A COMPARISON OF BREAST CANCER CLINICAL TRIALS IN THE UNITED STATES VS INDIA: ANALYSIS OF REGULATORY REQUIREMENTS

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ABSTRACT

Breast cancer is the most common malignancy among females worldwide. Breast cancer rates are particularly rising in developing countries such as India. The changes in the prevalence of cancer risk factors are resulting in more and more patients are diagnosed with breast cancer in India. Although the incidence of breast cancer is lower in India in comparison to the United States (U.S.), mortality rates associated with breast cancer are higher in India.

Breast cancer in India is often diagnosed at an advanced stage and a younger age in comparison to the U.S. Breast cancer clinical research involving human subjects aims to produce innovative treatments and procedures to combat the burden of breast cancer. Clinical research in breast cancer is growing in India due the rising incidence of and mortality rate from the disease. Globalization of clinical trials has become a trend for pharmaceutical companies as well as federal agencies. India was deemed one of the most attractive global destination sites for clinical trials until the incidence of unethical practice gained media attention nationally and internationally. Several incidents of unethical practice claiming altruistic motives were not the main focus, but rather profit was the concentration. The unethical practices involving Indian subjects tarnished the country's attractiveness as a site for clinical trials, resulting in a decline of clinical research in 2010-2012. India has since amended Schedule Y, the requirement and guidelines for conducting clinical trials established under Drugs and Cosmetic Act 1945. The amendments were in effort to resolve issues regarding clinical research, with hopes to regain trust in clinical research processes. To better understand if the claims of

unethical practice are a present-day issue, evaluating the process of clinical trials in India is necessary.

Clinical research in breast cancer worldwide provides multiple efforts to advance treatment of breast cancer. Comparing breast cancer trials in India versus the U.S., a country known for having the most regulatory rules and processes, could open up the discussion of similarities and possible shortcomings through a literary review of regulatory framework, roles and responsibilities of sponsor and investigators, recruitment and enrollment trends, informed consent processes, and post market access of approved marketed breast cancer treatments.

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LIST OF ABBREVIATIONS

AV	Audio-video
ACSCO	American Society of Clinical Oncology
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CDER	Center for Drug Evaluation and Research
CDSCO	Central Drug Standard Control Organization
CFR	Code of Federal Regulations
CTRI	Clinical Trials Registry-India
DCGI	Drug Controller General of India
DHHS	Department of Health and Human Services
DMC	Data Monitoring Committee
EC	Ethics Committee
et al.	*et alii* (and others)
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
ICH-GCP	International Conference on Harmonisation - Good Clinical Practice
ICMR	Indian Council of Medical Research
IDC	Invasive Ductal Carcinoma
IND	Investigational New Drug

IN-GCP	Indian - Good Clinical Practice
MCI	Medical Council India
MOH	Ministry of Health
NCBI	National Center for Biotechnology Information
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
SAE	Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
U.S.	United States
WHO	World Health Organization

INTRODUCTION

Breast cancer is the most prevalent female malignancy and the primary cause of death among women worldwide, being 100 times more common in women than men (American Cancer Society 2014). Breast cancer occurs when a malignant tumor originates in the breast and is typically presented in cells that line the ducts (ductal cancer) and cells that line the lobules (lobular cancer). There are rare breast cancer cases that occur in other tissue (Sharma *et al.* 2010) (Figure 1). The exact cause of breast cancer is unknown, although environmental and genetic factors play a role in developing breast cancer. Specifically, mutations in gene HER2, BRCA1, BRCA2, and p56 have been linked to breast cancer. The severity of breast cancer is defined in stages; the number of the stage is related to the size of the tumor and the spreading of the cancer. Stage 0, carcinoma in situ, is the earliest stage of breast cancer followed by stages I through IV, with stage IV being metastatic breast cancer (American Cancer Society 2014).

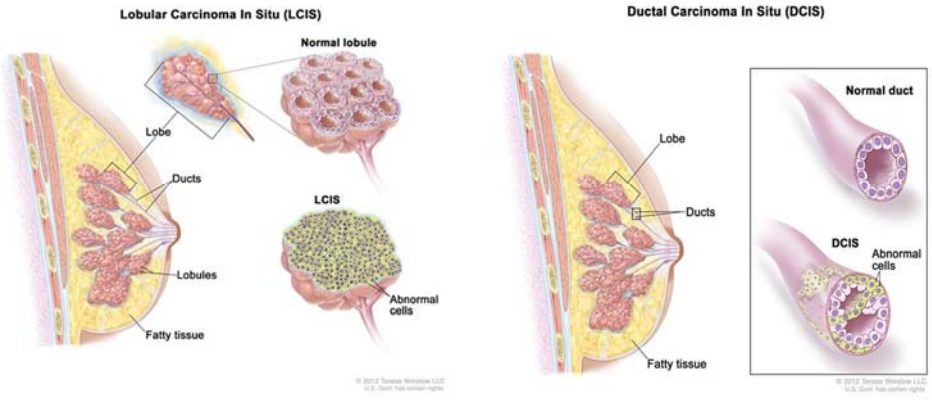

Figure 1. Lobular Carcinoma In Situ and Ductal Carcinoma In Situ (image from the National Cancer Institute)

The overall outcome of breast cancer depends on the type of cancer, stage at diagnosis, and the health and age of the patient (American Cancer Society 2014). Common procedures to treat breast cancer are surgery, radiation, chemotherapy, and biological therapy.

Since 2008, global breast cancer incidence has increased by more than 20 percent with mortality increasing by 14 percent (Ferlay *et al.* 2013). In 2012, there were approximately 1.7 million new breast cancer cases diagnosed worldwide (Ferlay *et al.* 2013). Nearly one third of these cases are in the U.S., India, and China (Ferlay *et al.* 2013). Clinical trials are an essential tool in the discovery of advances in breast cancer prevention, optimization of breast cancer diagnosis and treatment, as well as improvement of follow-up care for breast cancer survivors. In 2013, a total of 4,823 breast cancer clinical trials were registered in the worldwide database run by the U.S. National Institutes of Health (NIH) (Saini *et al.* 2013). Over half of these trials were conducted by government, academic, and research organizations within the U.S. while only 70 of the 4,823 were based in India (Saini *et al.* 2013). The breast cancer clinical research arena is minimal in India in comparison to the U.S., However the rise in breast cancer has produced growth in the field of breast cancer clinical research in India. (Burt 2013). Globalization of clinical trials is an intensively growing trend for government and pharmaceutical companies, and India is among the leading global destinations for outsourcing clinical trials.

