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REGULATING CLINICAL TRIALS IN INDIA: THE ECONOMICS OF ETHICS

ABSTRACT

The relationship between the ethical standards for the governance of clinical trials and market forces can be complex and problematic. This article uses India as a case study to explore this nexus. From the mid-2000s, India became a popular destination for foreign-sponsored clinical trials. The Indian government had sought to both attract clinical trials and ensure these would be run in line with internationally accepted ethical norms. Reports of controversial medical research, however, triggered debate about the robustness and suitability of India's regulatory system. In response to civil society pressure and interventions by the Supreme Court, the Indian government proposed additional measures aimed at strengthening protections for clinical trial participants. Whilst the reforms can be seen as a victory for human rights activists, they have also been criticised as being overly burdensome for sponsors. Indeed, their announcement prompted an exodus of clinical trials from India. Fearful of losing business to 'rival' countries, the Indian government is revisiting some of its proposals.

The Indian example suggests that research ethics frameworks and national policies for economic development are increasingly intertwined. Host countries are in theory free to improve the lot of research participants, but doing so may make them appear less attractive to foreign sponsors, who can simply shift their activities to more industry-friendly jurisdictions. Although these economic pressures are unlikely to lead to a regulatory 'race to the

bottom’, they may limit host countries’ ability to enact socially desirable reforms.

INTRODUCTION

From the early 1990s onwards, pharmaceutical companies and public sector researchers began shifting clinical trials from the well-established regions of North America and Western Europe to other locations; including India, China and countries within South America and Eastern Europe.¹ This trend - known as the ‘globalisation of clinical trials’² - is driven largely by economic considerations.³ When compared to the ‘traditional’ regions, emerging countries offer significant savings, due in part to cheaper labour costs. Furthermore, faster patient recruitment helps speed up the process of completing trials and bringing new drugs to market. Offshoring and outsourcing are facilitated by contract research organisations (CROs); independent companies which can organise and run trials on the sponsor’s behalf.

Far from being mere passive recipients, host countries may seek actively to attract medical research. There are clear incentives for doing so. As well as

¹ A. Petryna. 2009. *When Experiments Travel: Clinical Trials and the Global Search for Human Subjects*. Princeton, NJ: Princeton University Press.

² Department of Health and Human Services, Office of Inspector General (OIG). 2001. *The Globalization of Clinical Trials: A Growing Challenge in Protecting Human Subjects*. Washington, DC: OIG. Available at: <https://oig.hhs.gov/oei/reports/oei-01-00-00190.pdf> [Accessed 20 Feb 2017].

³ T. Lang & S. Siribaddana. Clinical Trials Have Gone Global: Is This a Good Thing? *PLoS Med* 2012; 9: e1001228;

bringing in large sums of money and increasing employment, exposing local doctors to cutting-edge practices may help strengthen a country's own medical research base and its domestic pharmaceutical industry.⁴

At the same time, responsible host countries must also protect the rights of their citizens. Medical research involving human subjects has a chequered history. Past examples of unethical abuses usually feature asymmetries of power and weak regulatory oversight as background factors.⁵ Both elements may be present in developing countries with little prior experience of medical research. Much of the academic discussion to date has therefore flagged the globalisation of clinical trials as a potential human rights concern.⁶ Commentators have underscored the need for host countries to establish robust regulatory systems and uphold appropriate ethical standards.⁷

As yet, however, little attention has been given to the ways in which host countries are attempting to achieve the twin goals of attracting clinical trials and protecting research participants. Are the two objectives mutually supportive, or might they pull in different directions? Analysis of other policy domains (e.g. labour standards) suggests that the desire for national economic

⁴ S. Sariola et al. Big-pharmaceuticalisation: Clinical trials and Contract Research Organisations in India. *Soc Sci Med* 2015; 131: 239-246.

⁵ A. Dhai. The Research Ethics Evolution: From Nuremberg to Helsinki. *S Afr Med J* 2014; 104: 178–180.

⁶ J.E. Jesus & E.S. Higgs. International Research Ethics: Progress but Not Perfection. *Trends Mol Med* 2002; 8: 93-95; Clinical Trials in India: Ethical Concerns. *Bull WHO* 2008; 86: 581-582.

⁷ S.W. Glickman, J.G. McHutchinson & E.D. Peterson. Ethical and Scientific Implications of the Globalization of Clinical Research. *N Engl J Med* 2009; 360: 816–823.

competitiveness can complicate the pursuit of more stringent regulations.⁸ It is therefore timely and important to assess whether a similar dynamic exists in the context of clinical trials and, if so, to consider its implications.

India offers an ideal case study with which to pursue this research theme. Within a relatively short period of time, India has witnessed a sudden boom in clinical trial activity followed by regulatory crisis, attempts at legal reforms and an exodus of clinical trials. This article draws out the tension between economics and ethics inherent within this narrative. The Indian example demonstrates that economic considerations are becoming an important factor in clinical trial regulation. It is not claimed that this policy dynamic is either entirely new⁹ or limited exclusively to developing countries.¹⁰ Rather, by offering the first application of this analytical lens to the Indian regulatory journey, the article shows how the intertwining of economic and ethics can unfold in different contexts in different ways.¹¹ In addition, the paper aims to advance understanding of this policy dynamic through connection with other literature. The ‘race to the bottom’ hypothesis has been tested in relation to other policy domains, but has yet to be applied systematically to clinical trials.

⁸ R.B. Davies & K.C. Vadlamannati. A Race to the Bottom in Labour Standards? An Empirical Investigation. *J Dev Econ* 2013; 103: 1-14.

⁹ T.L. Lai. Incorporating Scientific, Ethical and Economic Considerations into the Design of Clinical Trials in the Pharmaceutical Industry: A Sequential Approach. 1984 *Commun Stat Theory Methods*; 13: 2355-2368; N.G. de Santo et al., eds. 1997. *Human Clinical Research: Economics and Ethics*. Naples, Italy: Istituto Italiano per gli Studi Filosofici.

¹⁰ A.S. Kesselheim & J. Avorn. New “21st Century Cures” Legislation: Speed and Ease vs Science. *JAMA* 2017; 317:581-582; A. Ward. 2016. Fast-track Drug Approval Schemes Signal More US-EU Collaboration. *The Financial Times*. 16 May.

¹¹ N. Homedes & A. Ugalde, eds. 2014. *Clinical Trials in Latin America: Where Ethics and Business Clash*. Springer.

By connecting hitherto disparate bodies of literature in a critical way, the article contributes to scholarship on the globalisation of clinical trials and also to more general regulatory debates. The paper's main argument is that whilst commercial pressures are unlikely to lead to a straightforward race to the bottom, they may nevertheless limit a host country's ability to adopt ethics regulations that cohere meaningfully with the health needs and interests of its citizens. The discussion is focussed on India, but given the parallels with other jurisdictions, the conclusions are of relevance to the promotion of fair and just clinical trial regulation in developing countries more broadly.

THE INDIAN REGULATORY FRAMEWORK FOR CLINICAL TRIALS

The official position of the Indian government regarding the growth of its clinical trials service industry is difficult to ascertain. As yet, there have not been any overarching policy documents laying out a definitive stance. Nevertheless, insights can be gleaned from various sources. For example, in 2006, as part of the submission of Five Year Plans to cover the period 2007-2012,¹² two governmental Working Groups set out their views on the opportunities and risks presented. There were differences in perspectives, as well as overlaps.

