Structure, Organization and Knowledge Production of the Indian Clinical Trials Industry

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In India, the number of clinical trials has been radically transformed in two directions since 2005. In that year, legislation was changed to make it easier for 'Big Pharma' to carry out multi-sited trials in India and at the same time as elsewhere in the world. After a period of rapid growth to 500 in 2010, numbers of new trials registered with the Clinical Trials Register-India dropped to 321 in 2011 and 262 in 2012 (Chawan, Gawand and Phatak, 2015). Following a series of adverse reports, the number of approvals in 2013 dropped further to 107 in 2013, to 150 in 2014, 121 in 2015 and 6-7 a month in 2016. The future scale of the global clinical trials industry in India remains unclear.

This chapter reviews the evidence about the scale and significance of these trials, using a theoretical approach derived from the theories of 'global assemblages'. We set out some of the new social forms that have arisen to service these trials before assessing the growth in clinical trials in India since 2005. The chapter also analyses the ethical implications of clinical trials for India and its public health. We conclude by considering the implications of the reforms that have been introduced since 2012 as a result of several highly-publicized controversies that highlighted problems in the management of clinical trials.

Our main argument is that the nascent Indian clinical trials industry rapidly adjusted to the opportunities provided by the 2005 reforms, linked to India's signing of the TRIPs agreement. It exaggerated the potential benefits, but provided sites and supporting infrastructure to encourage trials to go ahead. On the other hand, Indian regulators were slow to come to terms with the challenges of responding to well-co-ordinated global assemblages (Yee 2012). Civil society institutions were able to mobilise a groundswell of opinion against trials, drawing on tropes such as the Indian population being used as 'guinea pigs'. Despite resistance from the industry, Indian regulations have been tightened, offering some prospect that at least the worst abuses are unlikely to be repeated.We draw on research funded by the UK's Economic and Social Research Council (ESRC) and its

Department for International Development (DfID), carried out between 2010 and 2013.[1] Our detailed understanding of the pharmaceuticals sector and the growth of clinical trials comes also from previous research (SS, RJ) and long-term engagement with issues of medical ethics (AJ) and medical law (GP).

1. Definitions of 'Clinical Trial' and Theoretical Approach

Medical experimentation takes a variety of forms. It ranges from computer simulations and testing of drugs on animals (pre-clinical), through initial testing of pharmaceuticals, appliances, biologicals or surgical techniques on healthy patients, to applying them to patients and finally reviewing their costs and benefits in 'real-world' use. The most common popular image is of the international, multi-sited clinical trial of new chemical molecules run by a contract research organisation, sponsored by a large pharmaceuticals company with the aim of establishing a patented drug that will win them large profits. But publicly funded trials, or indeed trials funded by a combination of public and private sponsors also take place. Some trials are community-based, some are conducted by and for particular hospitals or medical colleges, and some within the confines of pharmaceutical companies. The existing classification of clinical trials – by 'phase' – is not entirely satisfactory, since the boundaries between phase can be unclear and, occasionally, a subject of fierce dispute (Sarojini et al. 2010). Nonetheless, for heuristic reasons we focus in this chapter mostly on Phase III trials – trials carried out on large numbers of patients who are ill with the target disease, in order to compare new medicines or treatment protocols with an existing treatment or a placebo, to see if it is better in practice, and if it has important side effects. Most are carried out by commercial sponsors (many, but not all, based outwith India), for which the most common focus is on drugs and biologicals.

Until the late 1980s, most multi-sited Phase III clinical research trials were carried out in relatively wealthy countries in North America, Western Europe and Oceania (Theirs, Sinskey and Berndt 2008). Since the early 1990s, however, there has been a rise in the

[1] For more details of this project, see http://www.bhesa.org/. We would like to thank Vajira Dissanayake, Ian Harper, Neha Madhiwala, Jeevan Raj Sharma, Bob Simpson, Rekha Khatri, Anand Kumar, Deapica Ravindran, Tharindi Udalagama and other members of the project for their help in developing this paper. We also express our sincere thanks to the many people who generously gave of their time in interviews and discussions. The research was funded by the Economic and Social Research Council/Department for International Development [RES-167-25-0503]. Salla would also like to acknowledge the generous support of the Wellcome Trust Strategic Award for Global Health and Bioethics Network (grant no 096527).

proportion of clinical trials in north America taking place in private hospitals (Fisher, 2008), and also a sharp rise in the numbers of foreign- and locally-sponsored clinical trials conducted in the so-called 'pharmerging' regions of Africa, Asia, South America and Eastern Europe (Theirs, Sinskey and Berndt 2008). This shift was made possible by the adoption of the ICH-GCP guidelines (Abraham and Reed 2002) and it has also been linked to the rapid growth in these markets (IMS Institute for Healthcare Informatics 2011) and the possibility of using clinical trials to create a presence for the company or the drug. Other reasons cited include the increasing problems and costs of carrying out trials in relatively wealthy countries, difficulties in accessing patients who are 'treatment naïve', and restrictions posed by the regulators on the use of institutionalised people in the US (Fisher 2008). Nonetheless, the USA, Canada and Europe remained the dominant locations of clinical trials sites. Low- and middle-income countries hosted only 21 percent of clinical research sites (Drain et al., 2014a)