The average cost to bring a new drug to market is roughly 1 billion dollars. The bulk of this cost is attributed to the human clinical trial phase of development. The human clinical trial phases can last several years. A patent term for a new drug is 20 years from

the date on which the patent is filed in the U.S. (FDA 2014). Time is essentially money - the longer an approved drug is on the market with an active patent, the more financial gain the patent holder receives. Exclusivity also grants exclusive marketing rights for a prescribed period of time if the drug meets the statuary requirements under U.S. regulation 21 CFR 314.108. India offers a considerably shorter timeframe for the human clinical trial phase. Higher recruitment and enrollment rates decrease the cost and time necessary to produce final evaluable data from the trial. India is well known for their high recruitment numbers primarily due to a majority of the population not enrolled in health insurance therefore the only option many have for treatment is through clinical research (Singh *et al.* 2008). Other beneficial factors making India a desirable clinical trial location includes the large heterogeneous patient population, English speaking medical experts, and increasing number of quality hospitals and medical equipment. The most attractive benefit is the cost savings for sponsors financially supporting clinical trials in India, the costs for conducting trials can be up to 60% less in India than in other countries (Murari *et al.* 2012). According to Jean-Pierre Garnier, the former CEO of GlaxoSmithKline, a case report from a first-rate Indian academic medical center in India costs approximately $1,500 to $2,000. A report such as this from a second-tier center based in the U.S. would come with a tenfold increase in cost (Garnier *et al.* 2008). The financial and scientific gains put India in second place for the most preferred country to conduct clinical trials outside of the U.S. in 2009 (Gupta *et al.* 2011). India's continued growth in the clinical research arena provides the country with economic opportunity and possible advancements from clinical trials such as breast cancer diagnosis, treatment and prevention.

Breast Cancer Trials

Incidence rates of breast cancer are typically higher in developed countries in comparison to developing countries. However, India is one of the developing countries that has seen a vast increase in breast cancer. In addition, Indian women are too often diagnosed at advanced stages, which dramatically affects the mortality rate. Breast cancer clinical trials are essential for discovering survivorship tools and optimal disease management, with the goal to increase survival rates. Controversially, India has been criticized nationally and internationally for having a weak regulatory framework. This could possibly invite unethical practices in breast cancer clinical trials. Unethical practices for financial gain have generated societal concerns and fears (Bajpai 2013). The media bought the concerns front and center nationally and internationally with headlines such as “Illegal drug trials have claimed 32 lives and maimed 49 in MP” from India Today in 2012, and “Without consent: how drugs companies exploit Indian 'guinea pigs'” an article from The Independent based out of London in 2011. These media stories protest unethical trials and blame sponsors for taking advantage of a vulnerable population. This societal effect was evident in 2010 and 2012 when the number of clinical trials conducted in India began to decline due to the sponsor’s fear of ethical and scientific repercussions (Gupta 2011). Indian media stories and articles have focused on these concerns, claiming that the ruling class in India capitalizes on the economic opportunity of clinical trials rather than serving a philanthropic motive. Regardless of the cost savings, allegations of mediocre regulatory conditions threaten India’s status as an ideal global clinical trial setting (Burt *et al.* 2013). These concerns cause sponsors to be cautious when choosing India as the location to conduct clinical research. Unethical

clinical research involving human subjects falls on the shoulders of the stakeholders of the clinical trials; sponsors, investigators, ethics committees, and regulatory bodies are all at fault. As a result of the exposure of unethical practices, India's regulatory authority of clinical trials, the Central Drugs Standard Control Organization (CDSCO), amended their Schedule Y and cosmetic rules to better regulate and regain confidence in clinical research conducted in India (CDSCO 2004).

To gain a better understanding of how clinical trials are conducted in a developed country versus an under developed country; the U.S. was compared to India. Comparing regulatory guidelines and requirements along with the processes for conducting breast cancer clinical trials could provide awareness to the similarities and identify possible limitations that have triggered the concern for ethical standards in India.

Regulations and Guidelines

Clinical trial regulations and guidelines are put in place to ensure the protection of the rights, safety, and welfare of research subjects as well as the quality and integrity of data collected in the clinical trials. The U.S. is known for having extremely stringent regulatory requirements in comparison to other countries. The U.S. ethical guidelines and principles originated in the Belmont Report which was written in response to the revelations of the unethical Tuskegee Syphilis Study (DHHS 1979). The current Food and Drug Administration (FDA) guidelines and regulations are developed to meet the needs of the U.S. population and market. Trials in foreign countries, especially trials conducted in a developing country such as India, may have different standards and needs.

The International Council on Harmonisation Guideline for Good Clinical Practice (ICH-GCP) is a unified international guideline developed by the U.S., the European Union, and Japan regulatory authorities (CDER et al. 1996). ICH-GCP set an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve human research subjects (CDER et al. 1996). ICH-GCP facilitates the mutual acceptance of clinical trial conduct and data (CDER et al. 1996). Extensive acceptance of the guidelines may also have an influence on the globalization of clinical trials. Although the guidelines are acknowledged widespread, compliance with this standard is voluntary.

India's ethical guidelines were first implemented in 2000 and first revised in 2006; 'Ethical Guidelines for Biomedical Research on Human Subjects' by the Indian Council of Medical Research (ICMR). The 'Ethical Guidelines for Biomedical Research on Human Subjects' consist of twelve general principles to be implemented by all biomedical researchers working in the country (Sanmukhani 2011). The Institutional Review Board (IRB) or Ethics Committee (EC) helps enforce the regulations and ethical guidelines the country mandates. According to the World Health Organization (WHO), it was estimated that less than 40 ECs in India are properly constituted and functioning (Kadam 2012). This is one of many possible problems with Indian clinical research. Evaluating the similarities and differences in conducting breast cancer clinical trials between a developed nation, the U.S., and a developing one, India, could expose the truths, pitfalls, and possible false allegations of misconduct that the Indian media exaggerate and sensationalize without accurate information. Still, the hostile environment that the media creates is enough to deter any major pharmaceutical company from

selecting India as a clinical trial site. As a result, India could miss out on economic opportunities and the development of breast cancer treatment advancements that are not yet readily available to their population. Understanding and addressing shortcomings will only help the promotion of ethical globalized clinical trials in India and improve standard of care for breast cancer patients, ultimately resulting in the growth and development of the nation. Due to the prevalence of breast cancer in both the U.S. and India, evaluation of breast cancer treatment trials will give an insight on the similarities, discrepancies, and deficiencies of how clinical trials are conducted in U.S. versus India.

This paper will focus on comparing the incidence of breast cancer per country and the status of breast cancer clinical trials. The differences in regulatory oversight, roles and responsibility of sponsors and investigators, patient recruitment and enrollment, informed consent processes, and post-market access to breast cancer treatment in the U.S. and India.

RESEARCH METHODS

The largest numbers of breast cancer trials are conducted in the U.S. The U.S. was set as the target for a comparative evaluation of breast cancer clinical trials conducted in India. The U.S. has the highest incidence of breast cancer globally; the incidence in India is steadily rising. The study was done using data from various websites. Background information on breast cancer was obtained from the American Cancer Society website on breast cancer, www.cancer.org/cancer/breast-cancer.html, www.breastcancer.org, and http://www.breastcancerindia.net/. The Web Portal for International Cancer Research, Globocon 2012 on breast cancer provided the incidence, mortality rates, and prevalence in 2012, http://globocan.iarc.fr/old/FactSheets/cancers/breast-new.asp.

