial business with accordingly (high) salaries.

Table 14: CROs used by different research sponsors, Peru 2009

Sponsors	CROs
Takeda Global Research	Gotuzzo Asociados
Boehringer	PAREXEL Pharmaceutical Research PPD Quintiles
GlaxoSmithKline	PPD Quintiles
Angem	PPD Quintiles
Sanofi	ICON Quintiles
Astra Zeneca	ICON
Daiichi Sankyo	ICON Quintiles
Astellas	ICON PPD
Eli Lilly	PAREXEL Quintiles
Actelion	Kendle
Phenomix	INC
Otzuka	Kendle
Genentech	PPD
Tibotec	Quintiles
Merck Sonoro	Quintiles
Hoffman La Roche	Quintiles
Curetech	Genexion
Schering Plough	World Wide Clinical Trials
Pfizer	World Wide Clinical Trials
NIH	IMPACTA

The regulatory agency in Peru has a registry of CROs, which is exceptional compared to other countries. The percentage of protocols presented by CROs to regulatory agencies for approval is about 34%: 36 international and 10 national CROs out of a total 134 protocols.

4.5 India

CRO market in India

India has become an important clinical trial location in recent years, as it possesses the unique combination of low costs and an overwhelming population of over 1.15 billion people. India not only has a genetically diverse population compared with western countries, but it also has a population with a very large pool of different acute and chronic disease conditions. India is able to offer significant cost savings compared with conducting clinical trials in western countries. Phase I trials are approximately 50% cheaper than western equivalents, while Phase II and Phase III are 60% less expensive.¹²⁹

¹²⁹ Emerging Clinical Trial Locations Market dynamics and the changing healthcare and regulatory environment, Business Insights, July 2009.

Lack of access to even the most basic health care amongst the marginalised and socially disadvantaged population leads to the following motivations to participate in a clinical trial:

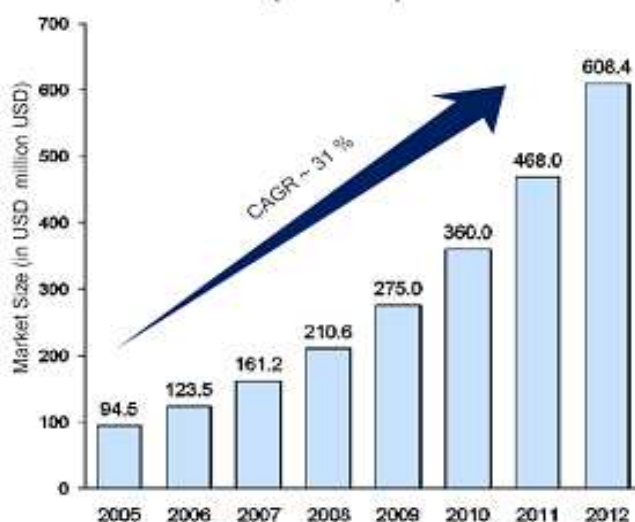
- 15% stated that they entered the trial because they were looking for a cure.
- 13% were looking for “observed benefits”.
- 15% were looking for a better treatment.
- 16% were looking for higher quality care.
- 10% were looking for free medication and medical care.
- 15% said the doctor advised them to enter the trial.
- 5% said they entered the trial to receive money for participation.
- 11% said they entered the trial to help advance scientific knowledge.

Source: results of a CRO initiated survey of trial participants¹³⁰

India offers high patient enrolment rates, which implies that clinical trials can be finished sooner, meaning that the profits of patent exclusivity can be enjoyed for longer.¹³¹ But also the availability of high-quality clinical and research manpower who are proficient in English, the expertise in all therapeutic areas, a highly enabled IT infrastructure and increased intellectual property protection make India attractive.

Although every article about India and clinical trials mentions the booming market for clinical trials, there is a slight difference in the expected growth figures. A study by research firm RNCOS Industry Solutions estimates that the clinical trial outsourced market in India will grow at a compound annual growth rate of at least 30% between 2010 and 2012 to around \$600 million.¹³² An analysis of the Indian CRO market by Zinnov Management Consulting dated from 2008, projected a CRO market of \$0.36 billion by 2010 (see Figure 6). A more recent source states that the CRO market is \$0.3 currently, with a projection of \$1 billion by 2014.¹³³

Figure 6: Growth of Outsourced Clinical Trial Market in India (2005-2012)



Source: Zinnov Management Consulting¹³⁴

¹³⁰ Srinivasan. Survey by CRO Excel Life Sciences in 2008, 2009, p. 10. 525 patients from 40 sites had been interviewed. Most were treatment naive (untreated for the condition for which the drug was being tested) when they entered the trial.

¹³¹ D. Normile. The Promise and Pitfalls of Clinical Trials Overseas, Science, 10 October 2008.

¹³² Radhika Pandeya. New code for inspecting human drug trials Mint, New Delhi, 10 November 2010.

¹³³ V Moza. Express Pharma Online, Opportunities and Challenges for Clinical Research in India, 2005, <http://www.expresspharmaonline.com/20051215/ipcspecial05.shtml> (11 June 2010).

¹³⁴ Zinnov Management Consulting Pvt Ltd, Pharmaceutical Offshoring Landscape – A Syndicated Report, 2008.

India is said to participate in seven percent of global Phase III and 3.2 percent of Phase II trials.¹³⁵ The growth rate of the Indian clinical sector has been estimated as two and a half times that of the global market.¹³⁶

Today, most of the big pharmaceutical companies are conducting multi-centric trials in India (where an Indian hospital is a small part of the overall trial), with some of them operating for more than 15 years in India. Eli Lilly and Pfizer were one of the earliest big pharmaceutical companies to conduct clinical research in India, and began their captive operations in 1995. This was followed by a clutch of other companies in the early to mid-2000s, like, Sanofi-Aventis, Bayer, Novartis Astra Zeneca and Johnson & Johnson. The last two to three years have seen the increased presence of other big pharmaceutical companies, like, Merck GlaxoSmithKline, Bristol-Myers Squibb and some of the larger biotechnology companies, like Amgen and Biogen Idec.¹³⁷ However, all leading global CROs have also set up services in India (see Table 6). India has about 30 established major international CROs and nearly 100 CROs of reasonable size that are currently involved in conducting clinical trials in the country.¹³⁸ (See also Annex 3: List of CROs in India).

It is not clear what percentage of the clinical trials in India is outsourced to CROs. The number of CROs established in India suggests a major role of CROs in carrying out trials.

Regulatory framework

The Indian regulatory authority is called the Drug Controller General of India (DCGI). The DCGI heads the Central Drugs Standard Control Organisation (CDSCO), which is India's main regulatory body for clinical trials; no company in India can initiate any clinical trial of a new drug without prior approval from CDSCO.¹³⁹ Clinical trials are permitted in the country as per Rule 122DA, 122DAA, 122DB 122E and Schedule Y of Drugs & Cosmetic Rules.¹⁴⁰ The Indian Council of Medical Research (ICMR) is funded by the Government of India and promotes biomedical research in the country through intramural as well as extramural research.

The DCGI has started adapting itself to meet the demands of the industry. Some of the recent initiatives by DCGI underscore the fact that the regulatory agency is becoming more pro-industry.¹⁴¹ This is especially true for the 2005 changes in the law and the reduced timelines for approvals (see below). However, some new registration requirements being set up and some new laws (that are still to be tabled in Parliament) are clearly in the interest of Indian patient's safety.

Of the changes in the law to promote the clinical trials industry that have already taken effect, it is important to mention the 2005 product patent protection law and the 2005 revision of schedule Y of the Drugs and Cosmetics Act of India. The latter allowed pharmaceutical companies to begin Phase II and Phase III trials concurrently with trials of the same phase conducted abroad, thereby significantly reducing clinical development time. Under the old rule, Phase II and III trials were only permitted after those phases were completed elsewhere and this was to create a "phase lag"

¹³⁵ Viveka Roychowdhury, "CROs evolve to a new level", Express pharma, 1-15 April 2010, <http://www.expresspharmaonline.com/20100415/market01.html> (31 January, 2011).

¹³⁶ V. Roychowdhury. Express Pharma Online, CROs evolve to a new level, 2010, <http://www.expresspharmaonline.com/20100415/market01.shtml> (11 June 2010).

¹³⁷ <http://www.biospectrumindia.com/makesections.asp/1009082.asp>
<http://pharmtech.findpharma.com/pharmtech/article/articleDetail.jsp?id=506157&sk=&date=&pageID=3> (11 June 2010).

¹³⁸ U. Sahoo, F. Kermani, PharmTech, India's CRO sector on the rise, 2008, <http://pharmtech.findpharma.com/pharmtech/article/articleDetail.jsp?id=506157&sk=&date=&pageID=3> (11 June 2010).

¹³⁹ Directorate General of Health Services, Ministry of Health and Family Welfare, Government of India.

¹⁴⁰ Government steps in to speed growth: <http://www.biospectrumindia.com/makesections.asp/1009082.asp>

¹⁴¹ Government steps in to speed growth: <http://www.biospectrumindia.com/makesections.asp/1009082.asp>

between India and the rest of the world to prevent foreign pharmaceutical companies from using Indians to test their unproven therapies.¹⁴²

Another tipping point was the change in patent law in 2005, which removed a crucial obstacle for pharmaceutical companies to invest in India. India became a signatory of the product patent regime after signing the World Trade Organisation (WTO) agreement on Trade Related Intellectual Property Rights (TRIPS). Until then, Indian pharmaceutical companies could manufacture drugs (generics) using reverse engineering processes. But with the imposing of the product patent, this was no longer allowed and Indian pharma companies were forced to engage in more research and development. This resulted in the opening up of the clinical trials sector in India. This change in patent law in 2005 also encouraged the western and other pharmaceutical companies to invest in clinical trials in India, as there was more protection to their intellectual property rights under the new law.¹⁴³ This led to an opportunity for the CROs to take up clinical research on behalf of Indian as well as international clients.

Prior to 2005, Indian CROs were concentrating on bioequivalent and bioavailability studies (testing generics). After 2005, India saw the emergence of a booming clinical trial industry with CROs diversifying their services to the clinical research field.¹⁴⁴ Data management, site management, patient recruitment, data analysis and pharmacovigilance (studies related to adverse effects) were added to the existing array of services that were being provided by the Indian companies. With the booming of the market, international CROs also started their operations.

To reduce the timelines of the approval procedures, a single window clearance for regulatory approval of clinical trials is being implemented in order to reduce the approval procedure.¹⁴⁵ Protocols from the US, UK, EU and Japan will get fast-track approval of six to eight weeks. The government will grant a license to import supplies within two weeks of the application being made. The DCGI has also promised that local EC review will be completed in six to eight weeks.¹⁴⁶

Further important measures to establish India as a reliable clinical trial destination and to build up a more robust regulatory framework are discussed in the following paragraph.

The launch of the mandatory registration of clinical trials in the Clinical Trials Registry of India (CTRI) has been an important step towards regulating the clinical trial sector in India.¹⁴⁷ CTRI provides transparency about the trials being conducted in India.¹⁴⁸ Mandatory registration with the CTRI website came into effect in June 2009 and saw a huge leap in the number of trials being

¹⁴² R. Maiti and M. Raghavendra. Clinical Trials in India. Pharmacological Research 56. 2007 (1-10).

¹⁴³ DT Kumaravel, DS Murugan, Express Pharma Online, Preclinical CROs in India : the next in thing?, 2009, <http://www.expresspharmaonline.com/20090731/management04.shtml> (11 June 2010); C Grace, DFID Health Systems Resource Centre, The Effect of Changing Intellectual Property on Pharmaceutical Industry Prospects in India and China: Considerations for Access to Medicines, 2004, http://www.dfidhealthrc.org/shared/publications/Issues_papers/ATM/Grace2.pdf (11 June 2010); V Raina. Doing cancer trials in India: opportunities and pitfalls, Annals of Oncology, 16 (2005), p.1567-8; D McDonald, Applied Clinical Trials, Demystifying India, 2009, <http://appliedclinicaltrialsonline.findpharma.com/appliedclinicaltrials/article/articleDetail.jsp?id=615145&sk=&date=&pageD=2> (Cited 11 June 2010); VVLN Sastry. Pharmabiz, Potential and trends of CRO industry: An analysis, 2004 <http://www.pharmabiz.com/article/detnews.asp?articleid=23127§ionid=46> (11 June 2010).

¹⁴⁴ PK Julka. Clinical Trials in India: Dilemmas for Developing Countries, The Monitor, 21 (2007), p.69-71.

¹⁴⁵ India: Preferred Destination for Outsourcing Clinical Trials Express Pharma October 1, 2010

¹⁴⁶ Srinivasan (2009)

¹⁴⁷ Mcdonald D, Applied Clinical Trials, "Demystifying India", 2009, <http://appliedclinicaltrialsonline.findpharma.com/appliedclinicaltrials/article/articleDetail.jsp?id=615145&sk=&date=&pageD=2> (Cited 2010 June 11).

¹⁴⁸ National Institute of Medical Statistics, ICMR, "Clinical Trials Registry India", 2007, <http://www.ctri.in/Clinicaltrials/index.jsp> (2010 June 11).

registered on the site.¹⁴⁹ The registry seeks information about 20 items that have been mandated by the WHO's ICTRP (International Clinical Trial Registry Platform). In addition to these 20 items, the registry is also seeking additional information on the principal investigator, ethics committee, DCGI clearance, duration, site and phase of the trial and also some information regarding the methodology adopted by the study.²⁰ The registry is available on the public domain and has contributed tremendously towards improving the transparency of the sector. According to the clinical trials registry of India, a total number of 1,158 trials have been registered in India as of 4 August 2010.

Very recently, in November 2010, a new clinical trial inspection programme has started by India's main regulatory body for clinical trials, CDSCO. CDSCO issued new guidelines¹⁵⁰ for inspecting clinical trials that are outsourced to India in an effort to ensure the safety of people who participate in such trials.¹⁵¹ CDSCO has set up an inspection programme to verify if clinical trial investigators and sponsors are complying with the safety guidelines listed in the Drugs and Cosmetics Act, and also to sign off on the authenticity of data generated by the trial.¹⁵² The new guidelines – which specify who will conduct the inspection, how it will be conducted and the documents required from trial sponsors and investigators – are expected to make such inspections the norm rather than the exception, as they currently are. CDSCO's drug inspectors have been trained by the US Food and Drug Administration.

This new inspection programme has drawn attention to CROs and this raised the question by a parliamentary committee of the ministry of health why CROs have been permitted to conduct trials when they have no legal status in India. They are not mentioned anywhere in the Drugs and Cosmetics Act and there has been no notification to clarify their status either. "The committee wants to know where they have come from, because CROs are not defined by law in India. So, how are they being given permissions to conduct trials?" said C.M. Gulhati, editor of the medical journal, *Monthly Index of Medical Specialities*. "And this is the bigger question because nearly 90% of the trials are being conducted by CROs".¹⁵³

Furthermore, to bring uniformity and control, it is proposed to register all ethics committees with ICMR. Ethics committees will be accountable to respond to enquiries from the regulatory agency to ensure that the conducted global trial is suitably monitored and in compliance with Indian and international GCP guidelines.¹⁵⁴ Other plans are: registration of investigation sites and investigators; GCP training of investigators by an accredited body; penal provisions for violation of clinical trial regulations.¹⁵⁵

The ICMR has made draft guidelines – still to be tabled in the Parliament – for compensation to participants for research-related injury in India, which state that "compensation will have to be paid to a child injured *in utero* through the participation of the parent in clinical research". The draft says compensation has to be paid, irrespective of whether the injury was foreseeable/predictable or not and whether the research participant had consented in writing to participate in the research study. Compensation will have to be provided to the participants when temporary or permanent injury

¹⁴⁹ Chatterjee P, "Clinical trials in India: ethical concerns", *Bulletin of the World Health Organization*, 86 (2008), p.577-656.

¹⁵⁰ <http://www.cdsc.nic.in/CLINICAL%20TRIAL%20INSPECTION%20PROGRAMME%20OF%20INDIA.pdf>

¹⁵¹ Aims of the program are: a) To verify GCP compliance to protect the rights, safety and well being of the subjects involved in clinical trial, b) To verify the credibility and integrity of clinical trial data generated and c.) To verify the compliance with various regulatory provisions as per Drugs & Cosmetics Rules.

¹⁵² They ordered the first audit at the Bhopal Memorial Hospital and Research Centre (BMHRC) for US-based firm Theravance Inc. Quintiles Transnational Corp., a CRO, carried out the trial.

¹⁵³ Radhika Pandeya, New code for inspecting human drug trials *Mint*, New Delhi, 10 November 2010.

¹⁵⁴ India: Preferred Destination for Outsourcing Clinical Trials, *Express Pharma*, 1 October 2010.

¹⁵⁵ India: Preferred Destination for Outsourcing Clinical Trials, *Express Pharma*, 1 October 2010.

occurs due to the clinical study.¹⁵⁶ The Union government is on the verge of amending Schedule Y in a bid to strengthen the pharmacovigilance programme by making the protocol for post-marketing of drugs more stringent in India.