Even for those trials that take place entirely within India, the form they take is heavily influenced by a global industry, one that has come to prominence in India since 2005. In the outsourcing of clinical trials to developing and transitional countries, complex mediations occur at a series of levels between sponsors and the populations that become clinical trials subjects. The flows generated by such biomedical research involve bilateral transfers within and between the global North and South; the mediations produce transnational networks. In joining the global assemblages (Collier and Ong, 2005; Sassen, 2008) that constitute international clinical trials, actors based in India look to capture the economic benefits of scientific innovation. The promise of these partnerships is of internationally transferable knowledge and commodities that generate other benefits along the way – employment, career development, infrastructure, medical and public health as well as entrepreneurial possibilities.

Global assemblages are constructed from institutions, roles and relationships that are global in origin and yet are locally specific in the particular forms of combinations that emerge. They involve expectations of and aspirations to universal standards of design, method, reliability, validity, ethics, and reporting of results. Although the sponsors – often but not always from 'Big Pharma' (Sariola et al. 2015) – take a leading role, and attempt to control the whole process, inevitably they lose a degree of oversight as they negotiate with local partners for trial approval, recruitment of patients etc. The local teams co-construct – from very unequal starting points – the practicalities of any particular research project, always within externally dictated protocols, rules and guidelines. They are also responsible

for communicating the risks and hazards that feature prominently as part of these processes. Thus clinical trial assemblages are the 'cutting edge' in a process of de-territorialisation (Deleuze and Guattari,1980; Deleuze and Guattari 1988) which bring global procedures into everyday settings [hospitals, laboratories etc.] and render them coeval and continuous with others around the globe (Timmermans and Berg 1997). Further, they manage trial subjects and induct them into the global laboratory that such procedures represent. They are gatekeepers to a global modernity for some members of these assemblages, who regulate access to different regimes of care but also to new temporalities (via the research process), new spaces (in the clinic/ hospital as laboratory, and most important, futures [as biological citizens (Rose and Novas, 2005), biomedical citizens (Petryna 2005), therapeutic citizens (Nguyen 2005), pharmaceutical citizens (Ecks, 2005), or bioethical citizens (Simpson et al., 2015)].

Entry into such global assemblages, however, presents challenges as well as opportunities for CROs, PIs and regulators in India (see, for example, Cassese 2004; Held and Koenig-Archibugi 2003; Slaughter 2004). The opportunities are largely financial – access to a world market-place for the skills and patient population available in the country – the advantages of the place they know well. The challenges arise from the mismatch between the interests of the various stakeholders, and because India's democracy ensures some voice to the patient population, to try to ensure that the industry works to their benefit as well. Foreign-sponsored clinical trials being conducted in India have to orient towards weak regulatory systems (Sama 2015) ; see also (Ana et al. 2013; Glickman et al. 2009; Jesus and Higgs 2002). With little experience of structured medical research and plagued by poverty, inadequate public medical facilities, excessively expensive private medical care options, and stark social inequalities, Indian regulatory institutions struggle to achieve their stated goals in the face of mounting public, legal and parliamentary criticism. These standards are not uniformly reached elsewhere in the world, including in developed countries, and a case can be made that such standards should be adapted to take account of local conditions in resource-poor settings. For most Indian commentators, however, the aspirational norms of Western regulatory structures and practices remain unchallenged. While commercial interests quickly took note of the new opportunities that outsourced clinical trials might offer them in India, the procedures to regulate these activities in the interests of wider societal goals were much slower to become established (Yee, 2012). After describing the legal framework for

regulating clinical trials in India (section 2) we will turn to evidence about the growth and form that clinical trial activity in India has taken since 2005.

2. Regulation of Clinical Trials

> The earlier attitude was that we should block [clinical trials development] because as I told you it was a nation of traders at that time and now because our own people are innovating, we want the innovation to be there, we want to be landscaped for the innovation, so the trials are to be permitted … you don't feel threatened; not at all. But the only thing, I feel heavy as a person. (Senior Government of India Official, Interview, 2008.)

The regulation of clinical trials in India consists of both a legislative framework and an active role 'on the ground' for research ethics committees (RECs). The Drugs and Cosmetics Act, 1940 (as amended) entrusts the approval of clinical trials to the Drugs Controller General of India (DCGI). The DCGI is part of the Central Drugs Standard Control Organisation (CDSCO), India's main regulatory body for pharmaceuticals and medical devices, situated within the Ministry of Health and Family Welfare. The Drugs and Cosmetics Act also gives the central government the power to draft secondary legislation for the regulation of clinical trials, mainly through Schedule Y of the Drugs and Cosmetics Rules 1945 (as amended). Criticism has been less addressed to the rules themselves, and more to their patchy implementation.[2] Nevertheless, the ICMR guidelines are arguably more flexible than the Declaration of Helsinki on controversial issues in international research including the use of placebo controls and post-trial access to medicines.