The information on breast cancer clinical trials was obtained from the ClinicalTrials.gov database maintained by the NIH, www.clinicaltrials.gov. Breast cancer trials in India were found on CTRI dataset, http://ctri.nic.in/Clinicaltrials/login.php, published by the Indian Council of Medical Research (ICMR). and BreastCancerTrials.org, www.breastcancertrials.org.

The U.S. regulatory guidance documents were researched on the FDA website at www.fda.gov. India regulatory guidance documents were researched on the website Central Drug Standard Control Organization (CDSCO) http://www.cdsco.nic.in, ICMR National Ethical Guidelines, and Schedule Y of the Drug and Cosmetic Act in 1945, www.cdsco.nic.in/html/D&C_Rules_Schedule_Y.pdf.

Standards for regulatory harmonization were researched using data from the International Conference on Harmonization's website at www.ich.org.

Scholarly journal articles were retrieved using PubMed, an online database found at www.ncbi.nlm.nih.gov/pubmed. The database is maintained by the National Center for Biotechnology Information (NCBI). A web search was conducted to review media stories and articles regarding clinical trials in India. The information in each search page was reviewed to ensure only relevant information was used.

RESULTS

In order to begin evaluating the significant difference in breast cancer clinical trials between the U.S. and India, the regulatory oversight per country was evaluated, reviewed, and analyzed, including the regulatory requirements for Investigational New Drug (IND) trials, clinical trial phases, ethical review processes, regulatory harmonization of clinical trials, the roles and responsibilities of the sponsor and investigator, enrollment and recruitment trends and techniques, the informed consent process, and Serious Adverse Event (SAE) reporting requirements. Next a closer look was taken at breast cancer clinical trials in both countries. Reviewing the trend presented in the International Agency for Research on Cancer, GLOBOCAN project, which estimates global cancers in terms of incidence, mortality, and prevalence for each country, gives an overall view of the breast cancer burden in the U.S. and India. Breast cancer research conducted per country was analyzed via literary review and clinical trial databases.

Finally, post market access to approved breast cancer drugs from the breast cancer clinical research was examined to determine whether the study population enrolled in the breast cancer trials benefit from the clinical research. This would include, but would not be limited to, access to improved methods of treatment and therapies.

Regulatory Oversight and Regulatory Requirements for IND Trials

Figure 2 is a partial view of the regulatory bodies involved in breast cancer research per country.

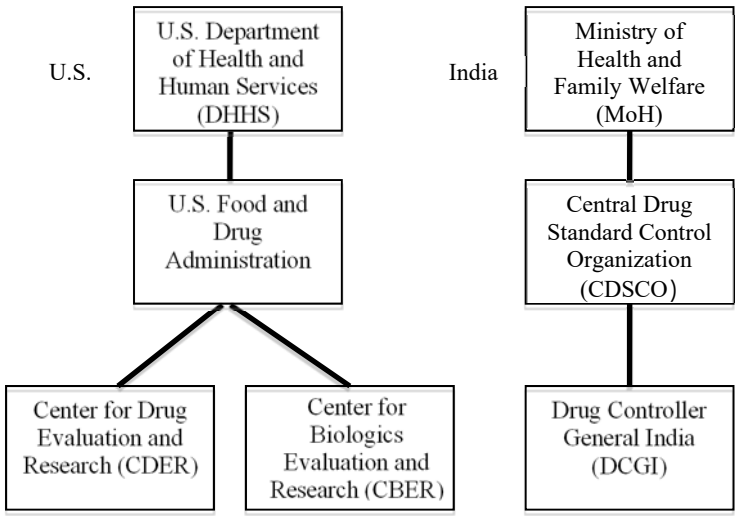

Figure 2 Partial Organizational Structures for Regulatory Departments in the U.S. and India

In the U.S., the abbreviated list of the governing agencies involved in breast cancer clinical trials includes DHHS, FDA, CDER and CBER; the FDA assures regulatory supervision and compliance of Title 21 of the Code of Federal Regulations (CFR). The CFR Title 21- Food and Drugs comprise a set of rules and regulations that sponsors and investigators must adhere to while conducting clinical trials. Clinical trials must also follow GCP guidelines that are codified in the FDA regulations at Parts 50 and 56 of Title 21 of the CFR (Table 1).

Code of Federal Regulations Title 21-Food and Drugs	
21 CFR part 11	Electronic submission and electronic signature
21 CFR part 50	Protection of human subjects
21 CFR part 54	Financial Disclosure by Clinical Investigators
21 CFR part 56	Institutional Review Board
21 CFR part 201	Drug labeling
21 CFR part 312	Investigational New Drug Application
21 CFR part 314	Application for FDA approval to market a new drug
21 CFR part 316	Orphan drugs

Table 1. Code of Federal Regulations Title 21- Food and Drugs that apply to clinical trials in the U.S.

The Ministry of Health (MoH) of India is in charge of health policy similar to the Department of Health and Human Services (DHHS) of the U.S.. In fact, the regulatory framework of both countries are similar. The CDSCO and the DCGI are the FDA counterparts in India. The DCGI is the Licensing Authority in the Indian regulations under the scope of CDSCO. The CDSCO is the regulatory authority responsible for clinical trial oversight, approval and inspections, and setting standards for ensuring safety and efficacy as well as quality of drugs, cosmetics, and medical devices. Schedule Y are laws enforced under the Drug and Cosmetics Act 1945 and regulated by the CDSCO. These laws document the requirements, guidelines and regulations to be followed when conducting clinical trials in India. The table below (Table 2) describes the rules of Schedule Y; these rules are equivalent to 21 CFR 312 in the US (Saxena 2014).

Rule	Description
122DA	Permission to conduct clinical trial
122DAA	Definition of Clinical trials
122DAB	Compensation in case of trial-related injury or death
122DAC	Condition of Clinical Trial permission & Inspection
122DD	Registration of Ethics Committee
122E	Definition of New Drug

Table 2. Rules of Schedule Y

There have been three recent amendments to Schedule Y. The first amendment, Rule 122 DAB, states the appropriate procedures and timeline when analyzing the SAE reports for clinical trials and payment of compensation in case of trial related injury or death (Karwa *et al.* 2013). Rule 122 DAC, the second amendment, specifies the prerequisites that are critical for clinical trials to be adequate to receive approval from a licensing authority. The licensed authority also has the power to implement extra conditions they deem necessary for approval. In addition, inspectors authorized by CDSCO are permitted to inspect the clinical trial sponsors, their subsidiaries, agents, sub-contractors, and clinical trial sites (Karwa *et al.* 2013). The third amendment, Rule 122 DD, requires mandatory registration of the Ethics Committees (EC) (Karwa *et al.* 2013). The EC is required to approve and review the clinical trials based on meeting the requirements of the amended Schedule Y and GCP guidelines and regulations (Karwa *et al.* 2013).