For an overview of the main legislation regarding clinical trials in India, see Table 15.

Table 15: Main regulatory developments regarding clinical trials in India

Institution and year	Content
Drug Controller General of India, 1988	Schedule Y of the Drugs and Cosmetics Act of India
Indian Council of Medical Research, 2000	Adoption Ethical Guidelines for Biomedical Research. http://www.icmr.nic.in/buoc2000.htm
Drug Controller General of India, 2005	Revision of schedule Y of the Drugs and Cosmetics Act of India to remove “phase lag” and thereby reducing clinical development time
Central government, 2005	Signing of WTO TRIPS and corresponding change in patent law
Indian Council of Medical Research National Institute of Medical Statistics, 2007	Launch Clinical Trial Registry of India
Indian Council of Medical Research National Institute of Medical Statistics, 2009	Registration with CTRI becomes mandatory
Central Drugs Standard Control Organisation, or CDSCO, November 2010	A new clinical trial inspection programme with new guidelines ¹⁵⁷ for inspecting human clinical trials for drugs in an effort to ensure the safety of people who participate in such trials ¹⁵⁸

¹⁵⁶ India: Preferred Destination for Outsourcing Clinical Trials, Express Pharma, 1 October 2010.

¹⁵⁷ CDSCO. ‘Guidance on clinical trial inspection’, 1 November 2010
<http://www.cdscsco.nic.in/CLINICAL%20TRIAL%20INSPECTION%20PROGRAMME%20OF%20INDIA.pdf> (accessed 7 February 2011)

¹⁵⁸ Aims of the program are: a) To verify GCP compliance to protect the rights, safety and well being of the subjects involved in clinical trial, b) To verify the credibility and integrity of clinical trial data generated and c.) To verify the compliance with various regulatory provisions as per Drugs & Cosmetics Rules.

5 Ethical concerns associated with offshoring and outsourcing

5.1 Introduction

As we have already discussed, clinical trials inherently bring up many ethical issues irrespective of where the trials are conducted or who is conducting them. This is because they involve exposing humans to health risks for the health benefits of other humans in the future. Clinical trials are crucial for the development of new drugs that might save millions of lives in the future. But certainly not all clinical trials serve this 'higher' goal of health for all. Many Phase IV trials are done for the purpose of marketing a new drug, and other trials are of products that may add little to the existing therapeutic arsenal (including the so called 'me too' drugs). Other trials are intended to develop so called 'line extensions' of an already existing drug (e.g. by changing the dosage form of the drug) as to extend a pharmaceutical company's patent and thus, profits. Many interests – both economic and non-economic – play a role in clinical trials: those of the sponsor, of the principal investigators, possibly that of the CROs, of participants and of future patients. These interests are weighed time and again, and create so-called ethical 'minefields' in which participants may suffer.

Although clinical trials are risky in themselves, in this report we focus on the risks of having CROs conduct a risky business (clinical trials) in a risky environment (non-traditional trial regions). However, the risks associated with the trial, the location and the actors involved are not always easily separated, although we attempt to do so in this chapter. First the ethical risks of offshoring are described, followed by the ethical risks of outsourcing.

5.2 Ethical risks associated with offshoring

It is widely acknowledged that the ethical risks of clinical trials increase when they are moved to non-traditional regions.¹⁵⁹ Compared to Western Europe and North America – the traditional trial regions – these regions are often less regulated, and have a relatively vulnerable population (less economic and educational development), and a less developed healthcare system. In addition, it is not always clear that the primary reason for conducting a trial in such countries is to eventually market the drug in that country so the local population can benefit; a major reason cited for the emergence of new trial hubs is the magnitude of volunteer pools, higher participant enrolment rates

¹⁵⁹ Wemos, *The Globalization of Clinical Trials: Testimonies from Human Subjects* (Amsterdam: Wemos, 2010); K. B. O'Reilly. "Outsourcing clinical trials: Is it ethical to take drug studies abroad?" *Amednews*, 7 September 2009, <http://www.ama-assn.org/amednews/2009/09/07/prsa0907.htm> (22 December 2010); H. T. Shapiro & E. M. Meslin. "Ethical issues in the design and conduct of clinical trials in developing countries". *New England Journal of Medicine*, Vol. 345, No 2 (2001), p. 139-142; S. W. Glickman, J. G. McHutchison, E. D. Peterson, C. B. Cairns, R. A. Harrington, R. M. Califf, and K. A. Schulman. 'Ethical and Scientific Implications of the Globalization of Clinical Research'. *New England Journal of Medicine* Vol. 360, No. 8 (2009) p.816-823.

and thus quicker trials. This suggests that vulnerable patient groups are used for the benefit of western health care.

In an earlier SOMO report, the ethical concerns associated with offshoring were summarised as follows:¹⁶⁰

- ❑ Failure to submit a protocol to an independent ethics committee
- ❑ Failure to obtain informed consent (see Glossary)
- ❑ Unduly influencing people to participate in research (including financial incentives and limiting or increasing access to medical care)
- ❑ Involvement of trial subjects from a vulnerable population while the tested medicine will not be of any benefit to the population, because the medicine will not be marketed in the country or will not be affordable for the patients
- ❑ Lower ethical standards than in the EU (no application of Declaration of Helsinki); for example, no justified use of placebos
- ❑ Testing of medicines that are not a major concern for the country
- ❑ No post-trial arrangements included in the study protocol (i.e. the end of the trial is also the end of the treatment)
- ❑ Limited framework for regulatory oversight/limited regulatory system
- ❑ Limited frameworks for ethical review
- ❑ Ethics committees are not properly established; ethics committee is not independent of the research team and sponsor, conflicts of interest
- ❑ Lack of transparency: no overview or details of clinical trials available
- ❑ The instruments to enforce GCP do not protect trial subjects sufficiently from inadequate reporting of serious adverse events (see Glossary)
- ❑ Failure to provide fair compensation by insurance or indemnity.

Despite these problems, medicines that have been tested in non-traditional trial regions find their way to Western markets while there are few inspections by overseas regulatory authorities such as EMA or FDA (although these are increasing). The regulatory authorities in Europe are not equipped yet to check compliance of these trials with GCP and international ethical standards.

The following paragraph describes some of the ethical concerns perceived and observed by the practitioners that were interviewed in the case study countries: Brazil, Argentina, Peru and India. This context analysis will then serve as a basis to interpret and understand the risks associated with the conduct of CROs in these contexts in paragraph 5.3.

Vulnerable population and informed consent

Interviewees in the Indian as well as the Latin American case studies have expressed their concern over the vulnerability of an important share of the clinical trial participants in their countries. This vulnerability is caused by poverty, illiteracy and limited access to health care. CRO representatives interviewed in Brazil have indicated that the majority of Brazilian trial participants belong to the lower social-economic class (interview with advisor of regulatory affairs at multinational CRO, Brasília, 10 August 2010; interview with head of clinical research at national CRO, Sao Paulo, 28 July 2010).

¹⁶⁰ Irene Schipper & Francis Weyzig, "Ethics for drug testing in low and middle income countries: Considerations for the European Market Authorisation", SOMO, February 2008.

In Brazil, the majority of the clinical trial participants are users of the Sistema Único de Saúde (SUS), the Brazilian healthcare system for the uninsured. Approximately 70% of the population uses this system. One principal investigator who was interviewed indicated that many clinical trial participants mainly participate in a trial to get a good check up, as they receive better treatment in a trial context than in a public hospital (Brasília, 24 August 2010). In search of adequate health care, these participants may underestimate the risks of participation in a clinical trial.

The vulnerability of trial participants was also pointed out in the India context: Indian trial participants are often highly vulnerable due to poverty and illness. As such, they are not in a position to refuse treatment and seek treatment outside the trial centre. The vulnerability of the majority of the trial participants in the case study countries has important consequences for the meaning of informed consent. In several interviews conducted in India, it was pointed out that an informed consent form has limited value in the Indian context, as most of the patients are illiterate and cannot understand the informed consent form.

The following quote from an interview with a clinical trial expert in India, illustrates this:

“... I will call all clinical trials in India as ethically vulnerable as none of us in India are going for clinical trials but for treatment. But yet, patients get enrolled in trials. In our settings, doctors instead of using the word trial use the word research. Then the whole situation changes and there is lot more respectability for the ‘researcher’ and the patient thinks that the doctor will do the best for them. They are told ‘here is a wonderful new drug which is costly but I am giving it to you for free’ and who will not fall for that? The word for our sector will be CARE CUM TRIAL”... Expert on clinical trial sector (New Delhi, 21 May 2010).

Participating in a clinical trial can thus be the only option for accessing health care, or an attractive alternative for malfunctioning healthcare systems for vulnerable shares of the population in non-traditional trial regions.

The quote above also points to the hierarchical doctor–patient relationship that is typical for India and other emerging trial regions. Doctors enjoy considerable authority, and thus many patients will follow their doctor’s advice without question. This contrasts with Western Europe, for instance, where second opinions are becoming more common. However, these doctors, when acting as a principal investigator for a clinical trial, may have a financial interest in recruiting as many trial participants as possible, which makes the abuse of their authority tempting.

Training of investigators and the use of independent third party witnesses are both used by CROs and sponsors to address these concerns. Several clinical trial practitioners who were interviewed indicated that CRO staff and principal investigators are specifically trained to deal with vulnerable sections of the trial population (CRO President, Mumbai, 28 May 2010; Clinical Research Associate CRO, Mumbai, 12 May 2010; Director of Ethics and Legal Affairs at CRO, ‘Ethica’, interview 8 October 2009). They are trained to spend more time with these participants, to explain the study’s benefits and risks, and to ensure that the consent process is truly informed. This type of procedure was confirmed by interviews with pharmaceutical companies (see Chapter 6). Furthermore, often a third party witness is required to be present during the informed consent process for illiterate participants.

However, as already indicated, other interviewees expressed their concern about the way in which studies are conducted on vulnerable participants in the case study countries, and fear a gap between policy and practice:

“... implementation of these [ethical, authors] standards is extremely poor. Breaches do happen. In a country where one teacher can give permission to conduct trials on his students, what can you expect about the degree of implementation of informed consent and all? It might look all good on paper, but in reality things might be entirely different”...
Expert on clinical trial sector (New Delhi, 21 May 2010).

Whether the informed consent process has been in line with ethical guidelines is not verified by authorities with participants themselves. Because of privacy considerations for the trial participants, monitoring of the informed consent process by authorities and ethics committees stops at the principal investigator. Principal investigators collect the informed consent forms and authorities and some ethics committees check whether they are signed, but the understanding of participants is not independently verified.

There have been events documented of unethical conduct of clinical trials in India, Argentina, Mexico and Costa Rica in which participants failed to understand that they were participating in a trial.¹⁶¹ Furthermore, there have been incidents of serious lapses that occurred while recruiting patients for studies and also reports of how patients are lured into participating in studies by offering them monetary benefits.¹⁶²

As one example, there was an incident in which a patient was reportedly being part of many bioequivalence studies conducted by different CROs. Critics argue that voluntary informed consent in many situations is not really voluntary or informed, as patients are left with no other opportunity than to be part of the study.¹⁶³

Another example is provided by Rajan in his case study of one of the oldest CROs in India, which has actually passed two FDA audits. The case study signals the inadequacies that are present even when a CRO claims that all guidelines are being followed. For instance, ‘literate’ participants need not necessarily be literate in English, while in this case there was only a single bulletin board in English explaining the disadvantages of participating in a trial.¹⁶⁴ Problems with the comprehensiveness of informed consent forms and inadequate translations of informed consent forms were also highlighted in an interview with several members of an ethics committee in Buenos Aires (29 April 2010).

Insufficient oversight

Authorities

Interviews in India and Brazil indicated a lack of oversight of clinical trials by the national authorities. In India, there are considerable concerns about the ability of regulatory authorities to

¹⁶¹ See for example S. Nundy and C.M. Gulhati CM. A new colonialism? Conducting clinical trials in India” The New England Journal of Medicine, 352(2005), p.1633-6; M. Singh, Should Clinical Trials Be Outsourced?, Time, 2008, <http://www.time.com/time/health/article/0,8599,1830334,00.html#ixzz0qWLaa1xl> (11 June 2010).

¹⁶² K.S. Rajan, “Experimental Values: Indian Clinical Trials and Surplus Health”, New Left Review. 45 (2007), p. 67-88; S. Nundy, C.M. Gulhati, “A new colonialism? Conducting clinical trials in India”, The New England Journal of Medicine, 352(2005), p.1633-6; National Institute of Medical Statistics, ICMR., “Clinical Trials Registry India”, 2007, <http://www.ctri.in/Clinicaltrials/index.jsp> (11 June 2010); S.K. Gupta. “India As An Emerging Destination for Outsourcing Clinical Research”, (ppt presentation) Institute Of Clinical Research, India.

¹⁶³ National Institute of Medical Statistics, ICMR., “Clinical Trials Registry India”, 2007, <http://www.ctri.in/Clinicaltrials/index.jsp> (11 June 2010).

¹⁶⁴ K.S. Rajan. “Experimental Values: Indian Clinical Trials and Surplus Health”, New Left Review. 45 (2007), p. 67-88.

keep up with the explosive growth that has occurred in the clinical trials sector. In the literature, it is often mentioned that the Drug Controller General of India (DCGI) is understaffed and lacks the expertise to evaluate complex protocols and heavily depends on the Indian Council of Medical Research (ICMR) for expertise.¹⁶⁵ Interviewees pointed out that, even though the ICMR has issued important ethical guidelines, the council lacks enforcement authority. The following two quotes from our interviewees raise compelling concerns over DCGI functioning:

“...I will sum up DCGI like this. It is understaffed, it is highly incompetent and most importantly it is a highly corrupt organisation.” Ethics committee member (Mumbai, 1 June 2010)

“...Basic problem in India is according to me is neither the CROs nor the client companies. The biggest culprit is the agency who is making rules and regulations or the drugs regulatory system, whatever you call them, DCGI or anything. If CROs are doing wrong it is also because the Government is allowing them to do so. They are only using the loopholes in the system. What is to be done is a thorough review of DCGI regulations.” Expert on clinical trial sector (New Delhi, 21 May 2010)

In Brazil, the principal investigators that were interviewed highlighted the lack of monitoring of trial sites by the national authorities. They indicated that they had never been audited by the Brazilian authority ANVISA, but one of them had been audited by the American FDA (Coordinator of research, São Paulo, 17 August 2010; Principal Investigator, Brasília, 24 August 2010).

The written response of pharmaceutical company GlaxoSmithKline to our interview questions provides a more positive view on monitoring by authorities in non-traditional trial regions:

“Inspections of investigators, clinical research organizations, independent ethics committees/Institutional Review Boards and sponsors of clinical trials are also carried out by regulatory authorities to ensure the safety of trial participants, the quality of data and that trials are conducted according to Good Clinical Practice. During 2009 there were more than 75 such inspections of GSK and investigators used by GSK to conduct clinical trials. These included inspections from regulatory authorities in Africa, Asia and Latin America.” (Written interview GlaxoSmithKline, 7 December 2010)

The collected data from Peru indicates that the national agency Instituto Nacional de Salud (INS), the regulatory agency responsible for authorizing and monitoring clinical trials, conducts clinical trial site inspections. During 2009, the INS conducted 42 inspections of research sites. Unfortunately we are unable to assess what percentage of trial sites was inspected that year, as the total number of trial sites active in Peru in 2009 is unknown.

18 inspections involved clinical sites monitored by CROs. Table 16 presents the results of the inspections to these trial sites monitored by CROs. The table shows that most of the problems (19) related to insufficient protection of the research subjects, including inappropriate reporting of adverse events; followed by deficiencies in the performance of the research team (10), paperwork errors (9), problems with the research product (7), problems with the infrastructure of medical equipment (6), lack of compliance with regulatory and monitoring mandates (6), and problems with informed consent (4).

¹⁶⁵ S. Nundy, C.M. Gulhati, A new colonialism? Conducting clinical trials in India”, *The New England journal of medicine*, 352(2005), p.1633-6; National Institute of Medical Statistics, ICMR, Clinical Trials Registry India, 2007, <http://www.ctri.in/Clinicaltrials/index.jsp> (11 June 2010); G. Mudur G, “India plans to audit clinical trials”, *British Medical Journal*, 331(2005); p.1044.