India signed the World Trade Organisation's [WTO] Agreement on Trade-Related Aspects of Intellectual Property Rights [TRIPS] in 1995. It then introduced three amendments to the Patents Act (in 1999, 2002 and an ordinance in December 2004 which was converted in to an Act in 2005) to implement TRIPS (Sengupta 2013). The Patents (Amendment) Act 2005 encouraged clinical trials to move to India by removing the fear that Indian firms would copy a test drug by 'reverse-engineering' and produce a generic competitor. A further boost to the Indian clinical trials industry was given in 2005, when Schedule Y of the Drugs and Cosmetics Rules 1945 was amended to remove the 'phase lag' requirement. This allowed companies to 'conduct trials of new drugs in India at the same time that trials of the same phase are being conducted in other countries' (Nundy and Gulhati,

[2] See (Parliament of India 2012; Parliament of India 2013a; Parliament of India 2013b)

2005: 1633; Sariola et al., 2015). Simultaneous Phase II and III clinical trials of molecules were thenceforth permitted, but not Phase I. An exception allows drugs developed abroad that relate to a pressing health need to be marketed without undergoing trials in India. This exception also permitted simultaneous Phase I trials of the AIDS vaccine (whose patent was held by a US firm) by the International AIDS Vaccine Initiative (IAVI) in collaboration with the Indian Council of Medical Research (ICMR).

The 2005 amendments to Schedule Y also require those wishing to conduct a clinical trial to first receive, *inter alia*, the approval of a properly constituted REC before the trial can be authorised by the DCGI. Approvals were also required by other Government agencies (see further detail on this below). RECs are expected to evaluate clinical trial protocols in light of the Indian Council for Medical Research's (ICMR) 'Ethical Guidelines for Biomedical Research on Human Participants', as well as India's 'Good Clinical Practice' guidelines[3] and the Declaration of Helsinki. In 2000 and 2006, the ICMR updated its guidelines to bring them more into line with the Declaration of Helsinki (Indian Council of Medical Research, 2006)..[4]

The Clinical Trials Registry-India (CTR-I), launched in 2007, is maintained by the ICMR's National Institute of Medical Statistics. Since 2009, the online registration of clinical trials in the CTR-I is mandatory. There are, nevertheless, recurrent concerns that the submitted data are often incomplete and fail to provide sufficient information, for example on sponsors, CROs and sites, and several amendments have been made to the form (Pandey et al, 2013; Pandey et al., 2009; Pandey et al. 2008). The editors of eleven major Indian biomedical journals declared that only articles emerging from registered trials would be considered for publication (Pandey et al., 2009; Pandey et al. 2008).

The changes after 2005 made it possible for Indian CROs to bid for work in multi-sited global trials. The requirement for all trials to be registered in the CTR-I gave the Government of India (and to some extent, the wider interested public) much useful information. However, identifying the scale and form that clinical trial activity has taken in India has remained hard to extract from the registration system, and many of the 'facts' that enter into public debate turn out to have been provided by interested parties for their own purposes. Separating facts from claims forms the focus of Section 3.

[3] CDSCO's Good Clinical Practice guidelines were based on a synthesis of the ICMR guidelines and international Good Clinical Practice documents (Central Drugs Standard Control Organization 2001).
[4] See generally (Nuffield Council on Bioethics 2002)

3. Scale and Nature of Clinical Trials Activity

According to many industry commentators, often accepted by academic commentators, India offered great cost-cutting opportunities to pharmaceutical companies and other research sponsors (van Huijstee and Schipper, 2011: 49-54). Compared to competitor countries, India seems to be very attractive for inclusion amongst the new countries considered for multi-sited trials. According to industry sources, in the late 2000s, costs for recruiting patients and managing data collection were as little as half those that obtained in North America. India's large pool of doctors, nurses and trial assistants usually have good English; and a huge number of patients, many of whom are treatment-naïve, provides a large pool of potential easily-recruited trial participants (Gupta and Padchy 2011). Carrying out trials also offers sponsors opportunities to build market access for patented drugs, by creating networks of key physicians who are well-disposed to prescribing their products, old and new (Glickman et al. 2009). Regulatory structures in India are simpler (and in English) compared to many other competing countries, and more likely to accommodate the demands of sponsors and Contract Research Organizations (CROs), allowing for quicker recruitment.