The Working Group on Drugs and Pharmaceuticals was composed of representatives from government bodies and the Indian pharmaceutical

¹² Government of India, Planning Commission. *Eleventh Five Year Plans 2007-2012*.

Available at: <http://planningcommission.nic.in/plans/planrel/fiveyr/welcome.html>

[Accessed 20 February 2017].

industry.¹³ This group viewed economic growth as a core objective. Seen in this light, the global industry's desire to contain the spiralling costs of clinical trials offered tremendous possibilities for India. Worldwide, the outsourcing market for research contracts and clinical trials was estimated at around US\$60 billion at the end of 2005.¹⁴ India's share of this market was thought to be around \$US100 million and predicted to grow at the rate of 80%.¹⁵ Clinical trials were thus framed as a major international business opportunity to be taken advantage of.

By contrast, the Working Group on Health Systems Research, Biomedical Research and Development and Regulation of Drugs and Therapeutics focussed more on addressing India's urgent health challenges.¹⁶ It included representatives from government bodies, health research institutes and NGOs. Its report highlighted the heavy burdens of infectious and non-communicable diseases in India, lamenting the low levels of investment in public health and the unsatisfactory state of the health system. Set against this backdrop, medical research was seen as important for encouraging the development of drugs, medical devices and vaccines relevant to the health needs of India's poor.¹⁷ The possibility of India becoming an international hub for clinical

¹³ Government of India, Planning Commission. 2006. *Report of the Working Group on Drugs and Pharmaceuticals for the Eleventh Five-Year Plan (2007-2012)*. Available at: <http://planningcommission.nic.in/plans/planrel/11thf.htm> [Accessed 20 February 2017].

¹⁴ Ibid: 25.

¹⁵ Ibid.

¹⁶ Government of India, Planning Commission. 2006. *Report of the Working Group on Health Systems Research, Biomedical Research and Development and Regulation of Drugs and Therapeutics: Eleventh Five-Year Plan (2007-2012)*. Available at: <http://planningcommission.nic.in/plans/planrel/11thf.htm> [Accessed 20 February 2017].

¹⁷ Ibid: ii.

trials was welcomed, as it would give an opportunity to be at the forefront of drug discovery; presumably to the benefit of the Indian population.¹⁸

The working groups' reports contained some conceptual tensions. For example, access to healthcare was cast ambiguously as both a serious problem and a helpful advantage. Inadequate spending on public health was criticised, yet the resulting high numbers of 'treatment naïve' patients was presented as a selling point. Indian patients would be eager to enrol in studies as a way to receive good quality medical care and dropout rates would be low.¹⁹ Whilst eliding the complex ethical concerns about structural exploitation that such observations raise,²⁰ both working groups emphasised the need for medical research to comply with "strict ethical norms".²¹ But what kind of normative vision would be enshrined in the regulatory framework?

Some background details are useful for addressing this question. As in other countries, the Indian legislation establishes ground rules and allocates responsibilities to various bodies. The Drugs and Cosmetics Act, 1940 (as amended) confers powers to the relevant licensing authority, namely the Drugs Controller General of India (DCGI), for the approval of new drugs.²² The DCGI heads the Central Drugs Standard Control Organisation (CDSCO); India's main regulatory body for pharmaceuticals and medical devices. CDSCO is itself part of the Indian Ministry of Health and Family Welfare.

¹⁸ Ibid: 32.

¹⁹ Government of India, Planning Commission, *op. cit.* note 13, p. 63.

²⁰ K. Sunder Rajan. Experimental Values: Indian Clinical Trials and Surplus Health. *New Left Review* 2007; 45: 67-88.

²¹ Government of India, Planning Commission, *op. cit.* note 16. p.10.

²² Drugs and Cosmetics Act 1940 (as amended up to the 31st December 2016). Available at: <http://www.cdsc0.nic.in/forms/contentpage1.aspx?lid=1888> [Accessed 20 February 2017].

The Drugs and Cosmetics Act also grants authority to the central government to create more detailed secondary legislation. This resulted in the Drugs and Cosmetics Rules, 1945 (as amended).²³ In 1988, Schedule Y was added to the Drugs and Cosmetics Rules, establishing the framework used by the DCGI when evaluating applications to commence trials.²⁴ The 1988 version was created mainly with the Indian generic pharmaceutical industry in mind. In 2005, however, Schedule Y was updated to position India as a player in the new era of globalised clinical trial activity.²⁵

A good starting point for understanding how ethical concerns were weighed against the goal of attracting clinical trials is the loosening of legal restrictions on the testing of drugs developed outside India. Previously, Schedule Y only permitted clinical trials of drugs developed abroad with a ‘phase lag’, e.g. a phase II trial could be conducted in India only if a phase III trial had already been completed abroad.²⁶ After 2005, Indian patients could be enrolled in phase II and III clinical trials of ‘foreign’ drugs.²⁷ Other administrative reforms were also aimed squarely at attracting trials. These included the speeding up of regulatory approvals before trials can commence, allowing the use of public hospitals as clinical trial sites and the abolition of

²³ Drugs and Cosmetic Rules, 1945 (as amended up to 31st December 2016). Available at: <http://www.cdsc.nic.in/forms/contentpage1.aspx?lid=1888> [Accessed 20 February 2017].

²⁴ Drugs and Cosmetics (Eight Amendment) Rules, 1988, G.S.R. 944(E), 4.

²⁵ A. Bhatt. Evolution of Clinical Research: A History Before and Beyond James Lind. *Perspect Clin Res* 2010; 1: 6-10.

²⁶ Drugs and Cosmetics (Eight Amendment) Rules, 1988, G.S.R. 944 (E), Schedule Y, 1.1.

²⁷ Drugs and Cosmetics (IInd Amendment) Rules 2005, G.S.R. 32 (E), Schedule Y, 1(1)(iv).

relevant service taxes.²⁸ Whilst not connected directly to encouraging clinical trials, changes to Indian patent law in 2005 were another key development. After accession to the World Trade Organization in 1995, India was required to allow product patents on pharmaceuticals. Although likely to exacerbate problems of access to medicines, product patents facilitated clinical trials by allowing sponsors to test drugs without fear of unauthorised copying.

The above reforms have been criticised for prioritising economic development over the interests of Indian patients.²⁹ The force of this argument is, however, lessened by a number of protective measures that were also put in place. For example, Schedule Y only permits phase II or III trials of drugs discovered abroad if conducted concurrently with other global trials.³⁰ Indian patients should therefore only be exposed to the levels of risks deemed acceptable in other, presumably well-regulated, jurisdictions. Second, foreign sponsors are generally not permitted to conduct phase I trials in India.³¹ This shows that the Indian government sought to shield its citizens by limiting their exposure to riskier ‘first-in-human’ studies, even if that would mean foregoing some economic benefits.

²⁸ S. Srinivasan. The Clinical Trial Scenario in India. 2009. *Economic and Political Weekly* 29August - 4 September; M. Imran et al. Clinical Research Regulation in India - History, Development, Initiatives, Challenges and Controversies: Still Long Way to Go. *J Pharm Bioallied Sci* 2013; 5: 2-9.

²⁹ V. Bajpai. Rise of Clinical Trials Industry in India: An Analysis. *ISRN Public Health* 2013; 167059.

³⁰ Drugs and Cosmetic Rules, 1945 (as amended up to 31st December 2016), Schedule Y, 1(1)(iv)(b).

