REVIEWS

More questions than answers

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Mariette van Huijstee, Irene Schipper, editors. *Putting contract research organisations on the radar.* Amsterdam: Centre for Research on Multinational Corporations (SOMO), Salud y Farmacos, Centre for Studies in Ethics and Rights; February 2011. ISBN 978-90-71284-68-7.

The past two decades have seen the emergence of third world countries as important sites for drug trials and related clinical research sponsored by the pharmaceutical industry. As the authors of the report under review have noted, "fast recruitment of trial participants, presence of a broad spectrum of diseases, availability of human resources and technical skills, different ethnic responses to drugs and the availability of treatment naïve population" are powerful drivers of this phenomenon. In addition to such off-shoring, the authors have also drawn attention to outsourcing of trials to clinical research organisations (CROs). Considering the potential for abuse of rights and ethical deviations, such a study of this phenomenon was a pressing need.

The research questions the authors have raised are:

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

The authors' expectations at the initiation of this study were that:

1. The same problems with outsourcing - like lowering of labour and environmental standards - that have been observed in other industries would be observed here, too.
2. Despite outsourcing being a widespread practice, pharmaceutical companies do not recognise, *and implement,* their responsibilities down the chain, and
3. Outsourcing being a relatively new phenomenon, the distribution of liabilities between sponsor and CRO would not have crystallised.

The study involved a preliminary literature review, country-level studies in Argentina, Brazil, India and Peru, and interviews with clinical trial experts and pharmaceutical companies. Not surprisingly, they report that the realisation of the research ambition proved much harder than anticipated *because of the* "extreme lack of transparency of CROs in particular and the pharmaceutical industry in general" - leading to delivery of "diverse and not necessarily comparable information". In other words, both CROs and pharmaceutical companies were not forthcoming with quality information.

The authors report on whether or not their expectations at the initiation could be conclusively confirmed:

1. Their first expectation that the standard of ethics would be lower was confirmed - ethics had to yield to speedy recruitment and cost containment.
2. Their second expectation - that industry may not take the responsibility for all players in the research and development process - could not be confirmed; while at the policy level protections seemed in place, there was lack of independent oversight on the part of regulators and ethics committees in the developing world.
3. Their third expectation also could not be confirmed, as responsibilities were fairly clear on paper with the sponsor remaining responsible for the ethical conduct of the clinical trial. What was not clear was: who would be responsible if there were negligence or misconduct, for example.

The authors have not been able to establish the extent of shift of responsibility from sponsor to CRO - for oversight and liabilities when there is an agreement to outsource. They were not privy to these agreements. As reported elsewhere (1)1, these agreements are not submitted to ethics committees or regulators; therefore, enforcement of this liability is a major issue.

The authors concede that the research throws up more questions than have been answered. Lack of investigative authority has forced them to depend on interviews rather than on documents. This is a major drawback. Pharmaceutical majors Bristol Myers Squibb, Eli Lilly, Merck/MSD, Pfizer-Wyeth and Roche did not participate at all. Janssen and Sanofi-Aventis only submitted written statements in response to questions. Abbot, AstraZeneca, GSK and Novartis gave complete interviews on the telephone or by email.

The report with seven chapters has been finalised after five phases of activity:

Phase 1 : preliminary, exploratory study; phase 2 : country-level studies; phase 3 : analysis and integration of country studies phase 4 : interviews with pharmaceutical companies; phase 5: review by partners and companies.

The greatest attraction of this report is its lucidity. The conclusions are predictable, if a trifle disappointing. Despite the handicaps of the study, the authors identified the following as measures to be taken for protection of participants' rights:

- Setting up a worldwide, compulsory trial register in which all involved parties including the contractors and subcontractors are disclosed.
- Increasing the number of regulatory inspections of trial sites in non-traditional trial regions.
- Including in Marketing Authorisation Application procedures independent verifications that the drugs have been tested in accordance with the Declaration of Helsinki.
- Involving independent organisations that promote the interest of clinical trial participants in audits of trial sites conducted by sponsors and CROs.
- Involving clinical trial participants in inspections and audits, so that their perspective on the ethical conduct of the trial is included.
- Making audit and inspection results publicly available.

That would be a good way to go.

Reference

1. Mohan A. Ethics and contemporary urology practice: setting out principles. *Indian J Urol* 2009;25:340-2.

Human building blocks of research

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Rebecca Skloot. *The immortal life of Henrietta Lacks.* Macmillan Publishers Ltd; 2010. pp. 368 £18.99

The immortal life of Henrietta Lacks is non-fiction of a rare quality in creative writing. The author, a science journalist, weaves a multilayered narration about medicine, medical research, faith, racism, poverty, and ethics with a skill that renders to her composition an "immortal quality".

Henrietta Lacks was an African-American woman, a mother of five children, who died of cervical cancer in 1951, at the age of 31. At the Johns Hopkins Hospital in Baltimore, United States, where she was receiving treatment, tissue specimens were taken from her cervix for research, without her knowledge. The specimens turned out to be the source of the first viable and amazingly productive cell line - the famous HeLa cells so familiar to all engaged in medical and cell biological research. The cells became the fountainhead of a range of medical discoveries, research applications, therapeutics and vaccines. The book provides a human face to the many ethical issues concerning the HeLa cell line.

The cervical tissue specimen was used by George Gey at Johns Hopkins. Gey's assistant labeled the tubes where the cells were stored "HeLa". The cells doubled in number every 24 hours and never stopped. Since then many trillions of cells have been produced and used in laboratories and factories all across the globe and are robust even after 60 years. The polio vaccine, the drug tamoxifen, gene mapping, in vitro fertilisation, treatments for influenza, leukaemia, Parkinson's Disease are all applications which have harnessed the biological potential of HeLa.

Science is not the only fascinating aspect of this book that lifts it to the rank of a best seller; nor is it the central theme. The author, in her exploration along with Deborah, the daughter of Henrietta, who did not know her mother, has been able to knit together a story of the sad life of Henrietta, the racist norms of that period, the deprivations of African-Americans, and the almost non-existent research ethics of the mid 20th century. It is shocking that even after 20 years after HeLa became a famous biomedical research tool, Henrietta's family was unaware of these developments. Needless to say, they did not receive even a few pennies of the profits from the multimillion dollar industry in biological and cell culture based on her cells. Much later, they were even subjected to investigations without their informed consent.

In February 2010, Rebecca Skloot spoke at the Kimmel Cancer Centre in Philadelphia to a crowd of physicians and scientists, most of whom knew HeLa cells, but nothing else of their origin or history. She told the story of the young black woman who reported to the clinic at Johns Hopkins for treatment for a tumour in her cervix. She received the treatment of the time, a course in radiation. The diagnostic sample took a course of its own. It went to a cell biologist who knew nothing about its origin until it started producing manically upon culture. Mass production ensued. HeLa was distributed around the world. Skloot described the family's anguish at the fact that a vial of HeLa cells costs $250 and some HeLa-derived products for treatment cost up to $10,000, while many members of the Lacks family go without health insurance and treatment for their illnesses.

As research and discovery activities go global, there may be some warnings for us in India. Human subjects who participate in experiments give "informed consent". How informed is this consent? Does the consent form list all possible uses to which a specimen may be put? For example, DNA material is collected