But these claims – and the estimates of the size of the industry and its actual or potential benefits to Indian business, its knowledge economy and its public health – were massively over-estimated. Indian CROs and their advisers had a vested interest in exaggerating the scale and opportunities of the benefits to be gained from hosting clinical trials, in order to attract Government support and to create an impression of a booming sector, to attract more business. International accountancy firms such as KPMG produced optimistic estimates of the size of the 'industry', both at the time the estimates were produced and also in the claims about the likely future scale of activity. Such industry analysts estimated that the burgeoning Indian clinical trial service industry was worth USD $450 million (£282 million) in 2010-11 and would pass the $1 billion (£594 million) mark by 2016. The predicted financial benefits were heavily over-estimated even at the peak of activity in 2010 (and not just because of the crisis in trial registration that developed in 2013, discussed below), for several reasons.[5]

Several of the presumed 'attractions' for trialists in India have a negative side as well. Weaker regulatory structures are vulnerable to accusations – by competitor countries, as well

[5] Other aspects of the benefits of clinical trials to India have also been exaggerated: we discuss these in Section 5 below.

as by international regulatory agencies and national and international activists – of unethical practice and poor quality observance of international standards in data collection and management. Sponsors are sensitive to the risk that data from India or one of its research sites might become suspect and unusable in the pivotal trials that are submitted to the US FDA or to European or Japanese drug regulatory bodies – and potentially raise questions about the quality of data from other sites as well (Ana et al., 2013; MacMahon, Perkovic and Patel, 2013).[6]

Managing trials in India – in some cases more so than elsewhere in LMICs – can also be a frustrating process, which may be an additional reason why the predicted numbers did not materialise. In India, multiple regulatory agencies have to be satisfied – not only the Central Drug Standard Control Organization (CDSCO) but also the New Drugs Advisory Committee (NDAC), Drug Technical Advisory Board (DTAB), Indian Council of Medical Research (ICMR), and Directorate General of Foreign Trade (DGFT) – several of which are under-staffed, with approvals ranging from five to eight months (Saini et al. 2013). Table 1 suggests that difficulties with conducting trials in India, compared to other countries, continue after the trial has received approval, with perhaps around 50 per cent of Indian trial participants initially identified failing to continue through to the end of the trial, thus adding substantially to the time to complete a trial, and reducing the overall financial benefits of choosing Indian sites.

Table 1 about here

In this context, what kinds of trials are registered to be undertaken in India and how does the Indian scenario compare to that elsewhere? The main sources of evidence are the CTR-I and the US FDA register at clinicaltrials.gov. These sources do not include those 'trials' that do not register; there is anecdotal evidence that off-register 'trial-like' activity is common practice, for example, in experimental treatment of autistic children or in the use of stem cells (Editorial, 2014) (Sleeboom-Faulkner and Patra, 2011). Furthermore, data entry into the CTR-I is not complete: for example, the trial design is not always recorded, with no real indication of why this is the case. The increasing numbers of BA/BE (Bio-availability and

[6] For example, in May 2015 'The European Medicines Agency (EMA) has confirmed its recommendation to suspend a number of medicines for which authorisation in the European Union (EU) was primarily based on clinical studies conducted at GVK Biosciences in Hyderabad, India' http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/GVK_Biosciences/human_referral_000382.jsp&mid=WC0b01ac05805c516f, accessed 15 August 2016.

Bio-equivalence) trials carried out on healthy subjects for testing generic drugs to satisfy regulators in developed countries for exports are also rarely listed in the CTR-I.[7] They probably number as many as the other clinical trials listed in the CTR-I. Large public health experiments are also often not listed unless they are using "new drugs".

Until 2008-09, clinicaltrials.gov was the main source of evidence about trial activity globally, but this covered only those trials for which a US registration was required or desired: in June 2009, the US FDA registered 1040 clinical trials with a site in India: 618 were active in some form; 422 were completed. The data kept on the CTR-I showed little information until after the registration of trials was made mandatory in 2009. The number of trials approved by the DCGI increased from a few per year until 2009 with over 500 registered in 2010 (see Table 2). As on 30 June 2010 CTR-I listed 1078 trials, out of which 757 were reported to be trials sponsored by pharmaceutical companies. Of these, 442 had multinational pharmaceutical sponsors (for more details, see Tables 3 and 4).

Tables 2, 3 and 4 about here

Our analysis of CTR-I registered trials at 30 June 2010 showed that substantial minorities of the trials registered do not involve pharmaceutical products. Table 5 shows the pattern for India's five largest medicines trial sites, and demonstrates that while trials of drugs are the largest category, other types are also carried on. For the purposes of this chapter, we restrict ourselves to the pharmaceutical trials, which nevertheless constitute the vast majority of the field.

Table 5 about here

The total number of trials being conducted in India has indeed risen sharply since the early 2000s, but different sources give different estimates of the actual total number of trials, and trial participants, depending on methodologies and definitions. One study gives a figure of 1156 trials active in 2012. This represents a growth rate from 2005-12 of over 30 per cent per annum (Drain et al. 2014a). Although this growth was faster than for Brazil, it was less than in China, South Korea, Egypt and Japan, and well below industry projections. According to the same study, India was involved in 3.7 percent of all registered trials in the world in

[7] Whereas clinical trials 'are required to be registered', BA/BE trials In addition, observational trials, 'bioavailability and bioequivalence trials as well as post marketing surveillance trials may also be registered in the CTRI' (http://ctri.nic.in/Clinicaltrials/faq.php, accessed 12 December 2016) and so estimates of the numbers of such trials are not available.