Table 16: Problems observed during 18 INS inspections to clinical trial sites monitored by CROs, Peru, 2009

	Type of problem	Frequency
Informed Consent (4)	Failure to register when (time) the patient signs the consent form	01
	Trial-related activities initiated before obtaining the informed consent	01
	Absence of information justifying the lack of parents' signature of informed consent in pediatric clinical trials	01
	Evidence that the trial participant had not understood the informed consent form	01
Failure to document key events (9)	The medical history does not include the time when a clinical consultation or exam was performed on the trial participant	01
	Follow-up visits are not registered in the patient's medical record	01
	The medical record does not include information about the existence of informed consent	01
	The medical record does not include the results of laboratory tests	01
	Interns (and not the researchers) sign the updates in the medical record	01
	The medical record does not include information on the administration of chemotherapy	01
	The medical record does not include clinical data	01
	The medical record does not mention the provision of health education and the dispensation of contraceptives	01
	Lack of correlation between the information in the medical record and the information in the case report forms (CRF)	01
Patient's Safety (19)	Failure to report adverse events in a timely manner to the regulatory agency (INS)	05
	Failure to report adverse events to the INS	03
	Incorrect information in adverse events forms	02
	The accreditation offered by the Ministry of Health to all health establishments has expired	02
	Protocol amendments are not reported to the INS	01
	The centre failed to comply with the instruction of the sponsor to interrupt the study	01
	Biological samples are obtained in violation of the protocol	01
	A serious psychiatric adverse event is not evaluated by a specialist	01
	Abnormal laboratory results are not treated in accordance with the study protocol	01
	Failure to inform ethics committee and the INS about adverse events	01
	Failure to inform the INS about safety events	01
Research product (7)	Expired research products	05
	Incomplete registers of temperature control	02
Infrastructure and medical equipment (6)	Lack of air extractors and safety measures as indicated in the protocol of tuberculosis studies	02
	Safety and confidentiality of research records not guaranteed	01
	Use of public laboratories without prior contractual arrangement	01
	Medical equipment not calibrated	01
	No potable water for processing biological samples	01
Problems related to lack of compliance with	Monitoring subcontracted to another CRO without informing the INS	01
	Failure to contract with tertiary hospitals for the provision of services to treat adverse events	01

regulations and monitoring responsibilities (6)	Patient recruitment occurs in centres not registered with the INS	01
	There is no monitoring record at the beginning of the study	01
	The final report is not shared with the INS	01
	The space for administration, archival and storage of biological samples is not registered with the INS	01
Research team (10)	The research team does not include a specialist in the area of the clinical trial being conducted that could provide services to the participants	02
	There is no curriculum vitae of the research team	02
	The principal investigator is not at the centre	01
	There is incomplete training to manage the research product and emergencies	01
	Lack of training in basic elements (Peruvian legislation, Good Clinical Practice, research ethics)	01
	Pregnant women and members of the research team are in contact with TB patients	01
	Tasks are delegated to people who do not fulfil the professional criteria to ensure that the tasks will be appropriately performed	01
	Tasks are delegated without proper documentation	01
Total problems observed		61

The trial inspection results presented in Table 16 provide some disturbing insights. First of all, although most of the observed problems only occur once, the nature of most of the problems is serious. For instance, the observation “trial-related activities initiated before obtaining the informed consent” indicates a grave violation of ethical guidelines for clinical trials. Furthermore, 19 problems were observed related to patient safety, of which 12 relate to violations of the principles surrounding the reporting and treatment of adverse events. This should be regarded as a major problem.

In total, 61 problems were observed in 18 site inspections, which translates to an average of 3.5 cases of non-compliance per trial site. Unfortunately, we do not have any insight into the way these observations were followed up, but we can safely state that many of these trials are being implemented in an unethical manner. One can only hope that these events do not represent the tip of the iceberg, but unfortunately the numbers suggest otherwise.

Ethics Committees (ECs)

The international standards of GCP require that research may only be undertaken if the research project has been approved by an ethics committee¹⁶⁶ (or by other bodies authorised to review clinical research on human beings) after independent examination of its scientific merit.¹⁶⁷ The ethics committee must be independent of the research team and sponsor, and any direct financial or other material benefit they may derive from the research should not be contingent on the outcome of their review.¹⁶⁸

¹⁶⁶ Synonyms used for ethics committees are Independent Ethics Committee (IEC) or Institutional Review Board (IRW)

¹⁶⁷ Art. 6 (2) and Art. 9 (2) of Directive 2001/20/EC, Art.9 and 10 Additional Protocol on biomedical research (COE), Paragraph 15 of Declaration of Helsinki, WHO (CIOMS) guidelines 2.

¹⁶⁸ WHO (CIOMS) guideline 2.

A review and approval of a clinical trial protocol by an EC before starting a trial is a mandatory requirement in all the countries under study. Nevertheless, interviewees in India, Argentina and Brazil raised serious doubts about the effectiveness of ECs in performing their controlling function.

In the literature, questions have been raised about the expertise, composition and quality of ethics committees.¹⁶⁹ Interviewees confirm persistent problems with the functioning of ethics committees. It was pointed out that even in big reputable healthcare centres, EC reviews might not be completely fool proof. Work load, lack of time, lack of dedicated and trained members, conflict of interest and interference with work are cited as the major reasons for imperfect reviews. An interviewee of an EC in Argentina indicated that many ECs complain because they do not have the time or the technical capacity to evaluate whether clinical trial protocols pose any threats to research participants (Buenos Aires, 19 March 2010). In Brazil, an interviewee of CONEP, the national authority that oversees ethics committees, also indicated that not all ethics committees are functioning well and that many of their evaluations are superficial (Brasília, 9 September 2010).

The following quotes from interviews conducted in India are illustrative of the concerns about the functioning of ECs:

"... in some private hospitals, in an IEC of 11 people I have come across situations in which only 3 people were present at the time of approving the study. So it is obvious what will be the quality of that review."... Clinical Investigator (New Delhi, 21 May 2010)

"... average time for reviewing one proposal is 90 seconds. Need I say more?"... Expert on clinical trial sector (New Delhi, 21 May 2010)

"...hospitals, at least many of them are in this for money. So the IECs are also forced to act according to the interests of the hospital. I was a member of the IEC of a hospital and was removed from that post as I did not give approval to some trials they were interested in."...Expert on clinical trial sector (New Delhi, 21 May 2010)

In one of the interviews, an EC member explained that, because of strapped resources and manpower, ECs often fail to provide meaningful information or to maintain a database of the studies being done in the institution. As this increases the risk for future scandals surrounding faulty trial approvals, it discourages many experts from becoming part of an ethics committee (Mumbai, 1 June 2010).

There are more factors that might inhibit the effective monitoring role of ECs. As indicated by the EC member interviewed in India, when faced with a negative review, CROs or sponsors might go shopping for a positive one. And since there is no culture of communication between ethics committees, this practice remains unregistered (EC member, Mumbai, 1 June 2010).

A factor that constrains effective oversight by institutional ECs specifically is that the institution and its principal investigator will financially benefit from the carrying out of a trial in their centre. Since a negative review may cause a prospective client to change centres, the ethics committee might be pressured for approval. The EC member that was interviewed criticised this attitude of the

¹⁶⁹ A. Bhatt, "Clinical trials in India: Pangs of globalization", *Indian J Pharmacol*, 36(2004), p. 207-8; G. Mudur "India plans to audit clinical trials", *British Medical Journal*, 331(2005); p.1044; S. Prakash. Evolution of regulatory system in India", *Indian Journal of Pharmacology*, 41 (2009), p.207; National Institute of Medical Statistics, ICMR, Clinical Trials Registry India, 2007, <http://www.ctri.in/Clinicaltrials/index.jsp> (11 June 2010), E.J. Emanuel, T. Lemmens, C. Elliot Should Society Allow Research Ethics Boards to Be Run As For-Profit Enterprises? *PLoS Med* 2006 3(7): e309. doi:10.1371/journal.pmed.0030309

institutions and investigators. He was of the opinion that researchers and institutes should be interested in trials for the scientific benefits of the study and not for the monetary benefits involved (Mumbai, 1 June 2010).

It should be noted that concerns over conflict of interest of ECs are not limited to India or the institutional type alone. There are also concerns about ethics committees that are not connected to a clinical institution, and are paid for their services. As a service provider, they might be tempted to satisfy their client: by approving the protocol.¹⁷⁰ The awareness of the variation in the functioning of ECs with prospective clients can be illustrated by an employee of a CRO in Argentina, who commented on the pros and cons of using the different independent committees with sentences like “*FEFYM approves everything; Barclay is stricter; Fleming and Hospital Italiano are good but they take their time*” (Buenos Aires, 28 May 2010).

It is important to highlight the protocol approval time of ECs here. Our research indicates that, in some Latin American countries, the time required by ECs to approve a clinical trial protocol is the most important criterion that applicants use to select the EC that will review a study.¹⁷¹ As there could be a trade-off between quality (which requires scrutiny) and speed, from a quality/ethics point of view, it is important to monitor the performance of those ECs that review a large proportion of clinical trials..

Another concern the study in India revealed was that one of the two CROs participating in the study has its own EC. The other CRO did not have such an EC, and the representative cited conflict of interest as the major reason for this. He explained that CROs usually approach the institutional EC of a hospital or an independent EC to get their proposals reviewed. Other interviewees confirmed the practice of some CROs floating their own ECs to facilitate ethics review of proposals, especially when using small private hospitals that do not have an EC (EC member, Mumbai, 1 June 2010). A widely shared opinion among interviewees was, however, that a non-clinical entity having an EC is totally worthless, and that the review in such a case should not be included in a trial approval procedure (EC member, Mumbai, 1 June 2010; Representative of the regulatory sector, Chennai, 7 June 2010; Expert on clinical trial sector, New Delhi, 21 May 2010).

In Argentina, a director of clinical operations of a CRO (Buenos Aires, 28 April 2010) and a manager of clinical research at a multinational pharmaceutical company (Buenos Aires, 27 May 2010) reiterated the above-mentioned concerns over the functioning of most ECs (conflict of interests, lack of resources, lack of expertise), and thought that the implementation of clinical trials would greatly benefit from improvements in the performance of the ECs. They even stated that the deficiencies of the ECs had forced ANMAT to perform tasks that are usually delegated to the ECs, such as the revision of the informed consent forms.

The monitoring role of ECs in India was formalised in the 2005 amendment of the Drugs and Cosmetics Act. However, there is no mechanism to ensure adequate monitoring by ECs. The lack of an adequate system to ensure EC functioning was also highlighted by an interviewee from the Brazilian National Commission of Research Ethics (CONEP) (Brasília, 9 September 2010). Furthermore, it was indicated that in India ECs do not have enforcement powers, and hence there

¹⁷⁰ E.J. Emanuel, T. Lemmens, C. Elliot. “Should Society Allow Research Ethics Boards to Be Run As For-Profit Enterprises?” PLoS Med 3 (7) (2006): e309. doi:10.1371/journal.pmed.0030309; S.E. Gonorazky “Independent ethics committees for clinical research in Argentina. An evaluation and a system to guarantee their independence”. *Medicina* 68 (2) (2008), pp113-9

¹⁷¹ N. Homedes and A. Ugalde, “Contract Research Organizations in Argentina, Brazil, Costa Rica, and Peru”, 30 September 2010

is a limit to how far they can pursue certain matters through for instance site inspections (interview EC member, Mumbai, 1 June 2010).

In summary, the following constraining factors for the functioning of ECs were mentioned by interviewees in India, Argentina and Brazil:

- Lack of expertise
- Lack of resources
- Work load
- Conflict of interest
- Lack of communication between ECs
- Inadequate archiving
- 'Shopping' behaviour by CROs/sponsors (except for Brazil).

Two more concerns relate specifically to the Indian context:

- Lack of enforcement power of ECs
- ECs connected to CROs.

Reporting and compensating adverse events

Some interviewees in India raised concerns over reporting and compensation for adverse events. According to schedule Y of the Drug Act: "*Any unexpected serious adverse event (SAE) (as defined in GCP Guidelines) occurring during a clinical trial should be communicated promptly (within 14 calendar days) by the Sponsor to the Licensing Authority and to the other Investigator(s) participating in the study*". The CROs interviewed in India stated that, in case of any adverse event during the study, they ensure care for the patient from the trial site, and the cost of care is later refunded by the sponsor. They report all the adverse events directly to the sponsor and to the EC. It was also pointed out that the clinical investigator has a moral responsibility as he/she has the role of primary care giver of the patient.

Nevertheless, there is lot of ambiguity surrounding the reporting of adverse events in India. The EC member who was interviewed indicated that, even though adverse events should be reported to the DCGI, this is not common practice (Mumbai, 1 June 2010). Furthermore, all serious adverse events also have to be reported to the EC within 24 hours. But EC meetings occur once in two or three months, and moreover, ECs do not have any enforcement authority, making this reporting requirement virtually useless. In some very reputed institutions in India, the head of the institute receives reports on adverse events associated with trials. A small number of institutes have their own permanent Data Safety and Monitoring Boards (DSMBs, see Glossary).

The inadequate reporting of adverse events was also demonstrated by the inspection data from the Peruvian authority INS (see Table 16 above). Of the 61 problems that were observed at 18 trial sites managed by CROs, 10 relate to inadequate reporting of adverse events to the authorities. In three of these instances, adverse events were not reported to the authorities at all.

Reporting of adverse events by principal investigators may be discouraged when investigators experience conflict of interest. The dual role of care giver and researcher that principal investigators fulfil is perceived as a problem by our Indian interviewees, since the investigator often receives monetary benefits to conduct the trial. The benefit may be a fixed amount of money for each patient that the investigator recruits for the study or per patient that completes the study, or may be provided 'in kind' by means of (expensive) gifts to the investigator or his/her institution

(interview with clinical investigator, New Delhi, 21 May 2010).¹⁷² It was suggested that the care giver for the trial participant should not be the principal investigator and that someone who is not associated with the trial should be in charge of reporting the adverse events.

“...whose interests are of paramount significance to the doctors while reporting an adverse event? There is a conflict of interest as the doctor here has multiple roles. Whom will he/she feel responsible to – the sponsor company or to the patient? And unfortunately in most of the cases doctors are interested in fulfilling their responsibility towards the sponsor before thinking about the patient. Conflict of interest is a major dilemma for doctors.”... EC member (Mumbai, 1 June 2010)

Conflict of interest is also a problem for principal investigators in Latin America. If the investigator is paid based on the number of patients that complete the study, the researcher may be reluctant to drop a research subject from a clinical trial or to report adverse events. As became apparent in the Vioxx case,¹⁷³ sponsors and CROs may also be careful of how they manage patients who have experienced adverse events, since this could jeopardise the statistical analysis of the trial data and imply a negative result for the working of the drug. In other words, principal investigators may receive strong incentives to report positive results. It should be noted that these concerns over conflict of interests of principal investigators are not bound to non-traditional trial regions and are present in the traditional trial regions as well, as the dual role of care giver and researcher of principal investigators combined with the (monetary) benefits they receive to conduct the trial is a widespread practice here as well

When adverse events are not reported to the clinical trial sponsor and/or the authorities, the safety data of the experimental drug is actually forged, which raises grave concerns about the safety of the drug once it enters the market. Apart from the safety of clinical trial participants and future users of the drug, this may also threaten the reputation of the pharmaceutical company marketing the drug. To bring drugs on the market that may later need to be withdrawn because of safety issues potentially involves major reputation risks for pharmaceutical companies. On the other hand, once a drug has managed to get through the R&D pipeline until a Phase III clinical trial, it has already cost millions of dollars, which clearly makes the interest for positive test results enormous. And large-scale safety and efficacy problems with a drug that has entered the market will normally only appear years after marketing approval, meaning profits can be made during these years. One can imagine that this major economic interest might work against safety and efficacy considerations.¹⁷⁴

Insurance coverage for trial participants was made mandatory in India in the year 2005. The CROs interviewed claimed that they provide insurance coverage to trial participants, irrespective of whether they are in the test group or the control group. They explained that Indian insurance laws are different from western laws, and the coverage is arranged for by the CRO and the funding for the insurance coverage is provided by the sponsor.

If clinical trial participants face an adverse event, they will have to know where to file their claim to access compensation. According to ethical guidelines, this should be indicated on the informed consent form, but there are indications that participants are often unaware of the route to

¹⁷² Also see the documentary *Body Hunters* by Paul Jenkins, 2010.

¹⁷³ See for example 'The other side of the story. The Vioxx drug case' available at <http://www.maryalice.com/cases/Vioxx.asp> (accessed 4 February 2011).

¹⁷⁴ This potential trade off between safety on the one hand and profits on the other is well illustrated in the documentary *Body Hunters* by Paul Jenkins, 2010.

compensation.¹⁷⁵ Then secondly, the responsible party, which is normally the sponsor (see further Chapter 6), will need to accept the responsibility for the adverse event. If the responsibility is rejected (e.g. by denying the injury or harm was related to the trial), the subject or family has to take legal action. As many clinical trial participants in India and Latin America are poor, illiterate and burdened with illness, patients and their relatives will normally end up not fighting for compensation since the litigation process involves time and money. Obtaining compensation becomes even more difficult when the defendant company is foreign and has its headquarters overseas, since then the case has to be presented overseas.

Public means for private benefit

In Latin America, the recruitment of clinical trial participants takes place almost exclusively in the public sector, even though the trial may be conducted in private clinics.¹⁷⁶ There are several concerns associated with this practice. First of all, in many Latin American countries, the public sector mainly serves the vulnerable share of the population, which means clinical trials mainly recruit vulnerable patients, with all the associated risks.