³¹ *Ibid.*

Measures were also taken to increase regulatory oversight. Steps towards improving transparency and accountability were made in 2009 when the online registration of clinical trials in the Clinical Trials Registry - India (CTRI) became mandatory.³² The ethics committee system was also overhauled. Previously, ethics committee approval before initiating a clinical trial was seen as “desirable” but not obligatory.³³ If none of the institutions or sites involved in a clinical trial had an ethics committee in place, a trial protocol could simply be accepted by the investigator and the DCGI. Since 2005, the DCGI has required the documented approval of a properly constituted ethics committee before it can allow a trial to begin.³⁴ Ethics committees must now review clinical trial protocols³⁵ with reference to three research guidelines: (i) the Declaration of Helsinki,³⁶ (ii) the Indian Council for Medical Research’s (ICMR) Ethical Guidelines for Biomedical Research

³² Clinical Trials Registry - India. Available at: <http://ctri.nic.in/Clinicaltrials/login.php> [Accessed 20 February 2017].

³³ Drugs and Cosmetics (Eight Amendment) Rules, 1988, G.S.R. 944 (E), 4.

³⁴ Drugs and Cosmetics (IIInd Amendment) Rules 2005, G.S.R. 32 (E), 3(2).

³⁵ Drugs and Cosmetic Rules, 1945 (as amended up to 31st December 2016), Appendix II, 6.

³⁶ World Medical Association (WMA). 2013. *WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects*. Available at: <http://www.wma.net/en/30publications/10policies/b3/> [Accessed 20 February 2017].

on Human Participants,³⁷ and (iii) the Indian version of international Good Clinical Practice (GCP) guidelines.³⁸

These changes to the ethics review process served two purposes. As well as promising tighter ethical safeguards, they helped transform India into a more credible destination for research. Compliance with GCP guidelines, in particular, is necessary to allow sponsors to use Indian clinical trial data to support applications to market drugs in the United States³⁹ and the European Union.⁴⁰ India's adoption of international norms, *inter alia*, would reassure a global audience concerned about the commercial usability of data.

Yet having incorporating international guidelines, India was then faced with the question of how to manage any differences between them. The Declaration of Helsinki and GCP diverge on several topics, including the

³⁷ Indian Council of Medical Research (ICMR). 2006. *Ethical Guidelines for Biomedical Research on Human Participants*. New Delhi: ICMR. Available at: http://www.icmr.nic.in/ethical_guidelines.pdf [Accessed 20 February 2017].

³⁸ Central Drugs Standard Control Organization (CDSCO). 2001. *Good Clinical Practices for Clinical Research in India*. Available at: <http://www.cdsc.nic.in/html/GCP1.html> [Accessed 20 February 2017].

³⁹ United States Code of Federal Regulations. Revised as of 1 April 2016. *Foreign Clinical Studies not Conducted under an IND, 21 CFR 312.120*. Available at: <https://www.fda.gov/RegulatoryInformation/Guidances/ucm126426.htm> [Accessed 20 February 2017].

⁴⁰ *Regulation (EC) No. 726/2004 of the European Parliament and of the Council of 31 March 2004 Laying down Community Procedures for the Authorisation and Supervision of Medicinal Products for Human and Veterinary Use and Establishing a European Medicines Agency, (16)*. Available at: <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:136:0001:0033:en:PDF> [Accessed 20 February 2017].

much-debated issue of post-trial obligations.⁴¹ Paragraph 30 of the 2000 version of the Declaration of Helsinki states that at the end of the trial, every participant should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.⁴² This prompted much international discussion due to the lack of even basic drugs in most developing countries.⁴³ In 2004, the World Medical Association (WMA) added a Note of Clarification on paragraph 30.⁴⁴ This reaffirmed its earlier position regarding post-trial access and went further by stating that post-trial access arrangements or other care must be described in the study protocol so the ethical review committee may consider such arrangements during its review. Both the international⁴⁵ and Indian versions of GCP guidelines,⁴⁶ by contrast, are notably silent on this issue. When updating its own bespoke research guidelines in 2006, the ICMR opted to follow the more beneficent

⁴¹ L.J. Burgess & D. Pretorius. FDA abandons the Declaration of Helsinki: The Effect on the Ethics of Clinical Trial Conduct in South Africa and other Developing Countries. *SAJBL* 2012; 5: 87-90.

⁴² World Medical Association (WMA). 2000. WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. Available at: <http://www.who.int/bulletin/archives/79%284%29373.pdf> [Accessed 20 April 2017].

⁴³ ICMR, *op. cit.* note 37, p. 30.

⁴⁴ World Medical Association (WMA). 2004. WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. Available at: http://www.chrt.org.hk/english/service/files/app_6_cop.PDF [Accessed 20 April 2017].

⁴⁵ International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). 1996. ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice E6(R1). Available at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf [Accessed 20 April 2017].

⁴⁶ CDSCO, *op. cit.* note 38.

approach taken in the 2004 version of the Declaration of Helsinki. Post-trial access to drugs ‘should’ be provided.⁴⁷ Nevertheless, as in the Declaration of Helsinki itself, the language used was of strong recommendation rather than compulsion. Despite being confronted with the problem of access to medicines on the ground in India, the ICMR appears to have been reluctant to go beyond the Declaration of Helsinki by changing a ‘should’ to a ‘must’ and thereby imposing concrete post-trial obligations on sponsors.

On the issue of compensation for injury, however, the 2006 ICMR Guidelines did forge something of a new path. Whereas the 2004 version of the Declaration of Helsinki does not mention compensation, the ICMR Guidelines establish that sponsors should agree to provide compensation for any physical or psychological injury for which participants are entitled or agree to provide insurance coverage for an unforeseen injury whenever possible.⁴⁸ The ICMR also recommended that an arbitration committee or appellate authority could be set up by the institution to decide on the issue of compensation on a case-by-case basis.⁴⁹ The institutional independence of such bodies, however, was not stipulated clearly. Again, both mechanisms appear to be weakened by their framing as strong recommendations rather than as mandatory requirements.

Overall, the Indian government was attempting to strike a complex balance of interests. Its reforms contained both liberalising and protective features. On the one hand, Indian patients were being made more accessible to clinical

⁴⁷ ICMR, *op. cit.* note 37, p. 30.

⁴⁸ ICMR, *op. cit.* note 37, p. 29. Following the debates and legal reforms in India, a paragraph addressing the issue of compensation was later included in the 2013 version of the Declaration of Helsinki. WMA 2013, *op. cit.* note 36, para. 15.

⁴⁹ ICMR, *op. cit.* note 37, pp. 29-30.

trial sponsors and CROs, but important safeguards - such as the requirement for concurrent trials and restrictions on phase 1 trials - were also established. India's ethics regime was brought into line with international standards through linkage with the Declaration of Helsinki and GCP, yet the 2006 ICMR rules reflected the uncertainties and compromises within those guidelines on the vexed issue of post-trial access to drugs. The ICMR did lay down recommendations on the issue of compensation for injury at a time when the Declaration of Helsinki had nothing to say on this particular issue, but ambiguities in the phrasing of the rules seem to undercut their force.

In terms of real-world impact, the new regulatory framework was successful in luring clinical trials to India. According to DCGI figures, the number of clinical trial approvals shot from a mere three in 2007 to a highpoint of 500 in 2010.⁵⁰ India's growth, however, should be placed in context. Compared to other countries, its overall level of clinical trial activity was still relatively small.⁵¹ Nevertheless, proof of concept had been established. India could now compete for an even larger share of the global market. Achieving this objective, however, would not be straightforward. Ethical controversies would later derail the government's aspirations.