2012 (Drain et al., 2014b: 166 & S2). Another study for 2012 found 2091 of the 129,099 trials listed on the clinicaltrials.gov registry involved India. Of 4,823 breast cancer trials, 70 had sites in India.[8] So India, with about 17 per cent of the world's population, was involved in between 1.5 per cent and 3.7 per cent of all clinical trials, depending on the indicator and the data source chosen (Saini et al. 2013).

The global significance of Indian clinical trial sites depends on whether the indicator chosen is the number of trials with an Indian site, the number of Indian sites, or the number of patients recruited. In addition, not all trials have the same significance to the sponsor. 'Pivotal' trials are the ones over which most care is taken, since these are the ones to be submitted to the US FDA or the EMA and are the trials used to make specific claims about efficacy and safety. While Indian trial sites may appear significant according to some indicators, they seem to be less important if pivotal trials are considered. One estimate, based on a sample of 650 completed industry-sponsored trials listed on clinicaltrials.gov on January 2011, and for which a publication could be identified, 53 (8.1 per cent) included a site in India (Hoekman et al., 2012: 4), making India 28th in a list of countries involved in such trials. For the European Medicines Agency (EMA) over 80 per cent of patients who participated in pivotal trials submitted to them in 2005-10 were recruited in North America, Europe or Australasia, and only 1.6 per cent in India (EMA 2012: 7). Of a sample of 15 PhRMA companies surveyed in 2010, 8 had allocated pivotal registration trials to India over the preceding 10 years, but in only 3 cases was this for more than 5 per cent of their trials (Scott et al., 2011: 610).

R&D offshore outsourcing amongst larger companies (so-called Big Pharma, who account for between 60 and 80 per cent of global pharmaceuticals R&D) remains predominantly within low value, low risk parts of the R&D value chain (Haakonsson, Jensen and Mudambi, 2013: 686, 687). In 2013, for example, Roche – one of the largest of the Big Pharma companies, with nearly 340,000 participants in clinical trials across the globe – recruited only 0.3 per cent of the total from low income countries, and 1.2 per cent from middle-income countries.[9] An analysis of data from ClinicalTrials.gov suggests that in the period 2008-2012 there was little change in the percentage of Phase III trial sites outwith Western Europe and North America. Over that period, however, the share of India declined,

[8] At the same time, the CTR-I listed 77 breast cancer studies.

[9] http://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials.htm, last accessed 5 January 2015.

while that of China increased (Glass, Glass and DiFrancesco 2014). This shift was recognised by some of our interviewees:

> India has participated in global research longer than China has. But we're also seeing a significant amount of turnover in our staff in India, but also wage inflation in the country, which leads to workforce migration, instability, which is a challenge for any company operating there, not just ours. And there are also concerns about the quality of the data at times that comes out of India, so we have to do a lot of additional work to make sure the quality is there, and that human subjects are protected. Literacy is kind of low for some areas. We have to make sure that people aren't coerced (Senior clinical research associate in an international CRO, Interview, 2011).

Thus the claims being made in the mid-2000s, that India would rapidly become a leading site for global clinical trials, were never near to being fulfilled. While India was 15th in a listing in terms of the total number of trials in the period 2005-12, and 11th in terms of trials as at 2012, its trial density, at 0.97 per million population, was well below that for high-income countries, where rates of 20 or more are common (Drain et al. 2014a: S5). Achieving even this limited level, however, has required the creation of a wide range of organisational forms, and transformations in others. In Section 4 we consider the most important of the new actors, the Contract Research Organisations (CROs).

4. Roles Played by CROs in clinical Trials

CROs commonly perform one or more of the sponsor's trial-related duties and functions on their behalf. The functions include, for example, regulatory submission, clinical operations, data management, biostatistics, medical writing, quality assurance, IT, human resources, training & development. Since January 2010, clinical researchers have started a journal, *Perspectives in Clinical Research* (http://www.picronline.org/) with financial support originally from Pfizer.[10] Commonly repeated estimates of the number of CROs in India are around 120, and they are probably involved in most trials reported in India. We analysed data on 101 CROs, using their websites as the source. Seventy-two were Indian companies (in some cases subsidiaries of Indian generics producers such as Zydus-Cadila or Ranbaxy), while 29 were branches of international CROs such as Quintiles or PPD. Some foreign multi-national pharmaceuticals companies established branches in India to run their own trials:

[10] This is mentioned neither in the print issue nor on the website.