Furthermore, the private clinics in which trials are conducted often lack the capacity to treat adverse events and thus usually there is a need to establish a contract with the emergency department of a hospital that has the resources to take care of these cases (interview with officer of a national CRO in Brazil, Sao Paulo, 28 July 2010). However, in the Brazilian context, it may be possible that public hospitals end up paying for the costs of medical procedures that are related to clinical trials. Public hospitals do not have a system of calculating the costs of medical procedures. This was the case at the Municipal Children's Hospital in Cordoba (Argentina) where a local CRO had its headquarters within the hospital. Since 1993 more than 2,000 children from poor families had participated in clinical trials. Public documents indicate that the hospital was unable to ascertain the amount of public resources (human and material) that were used without compensation.¹⁷⁷

One of the results of the above situation is that, if a subject in a clinical trial has a health problem related to the trial and has to be treated at the hospital, the costs of the intervention are hard to calculate. A further complicating factor is proving that the cause of the health problem is related to the clinical trial. If such proof is not apparent, the resources of public hospitals end up being used to clean up the mess of private clinics.

5.3 Ethical risks associated with outsourcing

The previous section has flagged several concerns associated with the conduct of clinical trials in the case study countries, irrespective of whether they are conducted by the sponsor directly or outsourced to a CRO. In this section, the risks of using CROs in these countries are analysed, based on the data collected in India, Brazil, Argentina and Peru combined with secondary data.

¹⁷⁵ See the documentary 'Body Hunters' by Paul Jenkins, 2010, and the Wemos report 'The Globalization of Clinical Trials: Testimonies from Human Subjects' (Amsterdam: Wemos, 2010)

¹⁷⁶ N. Homedes and A. Ugalde (eds). "Ética y Ensayos Clínicos en América Latina". (Buenos Aires: Editorial Lugar, Forthcoming)

¹⁷⁷ N. Homedes and A. Ugalde (eds). "Ética y Ensayos Clínicos en América Latina". (Buenos Aires: Editorial Lugar, Forthcoming)

Trade offs between costs, speed and quality

Most concerns related to the outsourcing of clinical trial tasks to CROs can be interpreted as concerns over trade offs between costs, speed and quality of clinical trials. In many outsourcing models, CROs must bid against other CROs to win research contracts. In competing for contracts “all the incentives are to do [the work] fast” with the risk of compromising quality. The CRO’s predominant interest is simply to deliver a product (often clinical data that meets EMA, FDA and NDA requirements) on time and under budget.¹⁷⁸

Experts and practitioners are worried about the ‘commodification’ of clinical trials by means of functional outsourcing to CROs: CROs meet their deadlines by breaking the conduct of each study into discrete steps – for instance, finding investigators, enrolling a specified number of patients and checking the case-report forms where patient-level data are recorded – and emphasising speedy completion of each step. As CRO critics have said: ‘commodification’ of research projects has begun ‘to kill’ clinical research, and a CRO is reduced to a ‘data-production sweatshop’ where “*everyone’s very focused on the data*”, rather than on the totality of the knowledge required to determine whether a drug is worth pursuing further.¹⁷⁹

The costs and time pressures on CROs seem to be aggravated by the trend towards performance based payments in sponsor-CRO contracts, as was observed by several interviewees in the Latin American case studies. Performance in this context is directly related to the number of subjects that complete a trial, and as such, this trend could encourage the use of strategies by CROs that are detrimental for clinical trial participants, such as flexibilisation of trial participation criteria (i.e. inclusion/exclusion criteria), or reluctance to withdraw a patient from the study.

A related concern of the ‘commodification of clinical trials’ – the fragmentation of tasks in combination with cost and time pressures – is that this could lead to a lack of oversight and comprehension of the full trial process. The director of clinical research of one of the most prestigious hospitals in Buenos Aires (Buenos Aires, 12 February 2010) said that often CROs are too specialised and they do not have a comprehensive perspective on the trial. According to this interviewee, the pharmaceutical industry is more knowledgeable and can anticipate problems more effectively. Another interviewee, the head of clinical operations of a large multinational pharmaceutical company, was critical of the overall performance of the CROs and favoured carrying out the tasks in house when headquarters would let him (Buenos Aires, 28 May 2010). This same interviewee pointed to a lack of training of CROs, when he commented that Quintiles – global CRO market leader – has a good reputation because “*it is the only one that trains its employees*” (Buenos Aires May 28, 2010).

Concerns over the quality of CRO personnel are more widespread. For instance, the head of clinical trials operations of a large multinational pharmaceutical company mentioned in an interview (Buenos Aires, 28 May 2010) that CROs typically have a high turnover of personnel, which might imply a lower level of job commitment and as such, might negatively impact the quality of the information gathered by the CRO. A top executive member of the clinical trials drug evaluation division of the Argentinean drug authority ANMAT confirmed this concern and said that “*the personnel in the pharmaceutical companies tend to be more stable and are more familiar with the procedures*” (Buenos Aires, 27 May 2010).

¹⁷⁸ Mirowski and Van Horn, “The Contract Research Organization and the Commercialization of Scientific Research”, *Social Studies of Science* 2005; 35; 503, <http://sss.sagepub.com/cgi/content/abstract/35/4/503>; M Shuchman, Commercializing Clinical trials-risks and benefits of the CRO boom, *New England Journal of Medicine*, 4 October 2007

¹⁷⁹ M Shuchman, “Commercializing Clinical trials-risks and benefits of the CRO boom”, *New England Journal of Medicine*, 4 October 2007

Problems with the CRO workforce are also observed in the literature. It is said that CRO employees are generally younger, less skilled, less experienced and less educated than researchers in the pharmaceutical industry or academia.¹⁸⁰ However, this is contrasted by an interviewee from the Brazilian drug authority ANVISA. This interviewee indicated that, when CROs prepare the clinical trial protocol for approval by the authorities, they tend to be more complete and there is less need for follow up (Brasília, 15 June 2010).

One interviewee estimated the total number of national and international CROs in India to be around 200. However, he added that the number of CROs with proper infrastructure, manpower and capacity to undertake large international trials would be around 50 out of 200 (expert on clinical trial sector, New Delhi, 21 May 2010). Overall, the interview data collected suggests that multinational CROs tend to do a better job than the smaller national CROs, because the multinational CROs cannot afford a bad reputation. National CROs sometimes lack the capacity to carry out all their projects, and therefore the quality tends to suffer.

Some of our interviewees from the CRO sector commented on their rationale for accepting a contract with a sponsor to conduct a particular clinical study. According to the manager of a multinational CRO (Buenos Aires, 9 February 2010), the main criteria used by the CROs to decide if they want a contract for a particular study is the result of a feasibility study. This study takes into account the technical capacity needed to implement the study, the availability of research centres and researchers to carry it out, the likelihood of being able to recruit the estimated number of patients, the likelihood of obtaining the clinical trial approval by the ethics committees and the regulatory agencies, and the financial terms of the contract. The representative of a multinational CRO in Brazil offered a similar response (Brasília, 10 August 2010), but the manager of a Brazilian CRO said that usually the pharmaceutical company decides with whom they want to contract, suggesting that CROs are likely to accept most offers, unless they consider that they will not be able to recruit the required number of patients (Sao Paulo, 28 July 2010). These comments suggest that multinational CROs are more selective in accepting contracts than national CROs are.

Several interviewees from Latin America have stressed the lack of independent decision-making authority by CROs, with CROs becoming mere intermediaries between researchers and sponsors (for example, interview with director of clinical research in hospital, Buenos Aires, 12 February 2010; interview with general manager of an international CRO, Buenos Aires, 9 February 2010). The lack of independence of CROs is confirmed by a study by Mirowski and Van Horn. They conducted a meta-analysis of clinical trial results and observed a bias: CRO-conducted trial results tended to deliver more positive test results about the tested drug. As an explanation for this bias they see that researchers at CROs are first and foremost employees whose motives are expected to be subordinate to the objectives of the firm. Another ground for the bias in results is the rarely acknowledged 'sweatshop' character of work in CROs. Compared with their counterparts in large pharmaceutical firms, researchers in CROs are insufficiently trained, poorly paid and discouraged from exercising any initiative, which is why they have extremely high rates of turnover.¹⁸¹

¹⁸⁰ M Shuchman, "Commercializing Clinical trials-risks and benefits of the CRO boom", *New England Journal of Medicine*, 4 October 2007

¹⁸¹ Mirowski and Van Horn, "The Contract Research Organization and the Commercialization of Scientific Research", *Social Studies of Science* 35, 503 (2005), <http://sss.sagepub.com/cgi/content/abstract/35/4/503>; also see: J. Lenzer. "Truly independent research?", *BMJ* 337, a1332 doi: 10.1136/bmj.a1332 (Published 21 August 2008)

Monitoring of trial sites

Because of our present interest in the maintenance of ethical principles in the clinical trial practice, the interviews inquired specifically about the quality of monitoring of the clinical trial sites by CROs. In India and Argentina, some interviewees raised concerns, while others did not see a problem.

The director of clinical research at a hospital in Buenos Aires commented that the quality of trial supervision is dependent on the person in charge, irrespective of whether the monitoring agent is contracted by a CRO or by a pharmaceutical company (Buenos Aires, 12 February 2010).

In India, both the CROs that were interviewed described that the frequency of their trial monitoring visits is monthly at the minimum and more frequent during the trial site initiation. They check the quality of the informed consent forms, protocol compliance, take stock of drugs, check the data on safety, the quality of data and the like. In the case that any deviations from the ethical guidelines are observed, corrective measures are recommended. One CRO representative mentioned that their site team spends an entire day with the trial participants to explain the trial process to them, and one more day is given to the participant to decide whether or not to participate in the trial.

The clinical investigator who was interviewed confirmed the periodic monitoring visits by CRO teams, but expressed his doubts regarding the quality of monitoring work that they do:

“They [the CRO monitoring teams, eds.] are all very enthusiastic in the beginning and will be more involved towards the beginning of the study. Later, they come and they sit with the investigator. It is true that they come periodically.[...]. But what if things go wrong inbetween? They come and see the files, stock of medicine, etc. Some of them [the CRO monitoring teams, red.] are good, but some are below average.” (Clinical investigator, New Delhi, 21 May 2010)

The representative of the EC that was interviewed in Mumbai, India, spoke at length about the monitoring role of CROs. He noted that in India, CROs might be the most effective monitoring organ at this point in time, with its large number of sites and insufficient oversight by authorities. However, the objectivity and quality of such monitoring may be questioned when CROs have a stake in the successful execution of the trial, which is the case when CROs are paid on a performance basis, or when they have a partnership with a sponsor. The quality of CRO monitoring of trial sites cannot be cross checked, as the findings of trial visits are not in the public domain:

“Where are their findings? If they are finding things which are going wrong they are not reporting it? I have never come across data reporting that. They are not in the public domain for sure. So I have my suspicions about the quality of monitoring by CROs. There is a veil of secrecy around its functioning and it makes me suspicious.” (IEC member, Mumbai, 1 June 2010)

Blurring responsibility

In Chapter 3 of this report, the increase in outsourcing of clinical trial-related activities from pharmaceutical companies to CROs was demonstrated. In the interviews in the case study countries, it was highlighted that CROs sometimes subcontract out some of their tasks to other CROs,¹⁸² and the studies in Latin America suggest that regulatory agencies and sponsors may not

¹⁸² Cf. R. Sing & V. Glozman. “Managing Clinical Trials in Emerging Markets”, Pharmaceutical Executive, 1 January 2011, <http://pharmexec.findpharma.com/pharmexec/article/articleDetail.jsp?id=703045&sk=&date=&pageID=3> (Accessed 1 February 2011)

always be informed about this. The regulatory agencies do not have any legal control over what a CRO does, unless the CRO is the sponsor. Legally, CROs are service organisations and not health organisations. They could contract another CRO or any other firm to import the drug for a specific trial, translate the consent form etc. There is no regulation that specifies how the many non-clinical management tasks that take place within a clinical trial have to be performed. There are some tasks that could be classified in the grey area between clinical and non-clinical tasks: obtaining informed consent for instance could be a clinical task or a legal task. Thus, authorities might not have the oversight of all the parties that perform tasks in a particular trial.

The pharmaceutical companies that were interviewed for this study indicate that they contractually bind CROs to inform them if they subcontract certain activities (see Chapter 6). We are unable to verify whether CROs keep their contractual commitments with sponsors. What we do have is an indication that authorities are not always informed, thanks to the Peruvian case study. The inspection results of 18 CRO-monitored trial sites by the Peruvian INS revealed one instance in which site monitoring was subcontracted to another CRO without informing the INS (see Table 16).

The present study has not collected proof that (sub)contracting in clinical trial research actually leads to more harm to participants. Actually, to prove this would require much more time, the use of ethnographic methods, and cases of misconduct to be brought to light. Furthermore, the lack of transparency of the industry, combined with the lack of accessible mechanisms for clinical trial participants and others involved in clinical trials to file these claims, hinders the research in this area. However, it is clear that the fragmentation of the implementation of clinical trials does increase ethical risks, even while lacking empirical proof that CROs contribute to increased risks. First of all, ethical risks increase because of the trade offs between costs, speed and quality of clinical trials that were discussed above. Furthermore, fragmentation of tasks among several actors in the R&D chain blurs the oversight of the full trial process, and as such, the perception of responsibility might also become scattered. This risk is confirmed in literature¹⁸³ and was echoed in the interviews conducted throughout this study.

For instance, an expert on clinical trial ethics, an associate professor in the faculties of Law and Medicine of the University of Toronto, Canada, stated: *"I do not know any statistics that prove that clinical trial participants are more often harmed in clinical trials conducted by CROs. But [in outsourcing relationships, eds.] it may be more difficult to discern which party is responsible for what"*. He also pointed to the possibility that pharmaceutical companies may transfer the blame of misconduct to CROs or ethics committees: *"CROs and Ethics Committees can more easily be eliminated from the scene in case of misconduct in trials, so pharmaceutical companies can keep their hands clean"* (telephone interview, 5 August 2009).

Another expert, a professor in theory and the history of science at Groningen University, The Netherlands, also confirmed that ethical risks increase with outsourcing: *"That ethical risks increase [with the outsourcing of clinical research] is evident. By working through CROs, the division of labour in the pharmaceutical industry continues. CROs have even been called 'data producing sweatshops' [...]. But every specific case of harm for trial participants has different characteristics. A CRO could follow ethical guidelines very strictly while the trial may involve enormous risks for participants"* (Amsterdam, 22 September 2009).

¹⁸³ Mirowski and Van Horn, "The Contract Research Organization and the Commercialization of Scientific Research", *Social Studies of Science* 2005; 35; 503, <http://sss.sagepub.com/cgi/content/abstract/35/4/503>; M Shuchman, "Commercializing Clinical trials-risks and benefits of the CRO boom", *New England Journal of Medicine*, 4 October 2007; R. Sing & V. Glozman. "Managing Clinical Trials in Emerging Markets", *Pharmaceutical Executive*, 1 January 2011, <http://pharmexec.findpharma.com/pharmexec/article/articleDetail.jsp?id=703045&sk=&date=&pageID=3> (Accessed 1 February 2011)

The fragmentation of clinical trial-related tasks might decrease with the sponsor-CRO partnership trend (described in Chapter 3). This might suggest that oversight would improve, but at the same time, other risks may increase. As the Director of Ethics and Legal Affairs of the CRO 'Ethica' noted: "*CROs do not profit from marketing the drug, although some CROs may when they engage in strategic partnerships with pharma companies. It is Ethica's policy that it will never acquire a share in any of its clients' business, because then Ethica would have a vested interest in getting positive test results*" (interview, 8 October 2009).

This quote suggests that interests and ethical risks differ between differing outsourcing models (e.g. transactional outsourcing vis-à-vis risk-sharing, fixed payments vis-à-vis performance-based payments). Furthermore, with the trend towards partnering and risk-sharing, it is likely that accountability also shifts. What is the accountability of a pharmaceutical 'network' compared to that of a pharmaceutical company? This accountability question is examined further in Chapter 6.

5.4 Summary

With regard to the offshoring of clinical trials, the following ethical concerns were identified through interviews:

- ❑ Vulnerable population and informed consent (India, Brazil, Peru and Argentina)
- ❑ Insufficient oversight by authorities (India, Argentina and Brazil)
- ❑ Insufficient oversight by ethics committees (India, Brazil, Peru and Argentina)
- ❑ Reporting of adverse events (India and Peru)
- ❑ Public means for private benefit (Brazil, Peru and Argentina).

With regard to the outsourcing of clinical trials in non-traditional trial regions, the following ethical concerns were identified:

- ❑ Quality of clinical trials suffers from cost and time pressures: lack of quality of CRO personnel, lack of oversight over clinical trials, dependence of CRO on sponsor with possible bias in trial results (India, Brazil and Argentina)
- ❑ Inadequate monitoring of trial sites by CROs (India and Argentina)
- ❑ Blurring of responsibility (based on literature and expert interviews in research phase one).

The picture that arises from the combined case studies is that the context for clinical trials in non-traditional trial regions is an ethical minefield anyway. When certain CROs are in charge of managing the clinical trials, chances are that the (ethical) quality of the trial will further suffer. The monitoring of the trial might be inadequate, while responsibility for possible malpractices and adverse events will be scattered across actors and blurred.