The process to begin a clinical trial is quite similar in both countries. Approval is necessary from the DCGI in India and the FDA in the U.S. The EC and IRB review the

methods proposed for research to ensure that ethical principles, including the rights of human subjects are followed. Registration of the clinical trial on a government-administered website is also mandatory in both countries to ensure transparency: ICMR in India maintains the website www.ctri.in and the National Institute of Health (NIH) National Library of Medicine (NLM) maintains www.clinicaltrials.gov.

Clinical Trial Phases

Conducting clinical trials is critical to determining the safety and efficacy of a new drug. A large percentage of drugs will never be approved or reach the consumer market due to the failure at one of the steps or stages of the drug development process. Years of extensive laboratory research, which typically involve animal models and human cells, are only the initial steps. Approval to continue research and testing in human clinical trials only occurs after the FDA deems the nonclinical data successful. Once testing in human subjects is approved, the clinical trials are usually conducted in four separate and sequential phases (Table 3). The investigators are required to submit data and protocols for FDA review before continuing to the next phase of clinical trials.

Phase	Description
Phase I	Human Pharmacology and Safety
Phase II	Therapeutic Exploratory
Phase III	Therapeutic Confirmatory
Phase IV	Post Marketing Surveillance

Table 3. Clinical Trial Phase I-IV with Descriptions

Both the U.S. and India require the completion of phases I-III before an investigational drug can be considered for marketing approval. Under certain circumstances, approval may be granted to expedite these phases in order to assist and

accelerate development and review of a new drug to address an unmet medical need for the treatment of a serious or life-threatening condition (FDA-Guidance 2014).

The initial phase of testing in human subjects is Phase I. The purpose of Phase I is to assess the safety and dosage of the investigational drug. These trials typically consist of 20 to 100 healthy volunteers that may be evaluated for several months. Approximately 70% of experimental drugs pass this phase of testing. Phase II clinical trials can last several months to two years and enroll hundreds of diseased subjects or subjects with specific conditions. This phase tests the efficacy and safety of the drug, typically by randomizing the subjects so that one group receives the experimental study agent and the other receives a placebo. These studies are often blinded so neither the investigator nor the subject know what treatment the subject has received. The comparative information regarding the safety and efficacy of the study agent is then reported to the FDA. Thirty-three percent of Phase II trials succeed and are granted approval to the next phase of human clinical trials. Phase III is the final study phase that needs to be completed before a sponsor can request FDA approval for marketing a new drug. Phase III consists of hundreds to thousands of diseased or conditioned subjects, evaluated for a duration of several years. This large-scale testing provides a comprehensive understanding of the risks and benefits of the drug along with the efficacy. Phase III clinical trials are usually comparative trials comparing the investigational drug to an effective approved drug or combination of drugs. Approximately 25-30% of the drug trials in this phase successfully move to market approval of the study drug. The last phase, Phase IV studies, are conducted after the drug has been approved and are known as Post Marketing Surveillance Trials. The objective of these trials is to monitor the long-term effectiveness

of a drug and quality of life of the drug consumer, compare the new drug to other related drugs on the market, and determine the cost effectiveness of the drug therapy relative to other new and older therapies on the market. Results of significant findings can lead to a drug being taking off the market or having restricted use (FDA 2014).

Institutional Review Board and Ethics Committee

The U.S. and India both have a decentralized process for ethical review of clinical trials. In the U.S., each research study must obtain institutional level IRB approval. Studies conducted in India require approval from an EC affiliated with the clinical or academic institution or from an independent EC for institutions that do not have their own EC or for researchers with no institutional attachment. A closer look was done to review the similarities and differences in the IRB in the U.S. and the EC in India.

According to the U.S. FDA regulation 21 CFR part 56, the IRB has the authority to approve, disapprove, or require modification for approval before implementation of a clinical trial and through its duration (FDA-IRB 2017). The IRB is a board that reviews the protocol and related documents with the main goal of protection of the rights and welfare of human research subjects (Enfield *et al.* 2008). The IRB monitors the progress of the trial by reviewing the protocol and protocol documents at a minimum of annually, as well as reviewing all amendments (FDA-IRB 2017). FDA regulations require an IRB to consist of at least 5 members with diverse backgrounds in experience and expertise. Nondiscriminatory efforts are made to ensure that the IRB includes a variety of races, genders, cultural backgrounds and sensitivity to issues within the community (FDA-IRB 2017). Typically, the IRB consists of, but is not limited to, medical scientists, clinicians, legal experts, ethicists or philosophers, social scientists, and a community member. Each

member of the IRB is required to be educated on the responsibilities and purpose of the IRB per FDA regulations. Johns Hopkins University publicly provides a description of the IRB that reviews all of its breast cancer trials; it consists of consumers, clergy, and healthcare professionals that review protocols to avoid extreme and unethical risk to subjects (JHM 2015). The IRB's responsibilities of safeguarding the rights and welfare of human participants involve reviewing the research protocol to assess the possible risks and potential benefits. The IRB reviews the informed consents to ensure the trial subjects are well informed. The IRB also reviews SAE reports and determines whether or not to amend the protocol, possibly suspend, or terminate the study if warranted. The FDA and DHHS have mandatory registration programs for IRBs; the Office of Human Research Protection (OHRP) maintains the electronic registration system for both agencies. Federal Wide Assurance (FWA) is a written assurance of compliance that is required for research conducted or supported by DHHS involving human subjects. An OHRP-approved FWA requires the institution to comply with DHHS regulations protecting human participants. The FDA had authority to disqualify the IRB for noncompliance per 21 Part 56.

In India the EC is responsible for ensuring a proficient review of the clinical trial protocol to evaluate the potential risks and benefits for the study participants. "All proposals of biomedical research involving human participants should be cleared by an appropriately constituted Institutional Ethics Committee (ICMR 2017)". The ICMR provides SOP guidelines for the EC, http://icmr.nic.in/ethics_SOP.pdf. An EC must consist of a minimum of 7 members with a diversity of representative capacities and disciplines similar to the composition of the U.S. IRB. The 7 committee members are comprised of a medical scientist, clinician, statistician, legal expert, social scientist, and a

common person from the community (Kumar *et al.* 2013). Members should have familiarity with the clinical regulatory requirements and should hold no conflict of interest. EC reviews are conducted in formal meetings where the trial application is categorized based on risk level: exception from review, expedited review, or full review (ICMR 2017). The EC confirms the credentials of the investigators, facilities, and methods of conducting the research study. The EC also determines the number of trials an investigator can undertake at one time. Currently there is no stated expiration date for an EC approval in the IN-GCPs, the ICMR Guidelines, or Schedule Y (NIAID 2016). The EC can retract its approval if necessary; in an event a protocol's approval is retracted, the EC must record the reason and inform the investigator and DCGI immediately. Protocol informed consent forms are thoroughly reviewed by the EC to confirm the research subjects are well informed with sufficient information regarding the trial (ICMR 2017). In agreement to G.S.R. 72 (E) of the Gazette, a legal document of the Government of India, an EC must be registered with the DCGI prior to reviewing and approving a clinical trial (G.S.R. 72 E). EC registration is valid for 3 years in accordance to rule 122DD. The DCGI has the authority to suspend or cancel registration if the EC fails to comply with the conditions of registration (Kumar *et al.* 2013). The EC has the responsibility to examine SAEs reported by the investigator. Once an SAE is reviewed, the EC is tasked to report to DCGI with a recommendation of proper compensation. Further SAE reporting will be discussed in the SAE Reporting section. Accreditation and Certification requirements for the EC, investigators and clinical trial sites can be found at the National Accreditation Board for Hospitals & Healthcare Providers site, http://www.nabh.co/Index.aspx. "National Accreditation Board for Hospitals &

Healthcare Providers (NABH) is a constituent board of the Quality Council of India, set up to establish and operate accreditation programs for healthcare organizations" (NABH 2017).