CONTROVERSIAL MEDICAL RESEARCH

⁵⁰ V.S. Chawan, K.V. Gawand & A.M. Phatak. Impact of New Regulations on Clinical Trials in India. *Int J Clin Trials* 2015; 2: 56-58.

⁵¹ Pugatch Consilium. 2015. *Quantifying the Economic Gains of Strengthening India's Clinical Research Policy Environment*. Available at: <http://www.pugatch-consilium.com/reports/Quantifying the Economic Gains from Strengthening the Clinical Research Policy Environment in India.pdf> [Accessed 20 February 2017].

There is disagreement about the extent of the problem of non-compliance with clinical trial regulations in India. Some argue that the Indian regulatory system is not adequately geared towards protecting patients, who may be treated as ‘guinea pigs’ by unscrupulous operators.⁵² On the other side of the debate, it is asserted that the vast majority of Indian clinical trials are run conscientiously and in line with regulations.⁵³ Even if a few ‘outliers’ can be identified, it is argued, comparable ethical lapses may also be found in other jurisdictions, including within North America or Europe.⁵⁴ It follows that it would be wrong to portray India as inherently worse than other countries in terms of research ethics compliance. Whilst acknowledging the dangers of overgeneralisation, some problematic clinical trials are recounted below to give context to the later discussion regarding legal reforms.

According to news reports and legal submissions, victims of the 1984 Bhopal gas explosion were enrolled in clinical trials at the Bhopal Memorial Hospital and Research Centre, often without their knowledge or informed consent.⁵⁵ When patients involved in trials died, investigations were not conducted by an independent body and nor was compensation offered to families of the deceased. Problems with informed consent also surfaced in a

⁵² S. Nundy & M.C. Gulhati. A New Colonialism? Conducting Clinical Trials in India. *N Engl J Med* 2005; 352: 1633-1636.

⁵³ K. Barnes. 2006. Indian Clinical Trials “Of No More Ethical Risk than in US”. 2006. *Outsourcing-Pharma.com* 22 September. Available at: <http://www.outsourcing-pharma.com/Clinical-Development/Indian-clinical-trials-of-no-more-ethical-risk-than-in-US> [Accessed 20 February 2017].

⁵⁴ Ibid.

⁵⁵ S. Chattopadhyay. Guinea Pigs in Human Form: Clinical Trials in Unethical Settings. *Lancet* 2012; 379: 26; N. Lakhani. 2011. From Tragedy to Travesty: Drugs Tested on Survivors of Bhopal. *The Independent* 15 November.

large-scale ‘observational study’ of vaccines for the prevention of Human Papilloma Virus (HPV). Vulnerable tribal girls in Andhra Pradesh and Gujarat were recruited into the study without proper parental consent.⁵⁶ Seven girls who received vaccines died. Although a later Parliamentary committee concluded that the deaths were likely unrelated to the vaccines, strong criticisms were expressed about failures to follow informed consent procedures and the lax reporting of adverse events.⁵⁷ The committee also stressed that the project should have been categorised as a phase IV clinical trial; with all the attendant procedural safeguards.

Such cases may reflect underlying issues within the regulatory system. Indian ethics committees are said to struggle with a lack of trained personnel, heavy workloads and inadequate support.⁵⁸ An ICMR survey has raised questions about appointment processes and more generally the independence and competence of some Indian ethics committees.⁵⁹ For its part, the DCGI is said to lack sufficient manpower to cope with the sudden rise in clinical trial activity.⁶⁰ Furthermore, once the DCGI has approved a clinical trial, it rarely follows up with inspections to ensure that regulations are being adhered

⁵⁶ P. Bagla. Indian Parliament Comes Down Hard on Cervical Cancer Trial. *Science* 2013. Available at: <http://www.sciencemag.org/news/2013/09/indian-parliament-comes-down-hard-cervical-cancer-trial> [Accessed 20 February 2017].

⁵⁷ P. Shetty. Collapsed Trial Fuels Unfounded Vaccine Fears. *Nature* 2011; 474: 427-428.

⁵⁸ A. Jesani. Ethics in Ethics Committees: Time to Share Experiences, Discuss Challenges and Do a Better Job. *Indian J Med Ethics* 2009; 6: 62-63; R. Kadam and S. Karandikar. Ethics Committees in India: Facing the Challenges! *Perspect Clin Res* 2012; 3: 50-56;

⁵⁹ M. Desai. Ethics Committee: Critical Issues and Challenges. *Indian J Pharmacol* 2012; 44: 663-664.

⁶⁰ B. Mamdani & M. Mamdani. Colonialism of Clinical Trials: Discerning the Positive Spin Offs. *Indian J Med Ethics* 2005; 2; 132-133: 132.

to.⁶¹ Grassroots activists have campaigned to change this general state of affairs.

LEGAL REFORMS

Several public interest litigation (PIL) petitions relating to clinical trials have been filed in the Indian Supreme Court.⁶² In terms of outcomes, the most significant to date was that brought by the Indore-based NGO Swasthya Adhikar Manch (SAM; 'Health Right Forum') in 2012.⁶³ Highlighting the kinds of improper practices and harms to patients discussed above, the broadly-focused petition requested that the Supreme Court end the

⁶¹ R. Talele. Getting Ready for Inspection of Investigational Site at Short Notice. *Perspect Clin Res* 2010; 1: 64-66.

⁶² C. Terwindt. Health Rights Litigation Pushes for Accountability in Clinical Trials in India. *Health Hum Rights* 2014; 16; E84-95. Available at: <http://www.hhrjournal.org/2014/11/06/health-rights-litigation-pushes-for-accountability-in-clinical-trials-in-india/> [Accessed 20 February 2017]. On 5 April 2017, during hearings in a PIL that seeks the cancelation of two licences for the HPV vaccines discussed above, the Indian Supreme Court referred the question of whether it could rely upon a Parliamentary Committee Report during proceedings for consideration to a Constitution bench: V. Misra. 2017. Can Supreme Court Rely upon Parliamentary Committee Report, Constitution Bench to Decide. *Bar & Bench* 6 April. Available at: <https://barandbench.com/parliamentary-committee-report-supreme-court/> [Accessed 20 April 2017].

⁶³ Writ Petition (Civil) No(s). 33/2012, Swasthya Adhikar Manch, Indore & Anr. vs. Ministry of Health and Family Welfare & Ors. with WP(C) No. 79/2012. Supreme Court of India: Record of Proceedings. 21 April 2014.

Available at: <http://courtnic.nic.in/supremecourt/temp/wc%203312p.txt> [Accessed 20 February 2017].

exploitation of Indian patients and scrutinise whether the Indian regulatory system is fit for purpose.⁶⁴ During the hearings, the Indian Ministry of Health and Family Welfare submitted an affidavit stating that between 2005 and 2012, a total of 2868 clinical trials participants died.⁶⁵ Of these, 89 deaths were considered to be related to trials and compensation was paid to relatives of the deceased in 82 cases.⁶⁶ It appears that in the outstanding cases, the compensation remained unpaid because the investigator could not trace the whereabouts of the legal heirs.⁶⁷ These statistics were summoned from the sponsors and collated by the CDSCO only after the Supreme Court PIL was filed. Prior to this, as of 2012, a smaller number of trial victims – just 22 - had received compensation, and these payments came after a committee chaired by Manekha Gandhi, Member of Parliament, had investigated the matter in 2011.⁶⁸

At the time of writing, the Supreme Court of India has not yet issued its final disposition in the case, but has given several interim orders that have

⁶⁴ Swasthya Adhikar Manch. 2012. Bhopal Gas Peedit Mahila Udyog Sanghatan Writ Petition No. 33 of 2012.