Because of the secrecy that surrounds the implementation of clinical trials, the unevenness of the collected data among the different case study countries, and the limited amount of interviews conducted per country, it is not possible to draw firm conclusions about the ethical conduct of CROs in the selected countries, or to make adequate comparisons between countries. For instance, some interviewees have suggested that the conditions for conducting clinical trials are worse in India than in Latin America, but the present research design does not allow for verification of this statement. Nevertheless, the interviews have demonstrated that concerns over outsourcing and offshoring exist across the case study countries. Considering the implications of those ethical

concerns – the health and safety of clinical trial participants and future drug users – it is imperative that these concerns are addressed. In the next chapter, we look at how pharmaceutical companies – the sponsors of clinical trials – approach these issues.

6 Responsibilities of pharmaceutical companies

In the previous chapters, field observations in the case study countries were presented. In this chapter, interviews with pharmaceutical companies and secondary data are used to explore the responsibilities of pharmaceutical companies for ensuring the ethical conduct of clinical trials that they outsource to CROs. First their formal responsibilities are reviewed (section 6.1). Then, the way pharmaceutical companies address their responsibility is explored (section 6.2). The chapter is wrapped up in section 6.3.

6.1 Formal responsibility

In the first instance, the responsibility question is easily answered: a pharmaceutical company remains responsible for the ethical conduct of the clinical trials it sponsors. This overall end-responsibility is echoed by all pharmaceutical companies that participated in this study: Abbott, AstraZeneca, GlaxoSmithKline, Janssen (the pharmaceutical division of Johnson & Johnson), Novartis and Sanofi-Aventis. As Novartis states in response to our responsibility question: “*the responsibility for compliance with ethical, quality and regulatory standards of a clinical trial remains with the sponsor and cannot be contracted. Novartis takes this responsibility serious and ensures that contractors follow Novartis policies and internationally agreed upon standards*” (written interview, 10 November 2010).

Indeed, GCP guidelines (which need to be adhered to for clinical trials conducted for drugs seeking European Marketing Approval) include a clear statement on the responsibility distribution between pharmaceutical companies and CROs for clinical trials. In section 5 of the guidelines, which addresses the sponsor, the second section is devoted to CROs:

ICH-GCP Guidelines, Section 5: SPONSOR

“.....

5.2 Contract Research Organization (CRO)

*5.2.1 A sponsor may transfer any or all of the sponsor’s trial-related duties and functions to a CRO, **but the ultimate responsibility for the quality and integrity of the trial data always resides with the sponsor.** The CRO should implement quality assurance and quality control.*

5.2.2 Any trial-related duty and function that is transferred to and assumed by a CRO should be specified in writing.

5.2.3 Any trial-related duties and functions not specifically transferred to and assumed by a CRO are retained by the sponsor.

*5.2.4 All references to a sponsor in this guideline also apply to a CRO to the extent that a CRO has assumed the trial related duties and functions of a sponsor”.*¹⁸⁴

This phrasing suggests that, if a clinical trial participant would experience a trial-related injury, the sponsor is liable. However, there appear to be exceptions to this general rule, and these are contractually allocated. When asked about the liability for trial-related injuries, the Director of Ethics

¹⁸⁴ ICH Good Clinical Practice Guidelines, section 5.2, http://ichgcp.net/?page_id=204 (accessed 1 December 2010).

and Legal Affairs at CRO 'Ethica', explained: "*It is a shared responsibility among investigator, sponsor and CRO, and the liability depends on the role of each party and the incident of harm. At the beginning of a clinical study, responsibilities will be divided amongst the parties. In general however, the sponsor will be responsible*" (interview, 8 October 2009).

The variation of responsibility distribution from contract to contract is also illustrated by the following quote from the 2008 '20F form' (a form submitted to the US Securities and Exchange Commission) by ICON (one of the top ten CROs globally): "*Indemnifications provided by our clients [i.e. pharmaceutical companies] against the risk of liability for personal injury to or death of the patients vary from client to client and from trial to trial and may not be sufficient in scope or amount or the providers may not have the financial ability to fulfill their indemnification obligations. Furthermore, we would be liable for our own negligence and that of our employees.*"¹⁸⁵

This quote makes clear that CROs may be liable for trial-related injury when negligence by the CRO or its employees is behind the injury. As the Director of Ethics and Legal Affairs of 'Ethica' stated: "*CROs and investigators could be held responsible in instances of scientific misconduct (not following standards of practice during the elaboration or management of the trial) or fraud could be proven (e.g. the hiding/ altering of data)*". The following quote from the Covance (a top ten CRO) annual report 2008 confirms this: "*Contractual indemnifications generally do not protect us against liability arising from certain of our own actions, such as negligence or misconduct.*"¹⁸⁶ Thus, the answer to the responsibility/liability question is highly dependent on the specifics of the case and the contractual agreements between the parties involved.

Interviewees from the CRO sector stressed that liability for incidental serious adverse events and side effects after marketing approval of a tested drug will almost always reside with the sponsor (interview with CRO President, Mumbai, 28 May 2010; interview with clinical research associate at CRO, Mumbai, 12 May 2010; interview with Director of Ethics and Legal Affairs at 'Ethica', 8 October 2009). It was explained that many clinical trials are large-scale international studies with multiple sites, in which individual CROs are only in charge of part of the study. A single site or a CRO that supported the study at that site cannot be held responsible for possible side effects. As evidence in support of the molecule is gathered from different sites, real life patients on whom drugs are administered might be different from the trial population who were carefully monitored and followed up.

The research indicates that responsibility and liability for trial-related injuries will in most cases lie with the sponsor, but that there are exceptions. The picture is blurred further in cases in which CRO and sponsor enter into a partnership. There is a specific type of sponsor-CRO contract that exposes the CRO to the risks of product performance and thus will be impacted by product safety and efficacy as well as the product's commercial success, the so-called 'Product-Risk sharing' contract. In this relatively rare type of contract, CROs trade part or all of their service fees for an equity stake in the sponsor company or a percentage of the out-licensing fees or product sales.¹⁸⁷ It seems logical that, in this specific type of contract, the CRO would share liability risks with the sponsor, as it would also share in the product's commercial success. It is important to note that although limited 'transactional' relationships between CROs and sponsors are still most common, professionals signal a trend towards closer sponsor-CRO relationships referred to as 'strategic partnership'.¹⁸⁸ Recently announced partnerships between pharma and CROs include links

¹⁸⁵ ICON Form 20-F 2008.

¹⁸⁶ Covance Annual Report 2008.

¹⁸⁷ N. Varawalla. "Risk Management". 2006 in: Outsourcing clinical development. Eds J.E. Winter and J. Baguley, p. 62-74

¹⁸⁸ Jeff Thomis and Smita Desai. Outsourcing strategies. 2006 in: Outsourcing clinical development. Eds J.E. Winter and J. Baguley, p. 14

between Sanofi Aventis and Covance, Eli Lilly and PAREXEL, and Bristol-Meyers Squibb and ICON and PAREXEL. This suggests that risk-sharing may increase accordingly. The present study did not investigate the risk-sharing provisions in these partnerships.

The ambiguity of the responsibility distribution between sponsors and CROs seems to extend as far as regulators' offices, as indicated by the following quote: "*The nature and extent of regulators' authority over CROs, however, are uncertain, according to Rachel Behrman, director of the Office of Critical Path Programs at the Food and Drug Administration (FDA). CROs are accountable to the FDA, said Behrman, but 'it's not clear whether their accountability is through the sponsor or directly to us.'*"¹⁸⁹ When we add to the equation that CROs also subcontract part of their clinical trial functions, this blurs the picture even further.

The present concern is that exceptions to the rule of sponsor responsibility might blur the picture for the clinical trial participants and might constrain their access to remedy in case of injury or harm. However, most interviewees from the pharmaceutical sector have indicated that the liability question may be a point of debate/litigation between the contracted parties, but not for the claimants. In Ethica's studies, for example, there will be provisions in place that guarantee that the participant will not bear the burden of assessing liability: the participant will be compensated directly, and then the parties will decide over who bears the costs.

GSK's response supports the recognition of a sponsor's responsibility for compensation to research subjects with their statement that: "*In all countries where we undertake clinical trials we commit to provide compensation to any subjects who unfortunately experience harm as a result of taking part in a trial. This will be in accordance with local compensation guidelines, or in the absence of local guidelines in accordance with the UK ABPI compensation guidelines*" (written interview, GlaxoSmithKline, 7 December 2010).

When scrutinised, the ABPI Clinical Trial Compensation Guidelines that GSK refers to indicate that there are exceptions to the rule of compensation by the sponsor, and that third parties (which may also be a CRO) might be responsible for compensation. Under section 3 titled 'Limitations', principle 3.4 states the following:

- "3.4 No compensation should be paid (or it should be abated as the case may be) to the extent that the injury has arisen:*
- *through a significant departure from the agreed protocol*
 - *through a wrongful act or default of a third party, including a doctor's failure to deal adequately with an adverse reaction;*
 - *through contributory negligence by the patient.*"¹⁹⁰

According to the ICH-GCP guidelines, informed consent forms should always include a clear reference to a contact person in the case of clinical trial-related injury. This should ease participant's access to grievance redress.

¹⁸⁹ M Shuchman, "Commercializing Clinical trials-risks and benefits of the CRO boom", New England Journal of Medicine, 4 October 2007

¹⁹⁰ The Association of the British Pharmaceutical Industry. Clinical Trial Compensation Guidelines. <http://www.abpi.org.uk/Details.asp?ProductID=156> (accessed 20 January 2011)

The following quote by Novartis confirms the importance of informed consent forms in guiding participants to find compensation to cover the costs for treatment of trial-related injuries, and in addition, provides insight in the conditions for such coverage:

“The informed consent form provides guidance and conveys the basic, necessary information to research participants in case of trial-related injuries. They are invited to contact the study doctor promptly for immediate treatment or referral, should they become ill or physically injured as a result of their participation.

Novartis typically covers the reasonable costs of treatment for research related injuries beyond the scope of research participant’s insurance provided that:

- *the research participant has received reasonable medical care by a licensed medical professional;*
- *the research participant has followed the instructions;*
- *the injury is related to the study drug or to study procedures performed in accordance with the protocol and that are not part of the research participant’s usual medical care; and*
- *the injury is not the result of the natural course of any underlying disease and/or pre-existing disease process present prior to the administration of the study drug.”* (Written interview, Novartis, 10 November 2010).

When scrutinised, the last two bullet points raise a point of concern. They suggest that participants will have to prove “causality” for injury (as being due to clinical trial procedure or drug) before compensation will be provided. For India, this finding is supported by research that reviewed policies for injuries to research participants.¹⁹¹ This finding is disturbing: how can one prove that the injury is indeed related to the trial, and would not have occurred if the claimant did not participate in the trial? And: who is responsible for gathering this proof? If the burden of proof is on the participant, and the participant is vulnerable and ill, this is potentially an enormous barrier for receiving compensation.

Abbott stresses that the burden of proof lies with the sponsor, and “*that the participant will not be asked to prove that harm was caused by the trial*” (telephone interview with Global Head of Outsourcing, Abbott, 9 November 2010). On the other hand, an Indian interviewee suggested that India uses a litigation-based system of insurance in which the burden of proof is on the participant, and that he never came across a single case in which a trial participant was compensated for harm caused by participation in a trial (EC member, Mumbai, 1 July 2010). This suggests injured participants need to enter into litigation before they may be compensated, and that compensation has never materialised until now. We have not been able to confirm this latter statement, nor did we scrutinise how claims of trial-related injury are generally verified and handled in practice, but this issue obviously deserves much more attention.

In summary, it appears that CROs in most cases will be indemnified through contractual arrangements with the sponsor (in accordance with the ICH-GCP guideline provisions), except in the case of ‘negligence’ or ‘misconduct’. It remains unclear what actions would actually be considered negligence and/or misconduct. Furthermore, contractual agreements between sponsors and CROs seem to develop into the direction of risk-sharing and partnership, with possible consequences for the liability and responsibility question.

¹⁹¹ U.M. Thatte, R. Kulkarni-Munshi and S. A. Kalekar, “Review of policies for injuries to research participants in India”. *Journal of Medical Ethics*, 35 (2009), p. 133-139

Although the liability distribution between sponsor and CRO may be unclear sometimes, pharmaceutical companies suggest that participants have a clear portal for compensation, which is communicated via informed consent forms. The sponsor is responsible towards the participants in this regard. Some sponsors suggest that claimants will not be burdened with the liability question between sponsor and CROs – that this is something for CRO and sponsor to negotiate/litigate – while others indicate there may be instances in which the sponsor directs claimants to the CRO. Many questions thus remain unanswered regarding the compensation of trial-related injuries: is the portal for compensation accessible for clinical trial participants? And does it provide adequate remedy? Under what conditions does the sponsor accept the responsibility for adverse events? Are there situations in which participants are re-directed by the sponsor to third parties (CROs, investigators)? And what role do insurance companies play? Answering these questions was outside the scope of this research, but these are valid and important questions to ask.

6.2 Policy and implementation of supply chain responsibility

Although we had anticipated that supply chain responsibility in the pharmaceutical sector would be underdeveloped, this research demonstrates that this is not the case: pharmaceutical companies have rather elaborate supply chain management mechanisms in place. In addition, pharmaceutical companies acknowledge the ethical risks that are associated with clinical testing in some non-traditional trial regions, and have policies and mechanisms in place to address these. This section describes these policies and procedures, based on the input provided by Abbott, AstraZeneca, GlaxoSmithKline, Janssen, Novartis and Sanofi-Aventis in answer to our questions.

Risk management in non-traditional trial regions

Each of the six companies that participated in this study declare that they apply the same principles (usually the ICH-GCP guidelines, sometimes also the DoH) in every context, for every study they sponsor, whether (partially) outsourced to CROs or not. The following quotes illustrate such commitments:

Copied from the Abbott 'Global Citizenship' web page:

“Abbott is committed to the highest standards of clinical practice in all of our research, including areas of bioethics bearing upon the complex interaction of human life, science and technology. Our global policy on clinical evaluation includes a requirement for compliance with the applicable International Conference of Harmonization (ICH) guidelines.

Our biomedical principles, embodied in our corporate policies, focus on safeguarding the volunteers and patients who participate in clinical trials. We take numerous steps – often going above and beyond what is legally required – to uphold our high standards of quality, safety and transparency at all stages and in all countries where we conduct trials.”¹⁹²

In response to our questions, Novartis replied:

“Novartis does not ‘offshore’ clinical trials to non-traditional countries. Novartis conducts clinical trials where medicines are needed, where regulations require the conduct of local

¹⁹² Abbott website.. “Global Citizenship - Innovating for the Future - Responsible Research” http://www.abbott.com/global/url/content/en_US/40.15.15:15/general_content/General_Content_00439.htm (Accessed 5 December 2010)

trials and where the infrastructure, competence of researchers and capacity of ethic committees allow us to do so. Novartis is committed to the ethical principles laid down in the Declaration of Helsinki and applies the same quality and ethical standards in all its trials wherever they are conducted. Trials are also only conducted if it is planned to apply for a market authorization after development is successfully completed. Conduct of trials in non-traditional regions is necessary to ensure that data are generated which are relevant for those populations which will be treated. Clinical trials have also been essential in improving the quality of healthcare in general.” (10 November 2010).

This latter quote by Novartis suggests that its trials are conducted in regions for which the medicines are developed and where they are needed, which includes non-traditional trial regions. The company distances itself from the suggestion that relocation of clinical trials is mainly motivated by efficiency (e.g. quicker patient enrolment), but instead, indicates that Novartis is entering new markets. Some pharmaceutical companies go one step further and indicate that they are actively involved in drug development for diseases that are typical for these regions:

“We are seeking to develop new treatments that can help many different patient groups and our pipeline includes new medicines and vaccines that are needed in both developing and developed countries. To achieve this goal, GSK sponsors clinical trials in many countries around the world. GSK does not conduct clinical trials in countries when we know at the outset that there is no intent to pursue registration and make the product available for use in that country. In addition, we have a long-standing commitment to develop new treatments and vaccines for diseases specifically affecting developing countries.” (Written interview, GlaxoSmithKline, 7 December 2010).

Notwithstanding these self-declared altruistic motives for testing in non-traditional trial regions, the literature – also the professional literature from the pharmaceutical sector – often stresses the efficiency of clinical trial conduct in non-traditional trial regions as a major advantage for testing there (see paragraph 3.2). The verification of these noble statements by sponsors falls outside the scope of this research, as another research design would be needed that includes cross-checking clinical trial databases with MAA in non-traditional trial regions.

Pharmaceutical companies recognise the ethical risks present in some non-traditional trial regions, which include lack of oversight by authorities and ECs, and vulnerable patient groups. Companies indicate that one cannot generalise the situation among countries. India is mentioned as one of the countries where oversight is at its lowest. Because of the higher risks in some regions, pharmaceutical companies indicate that sites, suppliers (e.g. CROs) and subsidiaries in these regions receive extra attention:

“Sites in non-traditional countries are more frequently subject to internal audits to make sure their capacity meets the standards.” (Written interview AstraZeneca, 30 November 2010).