ICH-GCP and IN-GCP

The ICH-GCP guidelines provide technical standards and guidance for ethical oversight of clinical trials. The U.S., European Union, and Japan developed these guidelines that are mutually accepted globally (ICH 2016). India developed their own Indian Guideline, Indian Good Clinical Practice (IN-GCP), "To ensure uniform quality of clinical research throughout the country and to generate data for registration for new drugs before use in the Indian population" (CDSCO 2004). The IN-GCP are aligned with ICH-GCP; however, there are differences that could make compliance difficult for the sponsors, investigators, and ethics committees. Below, Table 4 details the significant differences in ICH-GCP and IN-GCP guidelines.

IN-GCP	ICH-GCP
Section 2.4.3.1: The investigator should sign the Informed Consent Form	Section 4.8.8: The investigator, or person designated by the Investigator, conducts the consent process and signs the consent form.
The maximum number of EC members should be 12-15	There are currently no specified number of\ Ethics Committee (EC) members
It is recommended that the Member Secretary should belong to the same institution	There are no such recommendations
The monitor is responsible to ensure that the CRFs are legible.	The monitor is only responsible to verify the documents provided by the investigator are legible.
Record retention for 3 years after completion of the trial.	Record retention for 2 years after the marketing authorization approval.
The Investigator should be qualified as per Medical Council India (MCI)	The Investigator qualifications are confirmed via training and experience.
Upon trial completion, the investigator should sign and forward the data (CRFs, results, analyze, and reports) from the study to the sponsor and EC	Upon trial completion, the investigator has to provide the EC with a summary of the outcome of the trial
EC has the power to order discontinuation of a trial if the EC finds that the goals of the trial have already been achieved mid-way or unequivocal results obtained.	The responsibility to discontinue lies with the independent data monitoring committee (IDMC)
EC Quorum should be a minimum of 7 members	EC Quorum should be a minimum of 5 members
EC Quorum should involve at least one woman	EC Quorum has no gender requirements

Table 4. Differences in IN-GCP and ICH-GCP (https://issuu.com/cliniversity/docs/indian_gcp_and_ich-gcp_their_differences)

Sponsor Responsibilities

In the U.S., per 21 CFR 312.3, a "Sponsor means a person who takes responsibility for and initiates a clinical investigation", the sponsor could be a

government agency, pharmaceutical company, academic institution or private organization (FDA-CFR 21 2014). Sponsor responsibilities are described in the code of regulations, 21 CFR Part 312. 50, "Sponsors are responsible for selecting qualified investigators, providing them with the information they need to conduct an investigation properly, ensuring proper monitoring of the investigation(s), ensuring that the investigation(s) is conducted in accordance with the general investigational plan and protocols contained in the IND application, maintaining an effective IND with respect to the investigations, and ensuring that FDA and all participating investigators are promptly informed of significant new adverse effects or risks with respect to the drug. Additional specific responsibilities of sponsors are described elsewhere in this part" (FDA-CFR 21 2014). Per regulation, the sponsor of the trial will be considered the responsible party and required to register the clinical trial with clinicaltrials.gov as well as being responsible for maintaining adequate records showing the receipt, shipment, or other disposition of the investigational drug (FDA-CFR 2014). The sponsor is responsible for monitoring the results of a study. In multicenter clinical trials, a sponsor will utilize the services of an independent group of clinicians and statisticians known as the Data Safety Monitoring Board (DSMB). The DSMB reviews unblinded data to ensure the safety of the clinical trial; they also have the authority to terminate a trial if the study treatment is causing more SAEs and deaths in comparison to standard methods of treatment. Sponsors can also utilize Clinical Research Organizations (CROs) to meet some of their responsibilities and obligations, but ultimately the sponsor is responsible for the quality and integrity of the clinical data. The sponsor is also responsible for record retention for 2 years after a

marketing application is approved or until 2 years after shipment and delivery of the drug for investigational use is discontinued and FDA has been so notified (FDA-CFR 2014).

In India the CDSCO, IN-GCP, defines a sponsor as "An individual or a company or an institution that takes the responsibility for the initiation, management and/or financing of a Clinical Study" (CDSCO 2014). An Investigator who independently initiates and takes full responsibility for a trial automatically assumes the role of a sponsor (Parth 2013). A primary responsibility of a sponsor is to register the clinical trial with CTRI prior to enrolling. Sponsor responsibilities are located in the IN-GCP section 3.1, as well as in Schedule Y, "The clinical trial Sponsor is responsible for implementing and maintaining quality assurance systems to ensure that the clinical trial is conducted and data generated, documented, and reported in compliance with the protocol and Good Clinical Practice (GCP) Guidelines issued by the Central Drugs Standard Control Organization, Directorate General of Health Services, Government of India as well as with all applicable statutory provisions. Standard operating procedures should be documented to ensure compliance with GCP and applicable regulations". Prior to study start, the sponsor is responsible for selecting investigators and the institution for the clinical trial. The investigator and sponsor collaborate on the protocol, Standard Operating Procedure (SOP), monitoring, documenting preparations, and possible auditing preparations. The sponsor provides the investigator with all the proper information regarding the clinical trial, safety and efficacy data, and instructions for proper use of the study drug. The sponsor ensures the study staff is sufficiently trained and adequate facilities are available. The sponsor ensures the protocol has been reviewed and approved by the EC. To ensure the clinical trial is being conducted per the approved protocol, the sponsor monitors the

trial for regulation compliance oversight, accurate data entry, and that all adverse events are reported in the timeframe per regulation (Parth 2013). The sponsor is responsible for monitoring the results of a study. Similar to the DSMB, in India a Data Monitoring Committee (DMC) can be established to assess the progress of the study by reviewing safety data and making recommendations to the sponsor whether to continue, modify, or stop a study (CDSCO 2014). The sponsor has the authority to terminate prematurely or suspend a study. Record retention responsibilities are 3 years after the completion of the study or submission of the data to the regulatory authorities whichever is later (NIAID 2016). Noted in the sponsor responsibilities per IN-GCP is reference to compensation for participation "Subjects may be paid compensation for participation in accordance with the guidelines listed in 2.4.5". Foreign sponsors, per IN-GCP 3.1.17, are to appoint a local representative or CRO to fulfill the appropriate local responsibilities and adhere to DCGI regulations (CDSCO 2014).