GlaxoSmithKline (hereafter GSK), Roche, Pfizer and Sanofi-Aventis manage some or all functions for their clinical trials in-house, from Mumbai offices. Foreign-based CROs account for the majority of global trials. CROs have a variety of relationships with trial sponsors (Sariola et al. 2015). Some independent Indian companies provide capital to drug discovery enterprises. CROs usually manage trial design, trial management, data analysis, medical writing and assist with navigating regulatory requirements. Local Principal Investigators (PIs), or hospital doctors working with them, are responsible for patient recruitment, and host teams of clinical research assistants who manage the day-to-day relationships with patients, CROs and sponsors.

The number of full-time workers in the CRO sector has been estimated to have grown from 4,000 in 2008 to 20,000 in 2010, with site-workers expanding from 6,000 to 30,000. Such individuals occupy a plethora of specialist roles which are needed to accomplish internationally credible trials: Clinical Research Associates, Clinical Research Investigators, Clinical Project Managers, Study Co-ordinators, Clinical Research Managers as well as various managers, auditors, statisticians and safety officers. One estimate claimed that about 150 CROs registered with the US Food and Drug Administration (US FDA) operate in India (Srinivasan 2009).

Because of the role played by foreign sponsors and by CROs based abroad, there are few mechanisms that might ensure that the drugs being tested relate to Indian public health needs. Table 6 shows the distribution of trials active in 2015 by disease category. Since India is now facing an epidemiological transition that can be characterized by low mortality, high morbidity, and by the double burden of communicable diseases and Non-Communicable Diseases – a pattern that holds true to a considerable extent across regions, residence and class patterns (Yadav & Arokiasamy, 2014) – it is hard to say from this table whether the pattern of drugs being tested diverges markedly from India's current or immediate future public health needs.[11] Nevertheless, this suggests that the 10:90 rule ('that only a small proportion of global health research expenditure is spent on diseases that have a large burden of preventable mortality in low-income and middle-income countries') continues to have relevance in India (Røttingen et al., 2013).[12]

[11] For a stronger view – that the research shows little or no relationship to India's health needs – see Mondal & Abrol (2015)

[12] See also http://www.cohred.org/our-mission/ for the history of this argument, as applied to research funded in 2009. Since then there has been an increase in research funded by philanthro-capital and public sources.

Table 6 about here

Claims about the number of trials, or the foreign exchange earnings that would be generated, were only some of the benefits that were promised. We now turn to look in particular at how far knowledge production, and the possibilities for indigenous innovation in the field, have materialised.

5. Knowledge Production

> The academics have started to shape themselves based on clinical trials, which is really pre-cooked research. It is not research, it is operations, and I think it is a dreadful thing that has happened to India. India is becoming a service centre economy for the middle class, extending to academics and research (Retired dean of medicine in a prestigious medical faculty in India, Interview, 2011).

Commercial clinical trials in India produce particular forms of 'research culture' which may not neatly fit familiar conceptual frameworks (Simpson and Sariola 2012). Within these settings, the requirements of protecting their intellectual property from the scrutiny of competitors means that those on the periphery – including the PIs at Indian research sites – have little access to the fundamental knowledge behind decision-making about research protocols and are unable to challenge key decisions. Scientific leadership roles within these trials – trial design and authorship of results, in particular – remain very firmly within the countries where the trials are initiated, i.e. overwhelmingly in North America, Europe and Japan.

> [A]lthough clinical trial activities are now executed across the globe, scientific leadership in these trials is disproportionally concentrated in traditional research locations. This geographical decoupling of patient enrolment and clinical trial management is most pronounced in industry funded research (Hoekman et al. 2012: 4).

As peripheral participants in a global science network, Indian PIs and managers of CROs in India carry out the more replaceable tasks – following the rules laid down elsewhere, being concerned mostly with learning discipline in carrying out tasks that are complex, but which have been defined elsewhere. With respect to India, in the 53 trials in the Hoekman et al database, only 16 (30 per cent) of the linked publications listed someone based in India as a co-author, compared to 98 per cent in the case of the USA-based authors, 68 per cent for Germany, 65 per cent for the UK and 60 per cent for Canada (Hoekman et al. 2012:

6). Indeed, one analysis of the impact of this opening up of India to clinical trials concludes that it has had little impact on indigenous R&D:

> … a large number of R&D investment projects are focused on developing facilities for phase III clinical trials and other such modules that only integrate Indian talent and facilities into foreign pharmaceutical firms' global objectives (Abrol, Prajapati and Singh, 2011:342) … liberalisation of foreign investment has opened the door for outsourcing of clinical trials to India [rather] than to new investment on R&D from basic stages for the development of new drugs (Joseph 2011: 44).