“We have an even more intensive screening process for suppliers in emerging markets, where risk levels may be higher. In 2009, we conducted our first audits in India and Mexico, while continuing our focus on suppliers located in China.” (Abbott website).¹⁹³

¹⁹³ Abbott website. “Global Citizenship – Supply Chain Management”
http://www.abbott.com/global/url/content/en_US/40.55:55/general_content/General_Content_00480.htm (Accessed 5 December 2010)

Furthermore, sponsors highlight that many trials in non-traditional regions are run in parallel with studies in traditional trial regions. As all these trials are part of the same testing research, they are executed according to the same protocol and the protocol will have received approval by ECs in traditional trial regions:

“Novartis sponsored trials comply with internationally agreed ethical standards. Novartis does not sponsor trials abroad which would not be approvable at home. In many cases, the protocols for trials enrolling patients in non-traditional regions have previously received a positive vote from ethic committees in traditional regions.” (Novartis, 10 November 2010).

“The feedback and responses from ethics committees are reviewed across a trial and inconsistencies are investigated. The Medical Science Director reviews any inconsistency in relation to international ethical standards, good medical practise, company standards and freely consult with the local AstraZeneca subsidiary. In addition, studies in non-traditional countries are almost always multinational and the same protocols are subject to regulatory and ethics committee review in countries with since long established tradition of clinical studies.” (Written interview AstraZeneca, 30 November 2010).

Without exception, the companies included in this study showed themselves to be sensitive to the problems related to informed consent when dealing with vulnerable populations. Pharmaceutical companies address this by training clinical research staff, and in some cases, requiring the presence of a third party witness in the informed consent procedure, as demonstrated by the following quote:

“The informed consent may be adjusted to the needs of the respective population through consultation with local health care professionals, and where available with patient groups. It may also include the participation of community representatives, and/or a literate independent and trusted witness (in case of poor literacy).” (Written interview, Novartis, 10 November 2010).

An interesting finding is that the need for ethically conducted clinical trials in general, and of a genuine informed consent procedure in particular, is brought into connection with the reputation of the sponsor. Evidence for an unethically conducted trial could sincerely harm the reputation of the sponsor. The following quote illustrates this:

“It is in the interest of Abbott that the research is conducted in accordance with the Declaration of Helsinki and Good Clinical Practice including a thorough informed consent procedure. Patients’ ability to withdrawn their informed consent at any time is one of the basic foundations of the declaration of Helsinki. Abbott will ensure that any of the studies they sponsor is conducted in line with GCP and the Declaration of Helsinki. Non-adherence to these regulations may have an effect on a company’s reputation. When working with vulnerable patient groups, the procedure is that a witness is present when gaining informed consent. The informed consent form also includes a phone number for a confidant.” (Telephone interview with Global Head Outsourcing of Abbott, 9 November 2010)

However, as we have seen earlier, the studies conducted in India and Latin America indicate that there is pressure to recruit patients as fast as possible. Moreover, speedy recruitment is one of the main reasons why clinical trials are offshored. These (monetary) incentives can have perverse effects if it seduces investigators to deviate from an ethical informed consent procedure (see also p. 66). In other words, the combination of the findings in India and Latin America with the

responses provided by pharmaceutical companies, suggests that investigators might receive rather mixed signals – a demand for speed on the one hand, and ethical conduct on the other – which are not necessarily a good combination.

Risk management in outsourcing relationships

At the beginning of this study, the expectation was that pharmaceutical companies would not yet fully recognise and implement their supply chain responsibility since the outsourcing in this sector is newer than in other sectors. However, the pharmaceutical sector appears to deviate from other sectors because the responsibility for the conduct of clinical trials is not negotiable:¹⁹⁴ as the sponsors of clinical trials, pharmaceutical companies will always have the end responsibility over the trial (see section 6.1), and they appear to have elaborate processes in place to assess and monitor the conduct of CROs. Due diligence (see Glossary), contracts, auditing and training are the core mechanisms through which CRO-conduct is managed by the sponsor.¹⁹⁵ The following quote provides insight into these mechanisms:

“When something would go wrong in a clinical trial with vulnerable patients that lacked oversight, the sponsor, Abbott, will be responsible. For this reason, Abbott has an elaborate Office of Ethics and Compliance, and maintains thorough oversight of its suppliers [which include CROs, authors]. Abbott goes through great lengths for policy enforcement. On Day 1 of the contract of every employee, they will need to sign the ‘Ethics and Compliance’ code. Abbott also has an internal inspection team, that will conduct unannounced inspections throughout all the company divisions and activities, including trial sites [...] Every supplier will be thoroughly audited before being selected.”
(Telephone interview with Global Head of Outsourcing, Abbott, 9 November 2010)

Without exception, the pharmaceutical companies indicate that they use thorough due diligence processes in selecting CROs. For instance, in response to our interview questions, Sanofi- Aventis states: *“The same high ethical standards and the same level of control are applied worldwide when a clinical trial is outsourced to vendors, maintaining ethical values and regulatory compliance for the protection of human subjects. Sanofi-Aventis always exercises due diligence in selecting and monitoring vendor practices”*, (Written statement, 3 December 2010).

And Janssen notes: *“Clinical trials are regulated by local law as well as by international standards (declaration of Helsinki, ICH-GCP, European trial directive, own internal Company Standard Operating Procedures) to which we adhere to also if we work with CROs. We have a robust due diligence process for CRO selection”*, (Written statement by Vice President of Clinical Research EMA of Janssen, 23 November 2010).

By indicating that CRO selection is an intensive process, in which ethics criteria are among the core selection criteria alongside price and quality, the pharmaceutical companies that participated in this study suggest that differences between CROs with regard to compliance with ethical guidelines do exist. AstraZeneca pointed this out explicitly by making the following statement:

¹⁹⁴ In other sectors we see that brand companies do not take full responsibility for the conduct of their products when they have outsourced the production to contract manufacturers.

¹⁹⁵ In terms of risk management in outsourcing relationships in the pharmaceutical sector, it is good to note that the major pharmaceutical companies, including the ones that participated in this study, are involved in an initiative called the Pharmaceutical Supply Chain Initiative, which has developed Principles for Responsible Supply Chain Management that may be voluntarily supported by any business in the pharmaceutical industry. The principles set the standard for ethics, labour, health and safety, environment and related management systems for suppliers. These principles, however, are mainly focused on internal business processes of suppliers (e.g. workplace safety, waste and emissions) and are thus not that relevant for our present concern about the safety of clinical trial participants. For more information on the initiative, see: <http://pharmaceuticalsupplychain.org/>

“The CROs we engage operate to international standards & regulations, including patient ethics. In addition, we have rigorous standards and processes in place, which are monitored and inspected to ensure overall integrity and compliance. We realize there are differences between CROs, but we only contract CROs that meet the highest standards.” (Written interview, AstraZeneca, 30 November 2010).

Apart from due diligence in CRO selection and auditing of CROs once they are contracted, trial sites are also monitored through auditing by the sponsor, whether they are managed in-house or by CROs on their behalf: *“Trials are selected for audit and assessment based on risk. Risk factors include the complexity of the study, the patient population, the location of the study, previous audit history and any unusual findings during the conduct of the study”* (Written interview, GSK, 7 December 2010).

In its 2009 corporate responsibility report, GSK actually provides insight into the number and types of audits they have performed in 2009:

“In 2009 we conducted 209 audits and assessments. These included:

- *169 investigator sites conducting GSK-sponsored trials. This represents approximately five per cent of investigator sites participating in pivotal clinical trials*
- *Two GSK systems and processes*
- *32 clinical research organizations carrying out clinical trials on GSK’s behalf*
- *Six GSK local operating companies involved in clinical research activities.*

In addition, 14 investigations were conducted in response to suspected irregularities at investigator sites [...]. Any concerns or issues identified are fully investigated and appropriate corrective action is taken”.¹⁹⁶

That auditing of trial sites is a widespread practice is confirmed by a recent global survey by Applied Clinical Trials (ACT: a magazine for clinical trial professionals) and the Tuft Center under ACT readership. The survey results indicated a substantial number of formal interactions each year between clinical trial participants and study sponsors: *“Aggregated globally, the typical investigative site had 5.5 study monitor visits each month with half handled by CROs, and received three site audits from sponsors or CROs in 2008. Sites also report having been inspected by a regulatory agency once on average during the past five years.”*¹⁹⁷ Note that the numbers relate to auditing of trial sites, and not to auditing of CROs by sponsors. Trial sites may be audited by pharmaceutical companies and CROs.

Although the numbers might be impressive, such figures need to be interpreted cautiously. First of all, respondents belong to ACT readership, which may be well-established professionals presumably in mostly developed regions. Furthermore, the results are aggregated globally, while here we are interested in the monitoring by sponsors of clinical trials that are handled by CROs in the developing world specifically. Furthermore, the frequency of monitoring does not say anything about the quality of monitoring.

¹⁹⁶ GlaxoSmithKline, Our Responsibility. Report 2009, <http://www.gsk.com/responsibility/research-practices/training-and-auditing-performance.htm> (accessed 14 January 2011).

¹⁹⁷ K.A. Getz and R. Zuckermann, Today’s Global Site Landscape, 2010, <<http://appliedclinicaltrialsonline.findpharma.com/appliedclinicaltrials/CRO%2fSponsor/Todays-Global-Site-Landscape/ArticleStandard/Article/detail/673673#>>, (accessed 5 August 2010)

With regard to the monitoring of CROs by sponsors, statements of two interviewees from the CRO sector raise doubts about the quality and frequency of such auditing. For instance, a manager of an international CRO operating in Argentina noted that: *“On occasions, the sponsor might audit the work of the CROs but these audits tend to occur in the headquarters of the company not in the national offices”* (Buenos Aires, 9 February 2010). And the Director of Ethics and Legal Affairs at ‘Ethica’ indicates that there are huge differences between pharmaceutical companies in how they verify ethical compliance by the CROs they contract: *“As every CRO works differently, pharmas can not know from the outside how the CRO works and applies standards and procedures. Some pharmas are conservative and acknowledge this. These will conduct audits before entering a relationship with a CRO, and in case of a successful audit, will add the CRO to its ‘preferred vendor’ list. Others will just go with word of mouth and contract a CRO without previous inspection. Some pharmas do regular audits, others do not”* (telephone interview, 8 October, 2009). He also made the observation that pharmas will only audit the CRO’s standard operations and adherence to ICH-GCP guidelines, and not adherence not to the Declaration of Helsinki.¹⁹⁸

The Director of Ethics and Legal Affairs from ‘Ethica’ observed another loophole in the auditing practice of sponsors that is of direct concern for the adequate protection of clinical trial participants: *“If pharmas conduct audits, they normally do not audit the quality of ethics committees and institutional review boards. Ethical authority is transferred to these bodies, but little is known about the standards they apply”* (telephone interview, 8 October 2009). Furthermore, audit reports by pharmaceutical companies are not publicly available, and thus the information in them is not verifiable.

Apart from auditing on ethical compliance by CROs, pharmaceutical companies indicate that they use training of CROs and clinical investigators to ensure such compliance. Especially with regard to guaranteeing an ethical and adequate informed consent procedure when vulnerable patients are involved, pharmaceutical companies indicate they have developed ways to cope with this challenge. For instance, Janssen states:

“It is clear that some emerging countries pose their own specific ethical concerns like ‘Can illiterate persons provide consent?’. I don’t want to go into a philosophical discussion but in my view we should not confuse illiteracy with incompetence. A large portion of the Indian population is illiterate, however this does not call into question the credibility of the political vote they exercise every five years. What is important is that people should be capable of understanding and making choices. As a sponsor it is important to know the challenges and spend time to ensure doctors are well trained in how to inform patients about the trial, that they explain this is an ‘experiment’, that patient has a choice and what the alternative treatment options are, that they can say ‘No’ [...]” (Written statement by Vice President Clinical Research EMA of Janssen, 23 November 2010).

6.3 Contracting and subcontracting

An unexpected finding from the interviews with pharmaceutical companies is that not all sponsors prefer outsourcing of clinical trials above managing clinical trials themselves. For instance, Janssen indicates that its strategy is to build up its own businesses in the non-traditional trial regions. CROs

¹⁹⁸ The Declaration of Helsinki provides better protection of clinical trial participants than the ICH-GCP guidelines, as the DoH is clearer and/or stricter with regard to the use of placebos, post-trial treatment, vulnerable subjects and clinical trial registration. For a comparison between the two, see pages 34-37 of the report: Directorate-General for External Policies. ‘Clinical Trials in developing Countries: How to Protect People Against Unethical Practices?’ (Brussels: European Parliament, 2009)

are normally only contracted when Janssen's internal capacity is exceeded: "As a sponsor we indeed make use of CROs but most often this is to manage our peaks in workload and very often we 'insource' CRO employees (work under our management) to help us with the investigations", (written statement by Vice President Clinical Research EMA of Janssen, 23 November 2010).

Abbott also indicates that it minimises the use of CROs: "Abbott prefers to hold specific activities in its own hands, amongst others, to ensure adequate control and oversight. In this sense, Abbott is an exception from the trend of maximal outsourcing that is visible in the pharmaceutical sector. When Abbott uses CROs in non-traditional regions, it will never replace Abbott, but rather complement Abbott activities. Abbott will always retain oversight over its trials," (telephone interview with Global Head Outsourcing of Abbott, 9 November 2010).

Janssen explicitly challenges the statement that outsourcing of clinical trials offers the greatest potential for cost savings: "Outsourcing a trial to a CRO means that you have to build internal oversight of the CRO and these costs need to be added to the CRO costs of doing the clinical trial work," (written statement by Vice President Clinical Research EMA of Janssen, 23 November 2010).

The above statements points to inefficiencies in sponsor-CRO contracting. This is confirmed in research by Anderson that was already mentioned in Chapter 3 (p 24). This research indicates that the management costs of outsourcing contracts in the pharmaceutical companies are high compared to other industries, and that sponsors actually pay double when they outsource to CROs: once for the contract, and once for supervising the contract.¹⁹⁹ Strategic sponsor-CRO partnerships – in which sponsors have longstanding contracts with one or a limited number of CROs – are brought up as a means to counter inefficiencies,²⁰⁰ and thus the sponsor-CRO partnership trend that was highlighted by many interviewees can most certainly be explained from such efficiency considerations.

Interviewees in the case study countries also brought up the issue of subcontracting of CROs to third parties. Sponsors make clear that CROs are required to inform the sponsor about such subcontracting, which is illustrated by the following quote by GSK: "We require CROs to inform us of any further outsourcing. This will often require our prior consent, and even if consent is not required, the CRO will be required to ensure that any subcontractor continues to conform to the requirements that the CRO is operating under," (written statement, 7 December 2010).

6.4 Chapter conclusion

All in all, we can conclude that, contrary to our expectations, pharmaceutical companies have elaborate systems in place through which they manage their supply chain responsibility. Due diligence in CRO selection, contracts, auditing and training of CROs, clinical investigators and trial sites are the most important means in this regard. This finding can well be explained by the fact that sponsors bear the formal responsibility for the ethical conduct of the trials they sponsor, and following this, are liable in most cases when participants would be harmed as a result of the trial. Whether these systems are adequate in protecting trial participants is hard to verify independently, because of a lack of transparency of the audit results, in combination with instances of insufficient

¹⁹⁹ B. Anderson. 'How we fail to use CROs effectively'. 2008, <http://appliedclinicaltrialsonline.findpharma.com/appliedclinicaltrials/Project+Management/How-We-Fail-to-Use-CROs-Effectively/ArticleStandard/Article/detail/534160> (accessed 16 December 2010)

²⁰⁰ B. Anderson. 'How we fail to use CROs effectively'. 2008, <http://appliedclinicaltrialsonline.findpharma.com/appliedclinicaltrials/Project+Management/How-We-Fail-to-Use-CROs-Effectively/ArticleStandard/Article/detail/534160> (accessed 16 December 2010)

monitoring by authorities, as was indicated in Chapter 4. However, the fact that stories about participants that have been harmed and remained uncompensated keep emerging²⁰¹ indicates that there is a gap between policies and practice.

²⁰¹ Wemos, *The Globalization of Clinical Trials: Testimonies from Human Subjects* (Amsterdam: Wemos, 2010); Documentary 'Body Hunters' by Paul Jenkins, 2010

7 Conclusions

The current research aimed to provide insight into the CRO sector and to analyse the ethical risks and ethical risk management associated with outsourcing and offshoring of clinical trials. The realisation of this ambition proved much harder than anticipated, because of the extreme lack of transparency of CROs in particular and the pharmaceutical sector in general. As a result, the empirical research conducted for this study delivered diverse and not necessarily comparable information. This means that some findings remain anecdotal, and thus generalisation from these findings should be avoided. Nevertheless, the collected data do provide valuable insights that help to validate the expectations that were formulated at the beginning of the study, which is done in the following section. In section 7.2 several directions for further research are outlined. Section 7.3 wraps up the report by outlining some directions for policy reform that would address the problems with transparency and trial subject protection that were identified in this study.