Investigators responsibilities

Per the U.S. regulation 21 CFR 312.53, the Investigator has the responsibility to personally conduct the study in accordance with the current protocol and only make changes after notifying the Sponsor, unless the welfare of the subject is in question (FDA 2014). The investigator must agree to supervise all aspects of the protocol. The investigator is responsible for explaining that the study drug is investigational as well as meeting all requirements of 21 CFR part 56 in terms of obtaining proper informed consent. Guidance for Industry: Investigator Responsibilities — Protecting the Rights, Safety, and Welfare of Study Subjects, outlines the FDA expectations for study oversight. (FDA-Guidance 2009). The investigator is responsible for reporting all adverse

experiences that occur to the sponsor in the proper timeline. The investigator should ensure all study members are properly delegated and trained for study tasks and ensure the study team members understand their obligations both in terms of the protocol and general regulations and ICF/GCP guidelines (FDA-Guidance 2009). The investigator is ultimately responsible for conducting ethical clinical research involving human subjects. Compliance to applicable statutes and regulations provides assurance of clinical data integrity. Failure to comply may result in the FDA initiating a clinical investigator disqualification proceeding, resulting in the investigator no longer being eligible to conduct FDA regulated clinical research. An investigator could face disbarment and possible criminal charges if involved in criminal conduct, such as fraud.

Investigators roles and responsibilities in India are the same as the roles and responsibilities delegated to investigators in the US. The investigator is ultimately responsible and accountable for conducting the clinical trials. Investigators in India also face debarment if the clinical research they are conducting is deemed unethical. The Investigator is required to adhere to a fixed timeline when reporting adverse experiences. Investigators must possess the proper qualifications, education, and training to appropriately conduct the trial. It is expected that investigators in both countries are to follow the protocol meticulously, collect accurate data, as well as thoroughly inform and properly consent subjects for a clinical trial. The investigators must ensure that amendments to the original clinical trial protocol must first be reviewed and approved by the IRB and EC who are required to submit to the regulatory authorities before any changes are implemented. India proposes a limit of 3 clinical trials to be conducted by an investigator at one time to ensure that the investigator has adequate time to properly

perform each trial in full compliance with the responsibilities and duties. Currently there is not a federal mandate for the number of trials being conducted concurrently by an U.S. investigator.

SAE Reporting

The U.S. defines an SAE as follows: “An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse”. This definition is found in 21CFR 312.32, along with AEs, Life Threatening adverse events, Suspected adverse reactions and unexpected adverse reactions (FDA 21CFR 312.32). Suspected Unexpected Serious Adverse Reaction (SUSAR) that are fatal or life threatening are to be reported to the FDA within 7 calendar days, while non-life threatening adverse events are reported within 15 calendar days (Brahmachari *et al*. 2011). Sponsors and Investigators must be in compliance with the regulation’s SAE reporting requirements. All SAEs must be reported to the sponsor

immediately, regardless of whether they are study drug related or not. The sponsor ensures the FDA and all participating investigators are promptly notified and informed of adverse effects or risks. Study endpoints that are SAEs are required to be reported as specified in the protocol unless it is suspected that the study drug caused the event, in which case the SAE must be reported to the sponsor immediately. The reporting requirements for non-serious adverse events are detailed per approved protocol. The investigator is also responsible for reporting all unanticipated problems to the IRB.

In India, an SAE is defined in Gazette Notification G.S.R. 53(E) as "an untoward medical occurrence during a clinical trial that is associated with death, in patient hospitalization (in case the study was being conducted on out-patient), prolongation of hospitalization (in case the study was being conducted on in patient), persistent or significant disability or incapacity, a congenital anomaly or birth defect, or is otherwise life threatening"(CDSCO 2004). Schedule Y refers to the GCP definition of an unexpected SAE. The Investigator is responsible for reporting all SAEs to the DGCI, the sponsor, and the EC with 24 hours of the occurrence. After due analysis, the investigator is required to forward the SAE report within 14 days of the occurrence of the event to the DCGI, chairman of the EC, and the head of the institution where the trial is being conducted. Failure to report the SAE within the required timeframe then requires the investigator to provide justification for the delay to the DGCI along with the report (Gogtay *et al.* 2017). There are no prioritizing requirements for reporting, regardless of the severity of the adverse event and relativity to the study agent (Brahmachari *et al.* 2011).

Breast Cancer

In 2012, there were approximately 1,67 million new cases of breast cancer and 521,907 deaths (Ghoncheh *et al.* 2016). Breast cancer is the second most common cancer diagnosed in women in the U.S., exceeded only by skin cancer according to the American Cancer Society. Whereas in India the burden of breast cancer is the most common cancer in women (Ferlay et al. 2013).

The International Agency for Research on Cancer estimates global cancers with respect to incidence, mortality, and prevalence through its GLOBOCAN project (Figure 3) (Ferlay et al. 2013). The most current project, GLOBOCAN 2012, estimates India to have 145,000 cases of breast cancer with a population of over 1.2 billion versus 233,000 in the U.S. with a population 314 million.

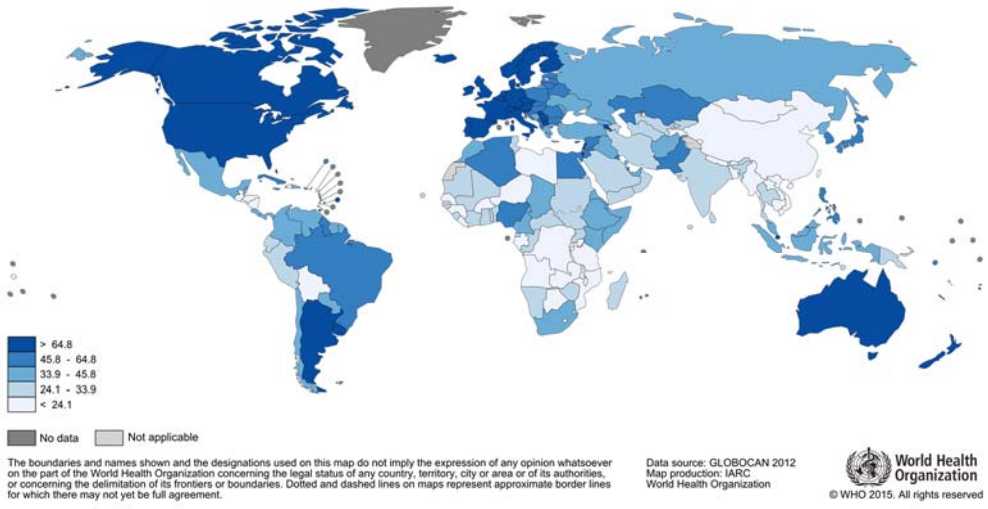

Figure 3 Estimated Breast Cancer Incidence Globally 2012

Country	Incidence	Death	% of Mortality	5 year Prevalence
United States	233,000	44,000	18.9%	971,000
India	145,000	70,000	48.28%	397,000

Table 5. Breast Cancer Estimated Incidence, Mortality, Prevalence, and Percentage of Mortality in the U.S. versus. India, in 2012

Although the incidence is higher in the U.S., the mortality rate is higher in India; 70,000 deaths due to breast cancer in India versus 44,000 in the U.S. (Table 5). The comparison of data from GLOBOCAN 2008 and GLOBOCAN 2012 shows a change in the trend of cancer present in Indian women; in 2012 breast cancer was the number one killer of Indian woman whereas 4 years earlier it was cervical cancer (Figure 4).