The US FDA and the EMA determine key elements in global approvals and resultant access to the markets where most profits are made. Therefore, key decisions are made outside India, in light of the superior knowledge held by sponsors about how to convince the USFDA and the EMA that they have robust evidence that their new product is safe and effective. Benefits and value flow to the active, managerial participants rather than to those whose involvement is more passive. Collaborations between sponsors, CROs and PIs rarely translate into equalizing or equal benefits, but rather serve to reproduce inequality in knowledge production. Nonetheless, involvement in clinical trials is attractive for some doctors who have the time and energy to spare. Outside government hospitals, PIs may be paid per participant recruited, but for others we interviewed, the possibility of acquiring more up-to-date equipment and improvements to laboratory facilities play a larger role.

In this context of feverish competition to join a global scientific research community, allied to a relatively low level of trial activity, it is not surprising that most of the global trials reported in the CTR-I are managed by CROs, many of which are either foreign-owned or have a close relationship with a foreign-based CRO, and that they use a research model that closely follows international standards. According to data supplied to the CTR-I, RCTs constitute 431 out of 644 trials in 2011, and 475 out of 787 trials in 2012 (see Table 7). Use of a placebo in study design is remarkably common, with 134 trials in 2011 and 149 trials in 2012, and also multiple arm trials might employ both active control and placebo controls (Ravindran 2013: 73).

Table 7 about here

In order to achieve their goals, sponsors engage in research capacity building and to deliver transferable methodological skills, enhanced employment opportunities, foreign exchange earnings and profits. Innovation, creativity and shifts in global economic and

political power in favour of Indian participants over the next 10 years cannot, therefore, be ruled out. A major threat to the scale of the industry, however, has come from the change in regulations following the ethical concerns raised by activist groups within India, and later championed by the relevant Parliamentary Committee. The international perception that India's clinical trials were not run on an ethical basis led to a dramatic loss of confidence in the industry. In Section 6 we look at the ethical issues, and in Section 7 at the impact this has had in generating reform processes.

6. Ethical concerns

The Indian clinical trials industry received a negative press on ethical issues, increasing in frequency around 2010. The media exposed improper informed consent procedures, dysfunctional ethics committees and failures to pay compensation for clinical trial-related injuries or death. These concerns, highlighted in a small number of cases, have been read as applying to the whole industry. Once trust in the trials industry was undermined by these examples, many international sponsors and CROs withdrew trials from India. In this section we describe the ethical concerns and the regulatory changes that followed the negative publicity. Before going into the detail, however, we note that, based on these cases, there is a danger of concluding that few trials in India are run in accordance with national and international ethical standards. However, if ethical concerns have been raised about a trial, its chances of acceptance by regulatory authorities are greatly reduced, so most CROs and sponsors have a strong incentive to follow the rules in spirit as well as letter. Despite the risk of generalisation to all trials, it is important to discuss these cases to put the most recent regulatory reform of 2013, and the events preceding it, into perspective.

To illustrate, survivors of the 1984 Bhopal gas explosion being treated at the Bhopal Memorial Hospital and Research Centre were enrolled in clinical trials without their knowledge or consent. Adverse events were not properly reported, deaths were not investigated and compensation was not paid to the families of patients who died during the trials (Lakhani 2011). Concerns over informed consent were also highlighted in a mass vaccination demonstration project (or a Phase IV trial – accounts differ) against Human Papilloma Virus. Tribal girls in Andhra Pradesh and Gujarat, many living in hostels, were enrolled when their wardens gave mass consent (PATH 2013; Sarojini et al. 2010; Talwar 2013). Seven girls who participated in the trial died. Their deaths were not promptly investigated by an independent body. Even though a later Parliamentary committee

concluded that the deaths were unrelated to the vaccine, the image of clinical trials remained badly affected (Terwindt 2014).

These examples highlight several weaknesses in the regulatory framework. The DCGI was under-staffed even in 2005, and has remained unable to cope with the surge in clinical trial activity that it is supposed to regulate (Nundy and Gulhati 2005). Furthermore, after the DCGI grants approval to commence a clinical trial, it plays little further role in monitoring trial activity. With respect to ethical review in India, it is claimed that members of RECs do not apply the relevant rules consistently; that their members are inadequately trained, have too little time to understand the implications of complex trials and often include people with conflicts of interest; that they do not inspect clinical trial sites to check that the promised procedures are being followed; and that they do not (or cannot) take decisive action when violations have been alleged (Desai 2012).[13] Grassroots activism, working through Parliament as well as the Supreme Court, has been an important driver for reform.

In 2012, two Public Interest Litigation (PIL) petitions were filed in the Supreme Court, one by the NGO Swasthya Adhikar Manch (SAM) and one by Dr Anand Rai, from Indore. The two petitions were combined when they came up before the Supreme Court in February 2013. They alleged that weak regulatory controls on the conduct of clinical trials, combined with their poor enforcement, have contributed to an unacceptable number of deaths and serious adverse events, for none of which had compensation been paid. They also sought to halt trials for drugs and devices that would not be sold or marketed in India, and would thus not advance Indian healthcare. SAM submitted documents claiming that over 2,262 clinical trial participants in India had died in 2006-11. In an internationally unprecedented interim ruling of 30 September 2013, the Supreme Court of India halted the approval by DGCI of new clinical trials, pending a more effective review and monitoring system.