7.1 Characteristics of the CRO sector

Pharmaceutical companies are under pressure to bring more new drugs to the market while at the same time they have to cut their R&D budgets. CROs offer pharmaceutical companies access to extra global capacity, access to extra knowledge and to new technologies without making huge investments, and enable them to shift large fixed costs to variable costs. Currently, about half of the clinical trial activities of pharmaceutical companies are outsourced to CRO's. The worldwide CRO market is estimated to account for \$ 24 billion in 2010. In the past decade, the global spending by pharmaceutical companies on contract clinical services has been growing at an annual rate of 13.4% on average. The way the major CROs profile themselves on their websites gives a good sight on the drivers for outsourcing: they can conduct clinical trial faster and at lower costs, and they have established facilities in all new popular trial locations: Latin America, India, China, Central and Eastern Europe and Russia. These regions are popular for their fast recruitment of trial participants, the presence of a broad spectrum of diseases, the availability of human resources and technical skills, differing ethnic responses to drugs, and the availability of a "treatment naïve population". In the last five years, 37.3% of the participants in pivotal trials used for Marketing Authorisation Applications (MAAs) submitted in the EU were recruited in non-traditional research countries.

The major CROs have billion dollar revenues and offer the whole spectrum of services in a drug development process. Of the major global CROs, Quintiles is the market leader, with 14% of the global market share. The five largest CROs hold 45% of the total market between them. Nine out of the top ten CROs are present in the study countries for this report: India, Argentina, Peru and Brazil. The national CROs operating in the study countries tend to be small and do not conduct many clinical trials, but instead provide specialised supporting services in certain areas, such as data processing, recruiting personnel and identifying research centres. In Peru, 70% of all clinical trials are conducted by CROs, in Argentina about 30%. In all study countries except for Peru, CROs can operate without registration or accreditation; to register at the chamber of commerce is enough to start testing drugs on humans. In India, as well as in Brazil, the regulatory process is recently modified to expedite the approval of clinical trials which is a decisive factor to attract CROs.

The trend is that pharmaceutical companies want CROs to take greater risks and responsibility in the R&D process. This can take the form in outcomes-based contracting but also in strategic partnerships in which risk-sharing plays an important role.

7.2 Validation of expectations

The first expectation that was formulated at the beginning of the current research project was that the problems with outsourcing that have been observed in other industries – i.e. lowering of ethical norms because of cost and competition pressures and scattered responsibilities among value chain actors – would also be present in the pharmaceutical supply chain.

Indeed, interviews and secondary data revealed concerns over trade-offs between speed and costs of the clinical trial managed by CROs on the one hand, and the ethical quality of these trials on the other. The suggestion is that sponsors expect CROs to conduct the trial as quickly as possible, which might put pressure on the CROs to be lax on the ethics (e.g. by circumventing informed consent procedures, not reporting adverse events etc.). The interviews also point to subcontracting by CROs. This fragments clinical trial-related tasks further and squeezes budgets even more. Cost and time pressures combined with the fragmentation of clinical trials can easily lead to fragmented oversight over and a lack of comprehension of the full trial process. Another concern related to the functioning of CROs that arises from both interviews and secondary data analysis is the high personnel turnover rates at CROs, which would affect their functioning in a negative way, as CROs lose experienced and trained personnel. There are more concerns about the quality of the national CROs than the multinational CROs.

In the interviews conducted for this study, sponsors confirmed the concerns over CRO performance. Because of this, they have developed mechanisms to select, monitor and evaluate CROs in order to guarantee compliance with relevant laws and ethical standards. In fact, these mechanisms greatly increase the costs of CRO-sponsor contracts, which affect the business case for working with CROs, and makes some sponsors wary of outsourcing clinical trial management altogether. Notwithstanding these claims of sponsors, interviews with CROs indicate that the stringency of monitoring mechanisms varies widely among sponsors, which obviously creates opportunities for under-performing CROs – CROs that may not effectively ensure the quality of the trial and the ethical protection of trial participants – to slip through these control mechanisms. Whether these risks actually materialise into more harm for clinical trial participants cannot be assessed with this study. However, since our data reveal that independent oversight of CROs and clinical trial sites by authorities and ethics committees is perceived to be insufficient in at least India, Brazil and Argentina, the concerns remain justified.

The second expectation was that, notwithstanding the widespread practice of outsourcing to CROs in non-traditional trial regions, pharmaceutical companies would not yet fully recognise and control their responsibility for all the actors in the research and development process. This expectation is not confirmed: according to international regulations, pharmaceutical companies remain formally responsible for the ethical conduct of the trial they sponsor, in sharp contrast to other sectors where supply chain responsibility is not enforceable but instead is characterised as a moral responsibility. Pharmaceutical companies claim they have several mechanisms in place to control the research and development process: due diligence in CRO selection, contractual arrangements, auditing and training of CROs, clinical investigators and trial sites are the most important means in this regard. But since documentation of these internal processes is not publicly available, it is impossible to verify the adequate functioning of these mechanisms.

At the policy level, the protection of participants in clinical trials managed by CROs in non-traditional trial regions seems to be in order, but what happens in practice is hard to verify. The design of the current research could not verify whether pharmaceutical companies indeed do what they claim to do and whether their monitoring of CROs is adequate. And as the study indicates, independent oversight by authorities in India and Brazil and by ECs in India, Brazil and Argentina leaves a lot to be desired. Furthermore, European MAA procedures for drugs that have involved testing outside Europe currently do not include independent verification of the ethical conduct of the trials. This situation obviously leaves a lot of room for improvement in the protection of clinical trial participants in non-traditional trial regions.

The third expectation that was formulated was that, because the outsourcing trend in the pharmaceutical industry is relatively new, the liability distribution in outsourcing relationships within the pharmaceutical industry would not be fully crystallised. This expectation is not fully confirmed either: responsibilities are fairly clear on paper, as according to drug laws and ethical guidelines, the sponsor remains responsible for the ethical conduct of the clinical trial. However, there are exceptions (e.g. negligence and misconduct by CROs or principal investigators), and the conditions for these exceptions are not strictly outlined. Furthermore, it remains unclear how responsibility will shift when sponsors and CROs enter into partnerships. And since such partnerships seems to be a trend, this leaves an important area unexplored.

Pharmaceutical companies suggest that participants have a clear portal for compensation if a trial-related injury occurs, which is communicated via informed consent forms. In most cases the sponsor is responsible for compensation, but there are exceptions (e.g. negligence of third parties). It remains unclear how and to what extent these exceptions are made. Furthermore, questions remain with regard to the burden of proving that an injury is trial related. Stories about participants who have been harmed and remain uncompensated keep on emerging.²⁰² Therefore, further scrutiny of the accessibility of compensation mechanisms for clinical trial participants seems to be necessary.

7.3 Recommendations for follow-up research

The current study points out several important areas for follow-up research. First of all, research findings indicate that several sponsor-CRO outsourcing models exist, and that the trend is moving towards risk-sharing partnerships. This might not only change the liability distribution for trial-related injuries between CROs and sponsors, but it also changes the interest of CROs in clinical trials. By changing outsourcing models and interests, the ethical risks may change as well. If CROs adopt risk sharing modalities, where they profit from developing a new molecule, they might experience conflict of interest in data collection. Another type of model, functional outsourcing (as opposed to full-service types of contracts), is associated with a different risk, namely the reduction of the general oversight over the trial. It is important to get a better understanding of the different outsourcing models, including the interests of sponsors and CROs in each model and the ethical risks that they entail.

An interesting aspect of such research could also be the study of the liability distribution between pharmaceutical companies and sponsors for trial-related injury in the different outsourcing models. Although the liability distribution seems fairly straightforward at first, the devil appears to be in the detail (e.g. under what conditions can a CRO be regarded as 'negligent?'). Furthermore, the

²⁰² Wemos, *The Globalization of Clinical Trials: Testimonies from Human Subjects* (Amsterdam: Wemos, 2010); Documentary 'Body Hunters' by Paul Jenkins, 2010

partnership trend will probably have consequences for CRO liability. From the perspective of clinical trial participants, the answer to this question is important, as it might influence the route to compensation in case of adverse events. Research of cases of litigation between pharma and CROs, and between clinical trial participants and sponsors seems to be the most straightforward way to address this question. However, this research might be unrealistic as many cases are not filed, others are settled out of court, and the judicial records of those that go to trial are not always available.

A third important area of research regards the procedures for compensation of clinical trial participants when adverse events occur. The impression that is provided by sponsors is that clinical trial participants have a clearly communicated portal for possible trial-related claims, and will not be sent from pillar to post. As was indicated above, it remains to be verified whether this portal functions adequately, and whether compensation is adequate. The development of an adequate research design for this will be challenging in itself, as it would ideally involve clinical trial participants who have been harmed by participating in a clinical trial. These people are hard to identify.

It would also be interesting to gather more information about the performance of several types of CROs. For instance, there are indications that multinational CROs significantly outperform local CROs. Such research would entail a series of studies comparing the completeness of the regulatory packages that are submitted to regulatory agencies; the quality of trial monitoring reports; the researchers' satisfaction with the CRO's performance; the sponsor's satisfaction with the quality of services provided to the sponsors. The main limitation to conduct these studies is the secrecy that surrounds all pharmaceutical research.

Particularly important is the quality of monitoring of trial sites by sponsors and CROs, since the upholding of GCP guidelines is largely in their hands in non-traditional trial regions. For instance, an insightful research design would be to compare trial site audit reports of CROs and pharmaceutical companies with inspection reports of regulatory agencies. Again, it seems highly unrealistic that such a research will ever be feasible while incentives for transparency of audit reports are lacking.

7.4 Recommendations for target groups

The research experiences and findings have possibly resulted in more questions than answers. In this light, this study might be interpreted more as a discussion document than as a concluding document. In fact, possibly the largest contribution of this study is that it highlights the lack of transparency of the pharmaceutical sector, which inherently implies that ethical concerns over the safety of clinical trial participants in non-traditional trial regions are justified.

From the problems we experienced in conducting this study, it is apparent that transparency of the sector needs to be greatly improved, along with independent oversight of clinical trial conduct. It remains an area of grave concern that the parties that earn most money with the trials – CROs and sponsors – seem to be the most important monitors in non-traditional trial regions. To improve transparency and independent oversight of clinical trials in non-traditional trial regions, several measures could be taken:

- Set up world wide compulsory trial register in which all parties involved in the trial, including contractors and subcontractors, are disclosed.
- Increase the number of inspections of trial sites in non-traditional trial regions.

- Include in MAA procedures independent verifications that the drugs have been tested in accordance with the DoH.
- Involve independent organisations that promote the interest of clinical trial participants in (CRO and sponsor) audits of trial sites.
- Involve clinical trial participants in inspections and audits, so that their perspective on the ethical conduct of the trial is included.
- Make audit and inspection results publicly available.

We sincerely hope that this study will help to persuade authorities in both traditional and non-traditional trial regions, as well as sponsors and CROs, that measures like these are crucial in order to protect vulnerable clinical trial subjects in non-traditional trial regions.

Annex 1: List of interviewees

Nº	Category	Firm or institution	Position	Date, place and length of interview
Phase 1				
1	Expert	University of Toronto, Faculty of Law	Associate Professor	05.08.2009, Telephone, 1 hour
2	Expert	University of Groningen, Faculty of Behavioural and Social Science	Professor	22.09.2009, Amsterdam, 1 hour 30 minutes
3	CRO	Ethica	Director of Ethics and Legal Affairs	08.10.2009, Telephone, 1 hour
Phase 2				
India				
4	CRO	Confidential	President	28.05.2010, Mumbai, 50 minutes
5	CRO	Confidential	Clinical research associate	12.05.2010, Mumbai, 40 minutes
6	Expert	Confidential	Journalist	04.06.2010, Mumbai, 45 minutes
7	Expert	Confidential	Editor/author	21.05.2010, New Delhi, 1 hour 15 minutes
8	EC	Confidential	Member	01.06.2010, Mumbai, 1 hour
9	Regulatory sector	Confidential	Retired from Indian Council of Medical Research	07.06.2010, Chennai (telephone interview), 40 minutes
10	Clinical investigator	Confidential	Professor of Oncology	21.05.2010, New Delhi, 40 minutes
Argentina				
11	Hospital	Confidential	Director of Clinical Research Unit	12.02.2010 Buenos Aires, 1 hour 45 minutes
12	Hospital	Confidential	Director of Clinical Research Unit	12.05.2010 Buenos Aires 2 hours
13	Pharmaceutical company	Confidential	Head of Clinical Operations	28.05.2010. Buenos Aires, 1 hour 20 minutes
14	Pharmaceutical company	Confidential	Head of Clinical Operations	04.02.2010. Buenos Aires,

				1 hour 40 minutes
15	Pharmaceutical company	Confidential	Clinical Research Director for Latin America	27.05.2010. Buenos Aires, 1 hour 20 minutes
16	Business Association	Confidential	President	17.05.2010 Buenos Aires, 50 minutes
17	EC	Confidential	Member	19.05.2010 Buenos Aires, 1 hour 15 minutes
18	EC	Confidential	Vice-President	23.05.2010 Buenos Aires, 1 hour
19	EC	Confidential	All EC members	29.04.2010 Buenos Aires (group interview) 2 hours
20	Regulatory sector	National Directorate for Personal Data Protection (DNPDP)	Lawyer	29.04.2010 Buenos Aires 45 minutes
21	CRO	Confidential	Manager of Regulatory Affairs	28.05.2010 Buenos Aires, 1 hour 30 minutes
22	CRO	Confidential	Director	28.04.2010 Buenos Aires, 1 hour 10 minutes
23	CRO	Confidential	General Manager Latin America	09.02.2010 Buenos Aires, 1 hour
24	CRO	Confidential	Clinical Operations Manager Argentina	27.04.2010. Buenos Aires, 1 hour
25	Regulatory sector	National Drug Administration (ANMAT)	Director of DEMA (Directorate for the Evaluation of Medicine)	27.05.2010 Buenos Aires, 40 minutes
26	Regulatory sector	National Health Commission	Advisor	23.04.2010 Buenos Aires, 1 hour 45 minutes
Brazil				
27	CRO	Large International CRO	Advisor of Regulatory Affairs	10.08.2010 Brasília 1 hour 30 minutes
28	CRO	National CRO	Head of Clinical Research	28.07.2010 São Paulo 50 minutes
29	CRO	National CRO	Auditor	28.07.2010 São Paulo 40 minutes
30	Clinical Investigator	Confidential	Coordinator of Research of private research institute	17.08.2010 São Paulo 1 hour
31	Clinical Investigator	Confidential	Principal Investigator	24.08.2010 Brasília 1 hour 40 minutes

32	EC	Regional Treatment Center against AIDS	Coordinator	13.08.2010 São Paulo 2 hours
33	EC	State Health Department of Federal District	Coordinator	13.08.2010 Brasília 45 minutes
34	Regulatory sector	ANVISA	Responsible for the area of new drugs and clinical research	15.06.2010 Brasília 2 hours 15 minutes
35	Regulatory sector	CONEP	Member	09.09.2010 Brasília 1 hour 10 minutes
Phase 4				
38	Pharmaceutical company	Abbott	Global Head Outsourcing	09.11.2010 Telephone interview 1 hour
39	Pharmaceutical company	Janssen (pharmaceutical division of Johnson & Johnson)	Vice President, Clinical Research EMA	23.11.2010 Written statement
40	Pharmaceutical company	Novartis	Responsible managers, coordinated by Corporate Communications	10.11.2010 Written interview
41	Pharmaceutical company	GlaxoSmithKline	Responsible managers, coordinated by Corporate Affairs	07.12.2010 Written interview
42	Pharmaceutical company	AstraZeneca	Responsible managers, coordinated by Corporate Communications	30.11.2010 Written interview
43	Pharmaceutical company	Sanofi-Aventis	Responsible managers, coordinated by Corporate Communications	24.11.2010 Written statement

Annex 2: Calculation of outsourcing percentages to non-traditional countries

The European Medicines Agency (EMA) keeps track of the number of patients in pivotal trials in marketing applications per region and year since 2005. However, these figures must be seen in the light of an historical situation as the recent increases in clinical trials in Asia are not reflected yet in the data provided. This is because there are several years between the time an MAA is submitted and the time the trials are completed. Besides that, the EMA only keeps track of the pivotal trials, which represents just a fraction of the total numbers. It is a possible scenario that a drug development process includes 50 trials, of which in the end only five are identified as pivotal and those are used for the marketing application. This means that in this case only 10% of the trials are included in the collected data. Supportive trials are not included – which means Phase I, most Phase II, and some Phase III trials. And we have to remember that many products never come to market so the clinical trials on those products do not appear in these data either. Even after all these disclaimers, it is worthwhile noting that the number of patients in clinical trials in MAAs for the EU conducted in non-traditional countries was about 35 per cent in the last five years (see Table 17).

The following table gives the number of patients in:

- EU-15/EEA countries: the member states of the European Union prior to the accession of the ten new countries on 1 May 2004, plus EEA countries (Norway, Iceland and Liechtenstein)
- North America: USA and Canada
- Rest of World (ROW) + EU-10 +EU-2:
 - Africa, Middle East/Asia/Pacific, Australia/New Zealand, Central/South America, CIS (Commonwealth of Independent States i.e. Russia, Ukraine, Georgia etc.), Eastern Europe (non EU) (i.e. Croatia, Serbia etc.)
 - 2004 accession countries (Cyprus, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Malta, Poland, Slovakia and Slovenia)
 - EU-2: 2007 accession countries (Bulgaria and Romania).