Available at: http://www.unethicalclinicaltrial.org/Awarness_Material.aspx [Accessed 20 February 2017].

⁶⁵ Clinical Trials in India. Ministry of Health and Family Welfare, Government of India. 30 Aug 2013.

Available at: <http://mohfw.nic.in/index1.php?lang=1&level=4&sublinkid=3719&lid=2641> [Accessed 20 February 2017].

⁶⁶ Ibid.

⁶⁷ Ibid.

⁶⁸ J. Puliyeel. Compensation for Victims of Clinical Trials: A Discussion of How Current Indian Rules and Guidelines are Hurting India. *J Clin Diagn Res* 2012; 6: 1367-1368.

had a far reaching effect.⁶⁹ In January 2013, in an internationally unprecedented move, the Supreme Court suspended the commencement of new clinical trials until a new regulatory framework was established.⁷⁰ The Ministry of Health and Family Welfare was required to bring clarity to the regime for ensuring that clinical trials are properly monitored and conducted in accordance with the Drugs and Cosmetics Rules. The government responded rapidly, making three amendments between January and February 2013.⁷¹ These dealt, *inter alia*, with compensation for injured participants. A more stringent 'three-tier' system of government approval for clinical trials - consisting of a New Drugs Advisory Committee (NDAC), a Technical Committee and an Apex Committee - was also put in place.⁷²

In a further order issued in July 2013, the Supreme Court suspended 162 clinical trials that were already in progress.⁷³ In October 2013, five of these

⁶⁹ P. Chatterjee. India Tightens Regulation of Clinical Trials to Safeguard Participants. *BMJ* 2013; 346: f1275.

⁷⁰ S. Bagchi. Indian Supreme Court Halts Approval of New Clinical Trials until Regulatory Framework is Set Up. *BMJ* 2013; 347: f5996.

⁷¹ Drugs and Cosmetics (First Amendment) Rules, 2013, G.S.R. 53 (E) (30 January 2013); Drugs and Cosmetics (Second Amendment) Rules, 2013, G.S.R. 63 (E) (1 February 2013); Drugs and Cosmetics (Third Amendment) Rules, 2013, G.S.R. 72 (E) (8 February 2013). Available at: <http://www.cdsc.nic.in/forms/list.aspx?lid=2057&Id=31> [Accessed 20 February 2017].

⁷² Central Drugs Standard Control Organization (CDSCO). 2014. *Notable Achievements and Initiatives Undertaken by the Central Drugs Standard Control Organization in the Year 2014*. New Delhi, India: CDSCO.

Available at:

[http://cdsc.nic.in/writereaddata/notable_achievements_\(2\).pdf](http://cdsc.nic.in/writereaddata/notable_achievements_(2).pdf) [Accessed 20 February 2017].

⁷³ P. Bagla. 2013. India's Supreme Court Mandates Videotaped Consent in Clinical Trials. *Science* 22 October.

trials were allowed to resume because they had undergone the more rigorous three-tier process before DCGI approval. The remaining 157 trials were remanded back for approval under the new system.

The CDSCO had already received censure in 2012 with publication of a Parliamentary report describing a “collusive nexus” between industry, government and medical experts in relation to dubious drug approvals.⁷⁴ Facing widespread criticisms, the Indian government initiated a further raft of changes aimed at strengthening the regulatory framework for clinical trials. These came in the form of the Drugs and Cosmetics (Amendment) Bill, first presented to the Indian Parliament in August 2013,⁷⁵ and a series of executive orders issued by the Ministry of Health and Family Welfare.⁷⁶ It is noteworthy that in early 2013 when the Indian government embarked on this process, neither the international or domestic ethics guidelines had much of substance to offer on the issues that were at the forefront of national debates; in particular, the broader social benefit gained by hosting clinical trials and

⁷⁴ Parliament of India, Rajya Sabha, Department-related Parliamentary Standing Committee on Health and Family Welfare. 2012. *59th Report on the Functioning of the Central Drugs Standard Control Organization (CDSCO)*. New Delhi, India: Rajya Sabha Secretariat. Available at:

http://164.100.47.5/newcommittee/reports/englishcommittees/committee_on_health_and_family_welfare/59.pdf [Accessed 20 February 2017]; S. Srinivasan & A. Jesani. Standing Committee Report on CDSCO: Hard Facts Confirm an Open Secret. *Indian J Med Ethics* 2012; 9: 148-150.

⁷⁵ Ministry of Health and Family Welfare. Drugs and Cosmetics Amendment Bill, 2013. Available at: <http://www.prsindia.org/billtrack/the-drugs-and-cosmetics-amendment-bill-2007-2903/> [Accessed 20 February 2017].

⁷⁶ P. Saxena and R. Saxena. Clinical Trials: Changing Regulations in India. *Indian J Community Med* 2014; 39: 197–202.

the need for causality assessments of injuries and deaths and related compensation, independent of the sponsor. The reforms were thus a fresh attempt to rethink the ethics rules so as to better serve the Indian national interest. Some key developments are summarised below.

Ethics committees

Ethics committees were the target of several reforms in the Drugs and Cosmetics (Amendment) Bill. In accordance with the recommendation of the Chaudhury Expert Committee report,⁷⁷ ethics committees would need to be formally registered with the DCGI before they can review and approve clinical trials.⁷⁸ Applications for registration must be made in accordance with defined criteria. Failure to comply with the conditions of registration could lead to authorisation being suspended or revoked. Other measures aimed to eliminate conflicts of interest amongst members⁷⁹ and to encourage ethics committees to take a more pro-active role in supervising clinical trials

⁷⁷ Ministry of Health and Family Welfare (MoHFW). 2013. *Report of Prof. Ranjit Roy Chaudhury Expert Committee to Formulate Policy and Guidelines for Approval of New Drugs, Clinical Trials and Banning of Drugs*. New Delhi, India: MoHFW. Available at: http://cdsco.nic.in/writereaddata/Report_of_Dr_Ranjit_Roy.pdf [Accessed 20 February 2017].

⁷⁸ Drugs and Cosmetics (Amendment) Bill, 2013, *op. cit.* note 76, s. 4T.

⁷⁹ National Accreditation Board for Hospitals and Healthcare Providers (NABH). 2015. *Accreditation Standards for Clinical Trial in India*. New Delhi, India: NABH. Available at: cdsco.nic.in/writereaddata/finalAccreditation%20Standards.pdf [Accessed 20 February 2017].

and protecting participants.⁸⁰ These changes all seem positive. Further research could examine the implementation of the reforms and their impact on the functioning of Indian ethics committees.

Mandatory audio-video recordings of the informed consent process

Prompted by an order of the Supreme Court of India, draft guidelines issued by the Ministry of Health and Family Welfare in January 2014 require audio-visual recording of the informed consent process.⁸¹ This aims to protect participant autonomy, but has been criticised on the grounds that it will be burdensome for large-scale trials (e.g. vaccine trials), increase costs and go far beyond the international approach whereby informed consent is simply obtained in writing.⁸² Nevertheless, it has been argued that repeated violations of informed consent procedures justify a radical solution of this nature.⁸³

⁸⁰ Drugs and Cosmetics (Amendment) Bill, 2013, *op. cit.* note 76, s. 4V.

⁸¹ Central Drugs Standard Control Organization (CDSCO). 2014. *Draft Guidelines on Audio-Visual Recording of Informed Consent Process in Clinical Trials*. New Delhi, India: CDSCO.