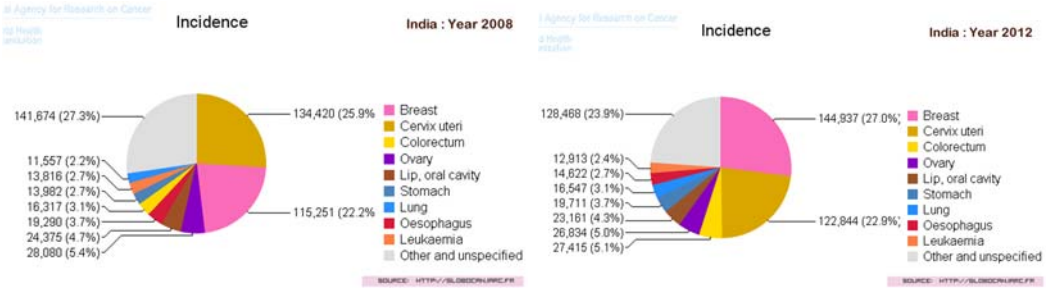

Figure 4 Cancer Incidence in Indian Women 2008 and 2012

Furthermore, the National Cancer Registry Programme in India conducted a 3-year report of population-based cancer registries from 2012-2014; breast cancer continued to be the leading cancer in 19 registry areas (Figure 5).

Figure 5 National Cancer Registry Programme- Network

The U.S. Centers for Disease Control and Prevention (CDC) National Program of Cancer Registries collected data from local cancer registries in 2014 (Figure 6) that show female breast cancer as being the highest incidence among other cancers (skin cancer was excluded from the data collected) (CDC 2017).

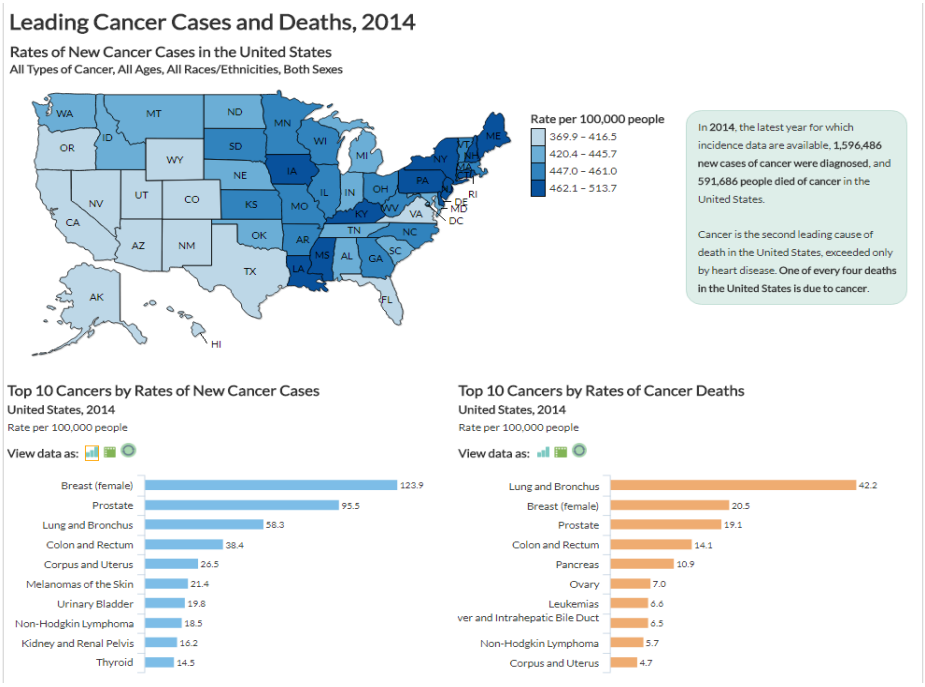

Figure 6. CDC National Program of Cancer Registries Data 2014

Over 70% of cases of breast cancer in India are diagnosed at an advanced stage ultimately decreasing survival rate, whereas in the U.S., 60-70% of breast cancer incidences are diagnosed at an early stage which increase the survival rate (Somdatta *et al.* 2008). The cancer-patient population to oncologist ratio in India is 1600:1compared to 100:1 in the U.S. (Suhag *et al.* 2015). In 2015, it was documented that India had merely 1,500 trained oncologists with a population of 1.25 billion (Suhag *et al.* 2015). The American Society of Clinical Oncology (ASCO) reported a total of 13,084 oncologists working in the U.S. in 2011 (ASCO 2015).

The majority of breast cancer patients in the U.S. are in their 60s and 70s and postmenopausal; approximately 50% of the breast cancers patients in India are premenopausal with an average age of 50-53 (Forouzanfar et al. 2011). Data from recent studies have shown a significant number of Indian women with breast cancer are younger than 35 years old (Das *et al.* 2015).

Next, a closer look at breast cancer trials registered per country was reviewed using the database clinicaltrials.gov. The Clinical Trials Registry in India (CRTI) was also reviewed, but due to the inconsistency of the search results (Table 6), clinicaltrials.gov was used to review the breast cancer trials registered per country.

CTRI Registered Breast Cancer Trials	
Total Breast Cancer Trials (planned, recruiting, terminated and completed) = 284	
Sponsor	**Number of Clinical Trials**
Pharmaceutical Industry- Global	1
Pharmaceutical Industry- Indian	1
CRO	0
Government Agency	0
Research Institution	0
Research Institution and Hospital	0
Government Medical College	1
Government Medical Hospital	0
Private Medical Hospital	0

Table 6 CTRI Review of Breast Cancer Clinical Trials Registered in India per Funding Sponsor

In order to begin evaluating breast cancer clinical trials in India and the U.S., a series of database searches was conducted using the criteria breast cancer, interventional studies (Clinical Trials), funding type, and Phase.

Reviewing the clinical trial registry database per country provides a complete evaluation of the status on breast cancer research in India and the U.S. A total of 6,507 breast cancer trials were registered as of February 2018 worldwide. Out of the 6,507 there are 93 breast cancer trials registered in India. Three are NIH funded, industry funded 70, and 20 are funded by other individuals, universities, and organizations (Table 6). Unsurprisingly, breast cancer research was more prevalent in the U.S., with a total of 3,574 breast cancer trials. Out of the 3,574 breast cancer trials registered in ClinicalTrials.gov; 1,103 are NIH funded, 54 are funded by other federal agencies, 1,372 are industry-funded, and 1,128 are funded by other individuals, universities, and organizations (Table 7). These results conclude pharmaceutical companies in industry are the major funders for breast cancer trials in both countries. A continued review of

ClinicalTrials.gov revealed that the majority of breast cancer trials in India are Phase III. and Phase II, where as in the U.S. Phase II trials are more prevalent (Table 8).