Table 17: Patient numbers presented from a pre-2004/2007 accession perspective

Patients per region/year	2005	2006	2007	2008	2009	Total
EU-15/EEA	27,822	30,714	42,894	27,561	33,711	162,702
North America	37,117	33,389	41,810	55,165	42,269	209,705
ROW + EU-10+ EU-2	21,653	48,384	40,895	64,101	46,059	221,092

Based on an assumption that many of the patients, particularly in the earlier years, may have been recruited prior to accession. (Note that totals do not include Switzerland)

Source: EMA, November 2010.

The table clearly indicates a shift of testing from traditional to non-traditional trial regions. The following conclusions can be drawn from Table 17:

- 72.6% of all patients in pivotal trials in MAAs in the last five years participated in trials outside Europe prior to accession (in third countries).

- 37.3% of all patients in pivotal trials in MAAs in the last five years participated in trials conducted in non-traditional research areas if we consider the category of ROW + EU-10 + EU-2 as such areas.²⁰³

The changes in the distribution of clinical trials globally can also be illustrated by looking at the number of clinical trial principal investigators per region in FDA filings. In 1990, 86% of clinical trial principal investigators were based in the US. By 2007, the figure stood at 57%.

In Table 18, the number of clinical trial sites registered with the FDA is presented for 1997-2007: 29% sites were located outside the EU and USA in 2007.

Table 18: Percentage of clinical trials registered with the FDA, by site

	United States	Western Europe	Rest of world
1997	86%	9%	5%
1999	80%	9%	12%
2001	77%	10%	13%
2003	70%	11%	19%
2005	62%	13%	25%
2007	57%	14%	29%

Note: Not all percentages total 100% due to rounding.

Source: Tufts Center for the Study of Drug Development analysis of FDA data.

²⁰³ Although Australia/New/Zealand are included here with 8,678 in the total numbers. Without these countries the percentage is 36.3%.

Annex 3: CROs in India

This list is compiled based on the website of ACRO India²⁰⁴ and the Biomedical Research Web.²⁰⁵ Only those CROs conducting clinical trials are included. The SMOs providing clinical trial services for CROs and pharmaceutical companies are not included. The service companies providing laboratory services for clinical trials (pre-clinical services) are also not included. The list was compiled on 20 December 2010. The descriptions and qualifications are copied from the internet listings and thus not formulated by SOMO.

APEX International Clinical Research Co. Ltd. – An Asia-Pacific based, ICH-GCP compliant CRO offering a complete range of clinical research and new drug development services. APEX is familiar with regulatory requirements for implementing clinical trials in Asian countries.
<http://www.apex-cro.com> (APEX is part of Paraxel)

AXIS Clinicals Ltd – Ten plus (10+) regulatory audits from global competent authorities Services offered: BA/BE, Clinical Trials (Phase 2-4), Clinical Reference Lab, Bioanalytical
<http://www.axisclinicals.com>

Abridge BA/BE Monitoring Services – Abridge is India's premier BA/BE and clinical endpoint audit and monitoring service. They specialise in helping USA, European and Australian sponsors insure accurate and complete reports of their BA/BE and clinical endpoint studies.
<http://www.abridgemonitoringindia.com>

Actimus Biosciences Pvt. Ltd. Visakhapatnam – Actimus Bio is a full-service BA/BE CRO dedicated to meeting the needs of pharmaceutical and biotechnology companies. Actimus Bio facility is approved by Drugs Controller General of India (DCGI).
<http://www.actimusbio.com>

Alticure Research Pvt Ltd – Alticure is a research company founded for overseeing and managing clinical trials of drugs and vaccines, for Indian and global pharma companies.
<http://www.alticure.com>

Asian Clinical Trials – Indian CRO designs and conducts preclinical and clinical Phase I to IV trials for pharmaceutical, biotechnology and medical device companies without compromising on ICH-GCP standards. This is a subsidiary of Suven Life Sciences.
<http://www.act-india.com>

Asiatic Clinical Research – A full-service CRO with core competency in late stage clinical trials in Oncology & Dermatology. With eminent oncologists and physicians on its advisory board and a network of 200+ investigator sites & tools for patient compliance.
<http://www.asiaticclinical.com>

²⁰⁴ <http://www.acroindia.org>

²⁰⁵ <http://www.biores.org>

Azidus Laboratories – Azidus is a full-service clinical research organisation catering to the technical needs of pharmaceutical and biotechnology industries for the conduct of BA/BE studies, Clinical trials, Clinical Data Management, Pharmacovigilance.

<http://www.azidus.com>

Member of ACRO India.

Biosen Group – BIOSEN Group is an independent, dedicated research facility that conducts Phase I-IV clinical research in collaboration with local community physicians in India. Their mission is to provide integral quality clinical research. <http://www.biosengroup.com>

Bioserve Clinical Research - India – Bioserve CRO offers regulatory Phase I/BA/BE services, ISO 9001:2008 Certified, DCGI/USFDA inspected, Our facility offers Clinical Services, Bioanalytical Services, Pharmacokinetic & Statistical Analysis and Regulatory Affairs support.

<http://www.bioserve.co.in>

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Catalyst Clinical Services – An independent full-service CRO offering GCP clinical research services in India. Clinical trials in India offer rapid enrolment, treatment naive patients, and economically favourable costs.

<http://www.catalystclinicalservices.com>

ClinInvent Research Pvt Ltd – ClinInvent Research Pvt Ltd is a fully-fledged Contract Research Organisation, which provides comprehensive services for complete clinical trial and data management.

<http://www.clininvent.com>

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CliniReach – CliniReach is a Contract Research Organisation that acts as a strategic partner to the organisations in clinical research, biotechnology, bioinformatics, pharmaceutical, biopharmaceutical, agrochemical and chemical industries.

<http://www.clinireach.in>

Clinical Research India - Altree Lab Pvt Ltd – Altree Lab Pvt Ltd, Cochin, Kerala.

ajay@altreelab.com

<http://www.altreelab.com>

Clinfocus – Clinfocus offer regulatory consulting service, site management service, Clinical Research training service, independent monitoring service

<http://www.clinfocus.com>

Clinigene International Limited is a full-service Clinical Research Organisation that partners with global pharmaceutical and biotechnology companies in their clinical development programmes. Clinigene specialises in Phase I-IV clinical trials and studies, using well-characterised clinical databases in diabetes, oncology, lipidemia and cardiovascular diseases.

<http://www.clinigeneintl.com>

CliniRx Research – CliniRx is a full-service Clinical Research Organisation with offices across India and the US. They offer clinical trial services to pharmaceutical and biotechnology companies ensuring that trials are ICH-GCP compliant.

<http://www.clinirx.com>

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Clinsys – Clinsys is a full-service Clinical Research Organisation that provides pharmaceutical, biotechnology and medical device companies with a broad range of clinical research services in support of Phase I-IV drug and device development, including project management, clinical monitoring, scientific and medical support, investigator and patient recruitment, site management, biostatistics, data management, drug safety, quality assurance, regulatory affairs and medical writing.

<http://www.clinsys.com>

Clintrac International Pvt Ltd – A Contract Research Organisation based in Bangalore, India.

<http://www.clintracintl.com>

Consortirum Clinical Research Pvt. Ltd. – Carries out clinical research related: audits, monitoring, Phase II-IV clinical trials, project management, CRO & vendor assessments, site management, SOP designing, training, regulatory affairs, study feasibility assessments, medical writing.

<http://www.ConsortiumCR.com>

Cqua Research International Inc – Full-services clinical trial management group, 200 clinical sites in India, and Canada and ownership of many research sites and a Phase I facility in India. Cqua provides access to India's quick, cost effective, and quality drug development research services to CROs and sponsor companies.

<http://www.cquaint.com>

DIL Limited – DIL Limited (formely Duphar-Interfran Ltd.) – A dynamic-intelligent-lively organisation located in Thane (India) that provides customised research solutions.

<http://www.dil.net>

Dabur Research Foundation – A Contract Research Organisation based in India, providing integrated research solutions for pharmacological, biological and analytical testing of drugs and chemicals in vitro and in vivo to pharmaceutical, chemical and biotechnology companies worldwide.

<http://www.daburresearch.in>

Diagnostic Immunology Lab Services – OncQuest's advanced clinical and research laboratories are fully equipped with molecular technology allowing for rapid advancement in the complex field of pharmacogenomics, proteomics, companion diagnostics, bioinformatics and biomarker studies.

<http://www.oncquest.net>

DiagnoSearch Life Sciences Pvt Ltd was one of the first clinical trials management companies to establish operations in India, and has since become an award-winning CRO with a substantial track record in conducting ICH-GCP compliant clinical research.

<http://www.diagnosearch.com>

Dr. Lal Path Labs, Clinical Research & Diagnostic Services – Dr Lal Path Labs has a rich working experience of 58 years as a reference laboratory and is one of the highest accredited laboratories in the country.

<http://www.lalpathlabs.com>.

Excel Life Sciences, Inc. – US-based India-focused clinical research solution provider. Special emphasis on PI & site identification and total study conduct.

<http://www.excellifesciences.com>

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Fermish Clinical Technologies Pvt. Ltd. India – Fermish Clinical Technologies Pvt. Ltd. India provides complementary services for clinical research and Pharmaceutical Regulatory Services.

<http://www.fermish.com>

GVK BIO – GVK BIO is a leading Contract Research Organisation from India, which provides contract research services to global pharma and biotech companies.

<http://www.gvkbio.com>

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Genomics/Proteomics Research & Consulting Services – Siri provides on-site and offshore services including data services, work on expensive technologies in drug design. Based out of Bangalore, India.

<http://www.siritech.com/life.htm>

Gleneagles CRC – A Pan-Asian Site Management Organisation and Contract Research Organisation headquartered in Singapore.

<http://www.gleneaglescrc.com>

Global Clinical Trials & Research Organization – GCTRO is a USA based CRO, specializing in doing Clinical Trials in India for US and Canadian Sponsors.

<http://www.gctro.com>

Hanul Medizin Pvt Ltd – A clinical research and medicomarketing consultancy based in India. They offer services for medical writing, and project management of clinical trials.

<http://www.hanulmedizin.com>

ICON Clinical Research India Pvt. Ltd.

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iGATE Clinical Research – iGATE Clinical Research International is a Contract Research Organisation offering a complete range of clinical trials support services for conducting Phase II-IV clinical trials in India.

<http://www.igate.com/icri/>

INTOX PVT. LTD. – INTOX is a toxicological CRO located in Pune, near Mumbai in India, and conducts toxicity studies on pharmaceuticals, agrochemicals and biological.

<http://www.intoxlab.com>

Integrity Healthcare Service (IHS) – Integrity Healthcare Service (IHS) is a Contract Research Organisation aimed at providing customised solutions for complete healthcare and pharmaceutical industry requirements.

<http://www.ihsindia.com>

Integrity Medical Group, Inc. – Delivering clinical trials on time and within budget, Integrity Medical Group offers a full range of contract research services to the pharmaceutical, biotech and medical devices industry through established global professional networks.

<http://www.imedgrp.com>

KPS Clinical Services Pvt. Ltd. – KPSCS is an Indian based CRO providing a variety of services for clinical trials and pharmaceutical regulatory affairs in India.

<http://www.kpsclin.com>

Lotus Labs – Offers the conduct of Clinical Trials – specifically the Phase II-IV trials, Clinical facilities at Lotus Labs are spread across four locations aggregating a capacity of over 360 beds. What's more, Lotus Labs has access to a database of over 18,000 active volunteers.

<http://www.lotuslabs.com>

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LAMBDA – A leading multinational CRO with head office in Ahmedabad, India and branch in Mumbai, India; Warsaw, Poland and USA. A team of over 500 committed personnel across its offices empowered by state-of-the-art infrastructure works on all aspects of clinical drug development including clinical trials, clinical laboratory, data management, Bioequivalence/Bioavailability studies.

<http://www.lambda-cro.com>

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Leads Clinical Research – LEADS is a clinical research consultancy and Site Management Organisation (SMO) headquartered at Bangalore, India, with a network of qualified and experienced professionals across the country.

<http://leadsclinicalresearch.com>

MakroCare – Full service CRO based in US/India/Japan/Europe works with pharmaceutical/biotech companies to conduct clinical trials in various therapeutic areas.

<http://www.makrocare.com>

Materiamedica Services Pvt. Ltd. – MMSPL is a Contract Research Organisation operating from Mumbai India since 1996, including multinational clinical trials and healthcare functions.

<http://www.dagaonkar.com>

Meddevices – A full-service CRO based out of India with the ability to do both medical device and drugs clinical trial, data management, site management, statistical analysis and publishing of results as per international/European guidelines.

<http://www.meddevices.net>

Micro therapeutic Research Labs (MTR) is a full-service Clinical Research Organisation that provides a broad range of clinical research services to the global pharmaceutical and biotechnology industry.

http://www.microtheraps.com/Clinical_trials.html

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Neeman Medical International (NMI) – Neeman Medical International (NMI) is an international Contract Research Organisation in India.

<http://www.neeman-medical.com>

Member of ACRO India.

Orange Lifesciences – Clinical Research Management Organisation operating in India

<http://www.orangeicr.com>

Progressive Life Sciences – Contract Clinical Research Organisation providing clinical trial management, data management, site management, clinical trial monitoring, medical consulting, regulatory consulting, medical writing, in India.

<http://www.progressivelifesciences.com/>

Prodia the CRO – Contract research organisation that provides full support to pharmaceutical industries or other CROs to conduct GCP clinical trials.

<http://prodiathecro.com>

Raptim Research is an established Contract Research Organisation located in Navi Mumbai, India. The BA/BE facility is situated in Navi Mumbai, about 40 minutes drive from the Mumbai Airport. The Clinical and Bio-analytical facilities are under one roof.

<http://www.raptimresearch.com/services.html>

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Rejuvendus Clinical Research Pvt. Ltd. – A full-service CRO dedicated to providing clinical trials management and support to pharmaceutical companies for Phase I – IV clinical trials.

<http://www.rejuvendus.com>

Reliance Clinical Research Services – Reliance Clinical Research Services (RCRS - www.relclin.com) is a leading full-spectrum Contract Research Organisation in India.

<http://www.relclin.com>

Research Support International Ltd – Incorporated in 2004, Research Support International Limited ('RSIL') is a 100% subsidiary of DIL Ltd. (formerly Duphar-Interfran Ltd.) providing Contract Research & Custom Synthesis.

<http://www.rsil.biz>

Sipra labs is a USFDA registered and DSIR approved Contract Research Organization engaged in drug development support services to the pharma industry. The centre has a team of 150 scientists engaged in different innovative research projects for global regulatory submissions. The thrust of the organization is to create one-stop-research solutions to the drug and pharmaceutical industry. Phase II to IV Studies.

<http://www.sipralabs.com>

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Siro ClinPharm Pvt Ltd – Full-service CRO based in India, works with pharmaceutical companies to conduct clinical trials in various therapeutic areas.

<http://www.siroindia.com>

Synchron Research Services Pvt. Ltd. – Indian CRO provides a broad range of Phase I clinical research services including bioavailability, bioequivalence and pharmacokinetic studies in their new clinical research unit.

<http://synchronresearch.com>

TCG Lifesciences Ltd. – A leading life sciences contract research and informatics solutions organisation focused on enabling Translational Medicine. Expertise areas - Discovery Research, Clinical Research & Development and Enterprise Informatics.

<http://www.tcgl.com>

Vedic Lifesciences Pvt Ltd – A Phase II-IV CRO that is committed to bringing down the cost of clinical trials through innovative trial design and conduct without compromise on ethical and regulatory standards. Founded in 2000, they manage 6-10 projects every year in urology, diabetes, inflammation, respiratory, etc.

<http://www.vediclifesciences.com>

Veeda Clinical Research is a full-service global CRO specialising in the early clinical development of drugs. The largest Phase I CRO in India. <http://www.veedacr.com/>

Vimta Labs is India's leading contract research and testing organisation. A full-service CRO for Phase-I/ Bioequivalence studies. Over 1,100 BA/BE studies conducted so far on various dosage forms such as tablets, capsules, extended release preparations, gels, jellies, solutions, transdermal patches, injectibles, etc.

<http://www.vimta.com>

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Wellquest Clinical Research – Mumbai-based CRO Wellquest is the clinical outsourcing division of Indian pharmaceutical company Nicholas Piramal. It has two facilities: one in Hyderabad and one at the Wellspring Hospital in Mumbai. Wellquest was established in 2000 by Nicholas Piramal and has conducted about 100 pivotal trials and 40 pilot studies. Both facilities are compliant with Good Clinical Practice and Good Laboratory Practice guidelines.

Member of ACRO India

Xcleris Labs is a specialty Contract Research and Services Organization delivering end to end solutions to global Pharma and Biotechnology communities.

<http://www.xclerislabs.com>