Available at:

http://cdsco.nic.in/writereaddata/Guidance_for_AV%20Recording_09.January.14.pdf

[Accessed 20 February 2017].

⁸² V. Sridhar. 2014. Indian Clinical Trial Regulations Impractical, Says Biocon Chief. *The Hindu* 23 Jan. Available at: <http://www.thehindu.com/business/Industry/indian-clinical-trial-regulations-impractical-says-biocon-chief/article5609631.ece> [Accessed 20 February 2017].

⁸³ A. Kondal, G.V. Murali Krishna and D. Bansal. Clinical Trial Regulations in India: Progress and Challenges Arising from Recent Amendments to Schedule Y of the Drugs and Cosmetics (D&C) Act 1940 (D&C Rules 1945). *Pharm Med* 2016; 30: 1-13.

Assessing clinical trial applications

A further reform ordered by the Supreme Court and then approved by the Ministry of Health relates to so-called ‘Global Clinical Trials (GCTs)/New Clinical Trials (NCEs)’.⁸⁴ Such trials must now be evaluated according to three parameters, namely: (i) assessment of risk versus benefit to the patients, (ii) innovation vis-à-vis existing therapeutic options and (iii) unmet medical need in the country. This innovative move was designed to ensure that clinical trials are of more relevance to India’s public health needs.⁸⁵ There is, however, little guidance on what these terms actually mean or how they are to be assessed in practice, which could lead to uncertain and variable outcomes.⁸⁶ The extent to which these new principles would actually help advance the Indian national interest is also open to debate.

Compensation

⁸⁴ Central Drugs Standard Control Organization Office (CDSCO). 2014. *DGCI/Misc./2014 (132)*. New Delhi, India: CDSCO.

Available at:

http://www.cdsc0.nic.in/writereaddata/Office%20Order%20dated%2005_09_2014.pdf

[Accessed 20 February 2017].

⁸⁵ On the importance of this objective, see: V.R. Kamat. Fast, Cheap, and Out of Control? Speculations and Ethical Concerns in the Conduct of Outsourced Clinical Trials in India. *Soc Sci Med* 2014; 104: 48-55

⁸⁶ A. Bhatt. Assessing Unmet Medical Need in India: A Regulatory Riddle? *Perspect Clin Res* 2015; 6: 1-3.

The most controversial aspect of the reform measures has been the shake-up of the framework regarding compensation for clinical trial-related injuries or death.⁸⁷ On 30 January 2013, the Drugs and Cosmetics (First Amendment) Rules, 2013 came into force following notification of in the Gazette of India.⁸⁸ Some of the changes brought to the Drugs and Cosmetics Rules, 1945, can be viewed as improvements. For example, the new regulations brought some clarity to the mechanisms for reporting adverse events to the Licensing Authority,⁸⁹ assessment by an independent Expert Committee⁹⁰ and ensuring that trial sponsors make prompt payment to participants - or their nominees - if clinical trial-related injuries or death occur.⁹¹

Other provisions in the Drugs and Cosmetics (First Amendment) Rules 2013 are more questionable. First, a new rule stipulated that: “[i]n the case of an injury occurring to the clinical trial subject, he or she shall be given free medical management as long as required”.⁹² This imprecise wording has raised concerns. Under one interpretation, the trial sponsor would be liable for the costs of medical care for the entirety of the participant’s lifetime, even if the injury was not actually caused by involvement in the trial e.g. if the participant was injured at work.⁹³ A second provision stated, without any

⁸⁷ A. Jesani. New Regulations on Compensation for Injury and Death in Drug Trials. *Indian J Med Ethics* 2013; 10: 76-79; Y.K. Gupta et al. Compensation for Clinical Trial-Related Injury and Death in India: Challenges and the Way Forward. *Drug Saf* 2014; 37: 995-1002.

⁸⁸ Drugs and Cosmetics (First Amendment) Rules, 2013, G.S.R. 53 (E), *op. cit.* note 72.

⁸⁹ *Ibid.*: s. 2.7(ii)(a).

⁹⁰ *Ibid.*

⁹¹ *Ibid.*: s. 2.7(ii)(b).

⁹² *Ibid.*: s. 2(i)(1).

⁹³ S. Reardon. NIH Makes Wary Return to India. *Nature* 2014; 506: 143-144.

further explanation, that subjects shall be eligible for compensation for “use of placebo in a placebo-controlled trial”.⁹⁴ It is not clear if this rule was intended to eliminate placebo-controlled trials from India altogether, or if its aim was just to allow redress for patients injured as a result of inappropriate use of a placebo arm e.g. when they are deprived of their usual medication.⁹⁵ It should be noted that placebos can be an appropriate research methodology and are endorsed by the Declaration of Helsinki under limited circumstances.⁹⁶ Third, an entitlement to compensation was established for “failure of an investigational product to provide the intended therapeutic effect”.⁹⁷ This is problematic, because at the outset of a clinical trial, the product’s efficacy profile in humans is not fully known - hence the need for research. At least without further clarification and limitation, it is difficult to formulate a moral argument to justify forcing sponsors to guarantee a beneficial outcome.⁹⁸ These proposals have met with concerns and scepticism.⁹⁹

⁹⁴ Drugs and Cosmetics (First Amendment) Rules, 2013, G.S.R. 53 (E), *op. cit.* note 72, 2(i)(5(d)).

⁹⁵ M. Larkin. Acoustic Separation and Biomedical Research: Lessons from Indian Regulation of Compensation for Research Injury. *J Law Med Ethics* 2015; 43: 105-115.

⁹⁶ WMA Declaration of Helsinki 2013, *op. cit.* note 36, para. 33.

⁹⁷ Drugs and Cosmetics (First Amendment) Rules, 2013, G.S.R. 53 (E), *op. cit.* note 72, 2(i)(5(c)).

⁹⁸ Larkin, *op. cit.* note 95.

⁹⁹ M. Barnes et al. India’s Proposed Amendments to the Drug and Cosmetics Act: Compensation for Injuries to Clinical Trial Participants and the Criminalization of Clinical Research. *Bloomberg BNA Life Sciences Law & Industry Report* 2015.

Available at: <https://www.ropesgray.com/newsroom/news/2015/January/Health-Care-Attorneys-Write-Bloomberg-BNA-Article.aspx> [Accessed 20 February 2017].

THE EXODUS OF CLINICAL TRIALS FROM INDIA

The recent policy changes have contributed to a drastic fall in the number of clinical trials conducted in India.¹⁰⁰ According to CDSCO figures, only 107 government approvals for new trials were issued in 2013, as compared to the peak of 500 in 2010.¹⁰¹ This reflects a major drop in applications. Both academic and industry sponsors have been deterred by the regulatory uncertainties, particularly the new compensation rules. In 2013, the US National Institutes of Health (NIH) suspended around 40 trials set to take place in India.¹⁰² Foreign and Indian pharmaceutical firms are reportedly shifting their research activities to other countries, including China, Thailand and Malaysia.¹⁰³ The Chinese government, in particular, has welcomed foreign-sponsored trials for economic reasons.¹⁰⁴ Analysts estimate a loss to the Indian clinical trial industry of at least US\$150-200 million for 2013.¹⁰⁵

¹⁰⁰ S. Shukla. India's Amended Trials Regulations Spark Research Exodus. *The Lancet* 2013; 382: 845.

¹⁰¹ Chawan et al. *op. cit.* note 51, p. 57.