The Supreme Court ruling prompted a raft of reform measures aimed at strengthening protections for Indian clinical trial participants. These include: (i) a more rigorous ‘three tier’ committee system for screening clinical trial protocols at the DCGI; (ii) three new criteria for evaluating clinical trials, namely (a) assessment of risk versus benefit to the patients, (b) innovation vis-à-vis existing therapeutic options, and (c) unmet medical need in the country;

[13] Results of a few surveys conducted by the ICMR are consistent with this conclusion; see, for more details, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3371548/?report=printable

(iii) audio-visual recordings of the informed consent process, and, (iv) the mandatory registration of Indian RECs.

The most controversial of the recent reforms, however, have been those relating to compensation for clinical trial-related injuries or death. Some measures, which aim to strengthen procedural oversight so that incidents are investigated properly and compensation paid if appropriate, are in line with international approaches. Yet some of the new criteria for compensation depart radically from the regimes in other countries. For example, one provision states that "In the case of an injury occurring to the clinical trial subject, he or she shall be given free medical management as long as required"' (Ghooi, 2013). This would seem to apply regardless of whether the trial itself had caused a medical problem. Another rule states simply that subjects shall be eligible for compensation for "use of placebo in a placebo-controlled trial". Entitlement to compensation was also established for failure of an investigational product to provide the intended therapeutic effect.

These changes caused serious concerns about legal risks and led to an exodus of clinical trials from India. The numbers of clinical trials approved by CDSCO fell from 500 in 2010 to just 107 in 2013 (see Table 8). It is reported that sponsors and CROs shifted their activities to other countries with more favourable regulatory systems. Alarmed by the impact on its clinical trial industry, the Indian government is currently watering down some of the reform measures for compensation. Furthermore, in January 2015, and in line with the Modi government's pro-business strategy, the Ministry of Health has proposed 'pre-submission meetings' between drug regulators and stakeholders so as to increase efficiency and speed up approval times (Nair 2015). It remains to be seen whether the efforts to entice business back to India can be made compatible with the enhanced protections for Indian trial participants that is – rightly – demanded by advocacy groups in civil society.

Table 8 about here

7. Conclusion

The controversies that have highlighted problems in the management of clinical trials have been widely publicised, and may have encouraged the managers of global trials to look elsewhere – particularly China – for a setting that is less likely to generate controversy. But the clinical trials industry in India has always massively exaggerated the potential for growth, whether in terms of total numbers of trials, of foreign exchange earnings, or of benefits to India's public health. Clinical trials are still taking place in large numbers – not of new drugs,

but of generics that need to be assessed for bio-equivalence or bio-availability. Now that these are also coming under threat the industry has a considerable job to do in reassuring external and internal regulators that their results can be trusted. For example, in September 2015, the Gujarat FDA called in some German and French media for "assuaging the fear and confusion emanating from the European nations over the quality of the drugs that are manufactured in the country after the GVK fiasco" (Anon. 2015).[14]

Although the Indian generics industry, and CROs seemed well prepared for joining the WTO in 2005, they under-estimated the cultural and regulatory shifts needed if Indian firms were to establish their position in the complex global assemblage that is the contemporary clinical trials industry. On the positive side, a necessary debate has begun about how this assemblage can be reshaped to maximise its benefits to India as a whole, and not just the pharmaceuticals industry, whether CROs, 'Big Pharma' or generics producers There are clear benefits for India that many international clinical trials left India in 2012-13 and that their return is slow, so that the protection and benefits to participants can be strengthened. The reduction of clinical trials taking place in India does not deprive it of the new drugs discovered, and even if India had been a site in a clinical trial, the global pharmaceutical companies rarely respected the principle of post-trial access to provide those drugs free or cheap, either to the trial participants or to the wider patient population. In terms of losing opportunities for science, our study shows that knowledge production processes were never under the control of Indian investigators, and showed little sign of becoming so.

With respect to attempts to use legislation and regulation to control the clinical trials industry to better serve health interests, India is leading the way internationally. The provisions such as independent authority (free from investigators, sponsor and its DSMB) to assess serious adverse events (deaths) and their relatedness (the specific criteria proposed), and on the compensation to be paid were the most radical, even as compared to most developed countries' regulations in that regard. The debate on serious adverse events and compensation, was reflected in the insertion of clear and definite guidance on compensation in the Helsinki Declaration for the first time in its revision of 2013. India is taking seriously issues of whether so-called 'new' drugs really offer advantages over existing ones, and trying to ensure that public health issues take precedence over profits. But this struggle has only started. Paradoxically, these moves are being played out against the backdrop of continued

[14] See footnote 6 for more detail of this judgement.

reductions in Indian government spending on healthcare, and by one of the most 'business-friendly' Governments India has ever seen. We cannot be sanguine about the outcome.

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