¹⁰² Y. Battacharjee. Clinical Trials Paused as India Adopts New Rules. *Science* 2013; 341: 327.

¹⁰³ Kondal et al. *op. cit.* note 84, p. 11.

¹⁰⁴ M. Cooper. Experimental Labour: Offshoring Clinical Trials to China. *EASTS* 2008; 2: 73-92.

¹⁰⁵ R. Devarakonda. 2013. Current Clinical Trial Scenario of India: Challenges and Solutions. *Pharma Bio World* July: 16-20. Available at: [http://voisinconsulting.com/sites/default/files/2013_Pharma Bio World_Rajashree.pdf](http://voisinconsulting.com/sites/default/files/2013_Pharma_Bio_World_Rajashree.pdf) [Accessed 20 February 2017].

Concerned by these repercussions, and under pressure from industry interest groups,¹⁰⁶ the Indian government has cut back on its reform measures.¹⁰⁷ Although the losses sustained in 2013 are perhaps not that significant for the Indian economy overall, the promise of future economic benefits on the scale of US\$1.5 billion per year, as estimated by consultancy firm McKinsey,¹⁰⁸ may still exert a powerful hold over the calculations of policymakers.¹⁰⁹ With regards to compensation, rules published in the Gazette of India December 2014 made several modifications to the January 2013 regulations.¹¹⁰ First, “free medical management shall be given as long as required *or till such time it is established that the injury is not related to the clinical trial, whichever is earlier*” (emphasis added).¹¹¹ Second, compensation for the use of a placebo shall only be payable “if the standard of care, though available, was not provided to the subject as per the clinical trial protocol”.¹¹² Third, entitlement to compensation for the failure of an

¹⁰⁶ P. Mansell. 2014. ACRO Warns on Indian Clinical-trial Regulations. *PharmaTimes* 17 July. Available at:

http://www.pharmatimes.com/Article/14-02-20/ACRO_warns_on_Indian_clinical-trial_regulations.aspx [Accessed 20 February 2017].

¹⁰⁷ M.K. Mallath and T. Chawla. Investigators’ Viewpoint of Clinical Trials in India: Past, Present and Future. *Perspect Clin Res* 2017; 8: 31-36.

¹⁰⁸ T.V. Padma. *India’s Drug Tests*. *Nature* 2005; 436: 485.

¹⁰⁹ See generally S. Jasanoff & S. Kim, eds. 2015. *Dreamscapes of Modernity: Sociotechnical Imaginaries and the Fabrication of Power*. Chicago, IL: University of Chicago Press.

¹¹⁰ Drugs and Cosmetics (Sixth Amendment) Rules, 2014, G.S.R. 889 (E) (12 December 2014). Available at: <http://www.cdsco.nic.in/forms/list.aspx?lid=2057&Id=31> [Accessed 20 February 2017].

¹¹¹ *Ibid*: s.2(a)(i).

¹¹² *Ibid*: s.2(a)(iii).

investigational product to provide its intended therapeutic effect is also limited to cases where the standard of care, though available, was not provided to the subject as per the protocol.¹¹³ A further notification published in July 2015 watered down the requirement to make an audio-video recording of the informed consent process.¹¹⁴ The new amendments to Schedule Y of the Drugs and Cosmetic Rules, 1945 only require audio-visual recording of ‘vulnerable subjects’ involved in clinical trials of new chemical entities or new molecular entities. Uncertainty surrounds the term ‘vulnerable subjects’, which is not sharply defined.¹¹⁵

Ongoing debates about the direction of the reforms are linked with Indian Prime Minister Narendra Modi’s explicit commitment to making India an easier place in which to do business.¹¹⁶ In line with this objective, in January 2015, the CDSCO proposed pre-submission meetings between drug regulators and stakeholders so as to increase efficiency and further shorten

¹¹³ Ibid.

¹¹⁴ Drugs and Cosmetics (Fifth Amendment) Rules, 2015, G.S.R. 611 (E) (31 July 2015), s.2(i). Available at:

<http://www.cdsc0.nic.in/forms/list.aspx?lid=2057&Id=31> [Accessed 20 February 2017].

¹¹⁵ M.M. Caron, B. Bierer & M. Barnes. Indian Ministry of Health and Family Welfare Amends Informed Consent Rules. *Bloomberg BNA Medical Research Law & Policy Report* 2015. Available at:

<http://mrcrcenter.org/wp-content/uploads/2016/01/2015-10-21-BNA-India-Informed-consent.pdf> [Accessed 20 February 2017].

¹¹⁶ 2014. India PM Narendra Modi Unveils ‘Make in India’ Campaign. *BBC News* 25 September. Available at: <http://www.bbc.co.uk/news/world-asia-india-29357627> [Accessed 20 February 2017].

approval times.¹¹⁷ Furthermore, it was announced in June 2016 that the Drugs and Cosmetics (Amendment) Bill, submitted to the Indian Parliament in 2013, was to be withdrawn. It will be replaced with an entirely new measure that better supports the growth of the Indian pharmaceutical sector.¹¹⁸ Shortly afterwards in August 2016, a CDSCO circular removed the restriction on Indian clinical trial investigators conducting more than three trials at the same time.¹¹⁹ Going forward, it remains to be seen how the Indian government will reconcile the various interests at stake.

DISCUSSION

Broader lessons can be drawn from this case study. India's experience of regulating clinical trials suggests that economic and ethical concerns are becoming increasingly intertwined. Government actors appear to view regulation as an exercise entailing trade-offs between the goals of economic development and protecting participants. Furthermore, the sudden exodus of clinical trials from India demonstrates that regulatory frameworks are now subject to market forces.

¹¹⁷ A. Bhavé & S. Menon. Regulatory Environment for Clinical Research: Recent Past and Expected Future. *Perspect Clin Res* 2017; 8: 11-16.

¹¹⁸ Press Information Bureau, Government of India, Cabinet. 2016. *Withdrawal of the Drugs and Cosmetics (Amendment) Bill, 2013*. Available at: <http://pib.nic.in/newsite/PrintRelease.aspx?relid=146413> [Accessed 20 February 2017].

¹¹⁹ Z. Brennan. 2016. India Looks to Further Ease Process of Running Clinical Trials. *RAPS* 2 August.

Available at: <http://www.raps.org/Regulatory-Focus/News/2016/08/02/25493/India-Looks-to-Further-Ease-Process-of-Running-Clinical-Trials/> [Accessed 20 April 2017].

It is important to consider how these dynamics might affect the regulation of clinical trials in low and middle-income countries. One possible scenario - which has been debated in relation to other policy domains - is a 'race to the bottom'.¹²⁰ This hypothesis is based on two key assumptions. First, high regulatory standards are unattractive to firms because they increase operating costs and reduce profits. Multinationals will therefore invest in countries with weaker regulatory standards. Second, host countries compete for investment by lowering standards; either in terms of the laws on the books or their willingness to enforce them.¹²¹ The end result is that all competing nations implement the lowest possible regulatory standards. Arguably, however, this dystopian vision is improbable in the context of Indian clinical trials.

There are several reasons why a straightforward race to the bottom is unlikely. First, India has a vigorous free press and active civil society groups. Both would likely act to highlight social problems and press for change. Second, the Indian Supreme Court is receptive to public interest litigation and prepared to hold the powerful to account when upholding constitutional rights. Third, the Indian government is not preoccupied solely with advancing commercial interests. Fourth, and zooming out to the international level, it is

¹²⁰ For a sense of the conflicting evidence-based literature discussing the 'race to the bottom' hypothesis in the context of labour standards, see: W.W. Olney. A Race to the Bottom? Employment Protection and Foreign Direct Investment. *J Int Econ* 2013; 91: 191-203; G. Distelhorst & R. Locke. Does Compliance Pay? Global Supply Chains and Trade-based Diffusion of Social Institutions. *Watson Institute for International and Public Affairs Research Paper Forthcoming, Paper No. 2017-37; MIT Political Science Department Research Paper No. 2017-1*. Available at: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=2885455 [Accessed 20 February 2017].

¹²¹ Davies & Vadlamannati, *op. cit.* note 8.

far from clear that a race to the bottom amongst clinical trial host countries would be desirable to industry. Clinical trials that violate ethical guidelines expose their sponsors to risks. Reputation and brand image can be tarnished following adverse publicity. In addition, costly trial data could be rejected on ethical grounds by regulatory bodies such as the US FDA or the European Medicines Agency. If anything, these structural factors could lead towards better enforcement of internationally accepted research ethics standards in low and middle-income countries over time.

Assuming that global industry does indeed have a preference for well-run trials, then a more optimistic picture emerges. India might be able to implement reforms that better protect trial participants and still attract inward investment. Foreign sponsors may be undeterred by regulatory changes that impose only modest cost increases. Indeed, a small premium could be viewed as worth paying for outsourced clinical trials that comply fully with GCP standards. Such trials are far less likely to embroil sponsors in unwanted ethical controversies. It follows that if the Indian government simply trims back on the ‘excesses’ of its recent reforms - especially those regarding compensation - trials may return to the country; and perhaps in even greater numbers.¹²²

Yet even if this optimistic reading is correct, the Indian case study also reveals some contrary and troubling aspects of the relationship between economics and ethics. It highlights the mobile nature of global capital, the powerful role of economic forces and the de facto limitations on host countries freedom to initiate socially desirable reforms. Cost-conscious sponsors and CROs can shift operations to other countries if regulatory

¹²² Bhave & Menon, *op. cit.* note 118.

reforms are perceived as too burdensome.¹²³ Host countries may therefore have little choice but to calibrate their research ethics frameworks to levels deemed acceptable to sponsors and CROs.

This raises questions about where the dividing line will fall between reforms that are commercially viable and those which are not. For example, would it be practicable for India to enshrine an obligation for sponsors to give participants free access to medicines after completion of a trial; as was recommended by the Indian Drugs Technical Advisory Board (DTAB) in 2015?¹²⁴ According to the limited ethnographic research, Indian investigators and ethics committee members currently treat post-trial provision as a business decision that falls to the discretion of the sponsor or CRO.¹²⁵ Formalising this duty could make a major difference to the lives of impoverished research participants, but would also make India a more expensive and less attractive place to conduct research. The risk of ‘capital flight’ arguably makes such a reform extremely hard to implement.¹²⁶ For the

¹²³ A. Gafney. 2012. As Regulatory Problems Accumulate in India, Clinical Trials Sector Looks Set to Flee. *RAPS* 14 June. Available at: <http://www.raps.org/focus-online/news/news-article-view/article/1763/> [Accessed 20 February 2017].

¹²⁴ Drugs Technical Advisory Board (DTAB). 2013. *Minutes of the 68th Meeting of Drugs Technical Advisory Board Held on 16th February, 2015 at CDSCO HQ, FDA Bhawan, Kotla Road, New Delhi*. New Delhi: DTAB, p.6. Available at: <http://www.fdanews.com/ext/resources/files/02-15/02-27-15-IndiaPhaseIII.pdf?1425068214> [Accessed 20 February 2017].

¹²⁵ Kamat, *op. cit.* note 86, p. 54.

¹²⁶ For discussion in the Brazilian context, see: D.W.L. Wang & O.L.M. Ferraz. Pharmaceutical Companies vs the State: Who is Responsible for Post-Trial Provision of Drugs in Brazil? *J Law Med Ethics* 2012; 40:188-96: 189.

time being at least, India and other host countries may be restricted to establishing ‘ethics light’ regulatory frameworks that closely mirror international GCP standards.¹²⁷ The resulting rules will likely meet with the approval of sponsors and CROs, but gloss over the structural inequalities that underpin the globalisation of clinical trials.

It would be beneficial for future research to track the ongoing development of the Indian regulatory framework with full awareness of this underlying policy tension. In addition, a number of reforms remain in place even after the initiation and subsequent dilution of policy measures from 2013 onwards. These include the new procedure for assessing the causal relationship between clinical trial participation, injuries and deaths;¹²⁸ the involvement of an independent Expert Committee to assess causality;¹²⁹ new responsibilities for ethics committees and new procedures for their formal registration;¹³⁰ the revised compensation formulas for determining the quantum of damages for clinical trial-related death¹³¹ or injury;¹³² and the new three-tier approval

¹²⁷ R. Ravinetto et al. It Is Time to Revise the International Good Clinical Practices Guidelines: Recommendations from Non-commercial North–South Collaborative Trials. *BMJ Glob Health* 2016; 1: e000122.

¹²⁸ A. Kulkarni & A. Bhatt. Causality Assessment: A Casualty of Compensation? *Perspect Clin Res* 2013; 4: 196–198.

¹²⁹ Drugs and Cosmetics (First Amendment) Rules, 2013, G.S.R. 53 (E), op. cit. note 72: s. 2.7(ii)(a).

¹³⁰ U.M. Thatte & P.A. Marathe. Ethics Committees in India: Past, Present and Future. *Perspect Clin Res* 2017; 8: 22–30.

¹³¹ CDSCO 2013. *Compensation Formula (Clinical Trial)*. Available at: <http://www.cdsc.nic.in/writereaddata/formula2013SAE.pdf> [Accessed 20 April 2017].

¹³² CDSCO 2014. *Formulae to Determine the Quantum of Compensation in Case of Clinical Trial Related Injury (Other than Death)*. Available at:

procedure for clinical trials at the CDSCO¹³³ using the three major criteria suggested originally by the Supreme Court.¹³⁴ Further studies assessing how the reforms are actually being put into effect and whether they are achieving their desired ends would also be helpful additions to the literature.

CONCLUSION

This article has given an overview of recent regulatory developments in India and made two main observations. First, research ethics frameworks and economic concerns are increasingly bound together in problematic ways. Although host countries are, in theory, free to initiate reforms that improve the lot of clinical trial participants, doing so may make a country less attractive to sponsors, who can relocate elsewhere. Host countries may therefore need to give significant weight to commercial considerations when (re)designing regulatory regimes. In this way, economic logic comes to shape thinking about ethical issues.

The second contribution of the paper was to consider the implications of this policy dynamic. The possibility of a ‘race to the bottom’ was discussed, but discounted because of the presence of various structural factors. More likely is a situation where host countries are restricted to a kind of ethical middle ground. Sponsors may welcome improved compliance with some basic ethical requirements, such as informed consent. However, other socially

<http://www.cdscn.nic.in/writereaddata/ORDER> and Formula to Determine the quantum of compensation in the cases of Clinical Trial related serious Adverse Events(SAEs) of Injury other than Death.pdf [Accessed 20 April 2017].

¹³³ Bhave & Menon, *op. cit.* note 118.

¹³⁴ Bhatt, *op. cit.* note 87.

desirable reforms that would increase costs significantly - such as the post-trial provision of drugs - may be discouraged. Questions of whether and how to advance beyond this paradigm are of major concern. This article has offered a framework for better understanding the position of clinical trial host countries in relation to such challenges.