Country	**Breast Cancer Trials** (planned, recruiting, terminated and completed)	**NIH**	**Other Federal Government (U.S.)**	**Industry**	**Other** (individuals, universities, organizations)
United States	3574	1,103	54	1,372	1,128
India	93	3	0	70	20

Table 7* ClinicalTrial.Gov Review of Breast Cancer Clinical Trials Registered in U.S. and India per Funding Sponsor
*The numbers may not add up to the total as some trials are sponsored by more than one entity. Each search was done independently per funder type using Breast Cancer in the condition or disease field.

	Early Phase I	**Phase I**	**Phase II**	**Phase III**	**Phase IV**
United States	75	974	1514	348	47
India	0	6	35	47	6

Table 8 ClinicalTrial.Gov Review of Breast Cancer Clinical Trials per Phase Registered in U.S. and India per Funding Sponsor

A literary search of the U. S. and India contribution to breast cancer reseach lead to a recent bibliometric report on breast cancer research in India; “Indian contributions to breast cancer research: a bibliometric analysis” authored by Dr. Shri Ram (Ram 2017). Records of breast cancer were searched via the Scopus multidisciplinary database using breast cancer key words resulted in a total of 368,801 records retrieved from Scopus (Ram 2017). Below in Figure 7 is the table from the biliometric report that presents the publication productivity of the top twelve countries on breast cancer research (Ram 2017).

Table 1—Most productive countries and their publication share on breast cancer research

Sl. no.	Country	No. of publications					Share of publications (%)				
		1975-1984	1985-1994	1995-2004	2005-2014	1975-2014	1975-1984	1985-1994	1995-2004	2005-2014	1975-2014
1.	United States	10098	14624	37325	73046	135093	41.86	29.94	36.97	37.48	36.63
2.	United Kingdom	2193	4305	8852	15768	31118	9.09	8.81	8.77	8.09	8.44
3.	Germany	1681	2438	6258	12016	22393	6.97	4.99	6.20	6.17	6.07
4.	Italy	1375	2717	5392	10780	20264	5.70	5.56	5.34	5.53	5.49
5.	France	1279	2643	5205	9132	18259	5.30	5.41	5.16	4.69	4.95
6.	Japan	1296	2231	5129	8561	17217	5.37	4.57	5.08	4.39	4.67
7.	China	43	224	1080	15680	17027	0.18	0.46	1.07	8.05	4.62
8.	Canada	710	1351	4043	9428	15532	2.94	2.77	4.00	4.84	4.21
9.	Netherlands	406	1118	2631	5496	9651	1.68	2.29	2.61	2.82	2.62
10.	Australia	392	735	2326	5873	9326	1.63	1.50	2.30	3.01	2.53
11.	Spain	156	517	2239	5954	8866	0.65	1.06	2.22	3.06	2.40
12.	India	216	227	850	5403	6696	0.90	0.46	0.84	2.77	1.82
	Others	4277	15721	19622	17738	57358	17.73	32.18	19.44	9.10	15.55
	World	24122	48851	100952	194876	368801	100.00	100.00	100.00	100.00	100.00

Figure 7 Table 1 from "Indian contributions to breast cancer research: a bibliometric analysis"

The U.S. produced the most publications on cancer reseach at 36.63%, India had 1.82% resulting in 12th place in global breast cancer literature (Ram 2017). The paper further explains that Indian breast cancer research is continuosly increasing with 80% of the Indian publications occurring within the last decade (Ram 2017).

Enrollment and Recruitment

Enrollment is an essential element of a successful clinical trial. The sponsor/investigator targets a specific number of subjects to enroll to produce statistically significant results. Inclusion and exclusion criteria determine eligibility to participate in a clinical trial. Identifying potential barriers, such as subject retention and percentage of screen failures, provides a study team with a goal of enrollment for the duration of the clinical trial, study initiation to study close out. Clinical trials with a high screen failure rate increase the cost of the clinical trial and could prolong the accrual period (Mahajan *et al*. 2015). A study in India evaluated reasons behind screen failures by collecting retrospective data from a Phase 3 clinical trial of human epidermal growth factor receptor (HER2) positive Indian breast cancer patients. A total of 727 patients at 14 Indian sites

were reviewed and 408 patients out of these 727 failed screening (Mahajan *et al*. 2015). Screen failures were a result of patients not meeting selection criteria, logistical issues such as inadequate breast tissue samples, and withdrawal of consent (Mahajan *et al.* 2015). Studies done in the U.S. involving cancer trials, not breast cancer specific, reported the reasons behind screen failures as inadequate organ functions or laboratory parameters, estimated short life expectancy, lack of a specific biomarker or lack of archived tumor tissues, low education, subject being a minority, and longer screening delays (Mahajan *et al.* 2015).

Evaluation of a Phase II breast cancer clinical trial, "A double-blind, randomised, placebo-controlled, phase 2b study evaluating sorafenib in combination with paclitaxel as a first-line therapy in patients with HER2-negative advanced breast cancer", provides an example of the difference in the enrollment numbers in the U.S. and India. The study enrolled subjects from India, the U.S., and Brazil. India randomized more than 3 times the number of subjects as the U.S.: India n = 170, the U.S. n = 52, and Brazil n = 15 (Gradishar *et al.* 2013).

The results of a survey conducted by CRO Excel Life on the informed consent process of subjects participating in clinical trials run by their physicians concluded that 76% of subjects enrolled in a clinical trial were enrolled under their physician who was also an investigator on the trial and 21% claimed their physician referred them for the trial (Srinivasan *et al.* 2010). Physician referrals for a clinical trial are not an unusual occurrence; in fact, in the U.S. it is recommended to increase overall recruitment. A study in 2006, highlighted the factors associated with participation in breast cancer treatment trials in the U.S. The study determined that minimal disadvantage, reasonable travel time,

and physician recommendation would increase enrollment (Avis *et al.* 2006). Physician referral can be beneficial to a patient that would not have access to adequate treatment or expensive chemotherapy drugs otherwise. Conflict arises when the recommendation is based on personal gain not the welfare of the breast cancer patient. As previously discussed, the ratio of oncologists to patients in India is disproportionate. Due to the scarcity of oncologists in India, patients are more compliant and easily influenced for fear that if they refuse to enroll they would not receive further health care treatment. The Declaration of Helsinki, paragraph 31 states "The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship." There are a large number of people in India and the U.S. that are unaware of these guidelines. Unfortunately, due to the lack of specialized doctors in India it is more difficult to find a local physician qualified to treat breast cancer. Whereas in the U.S. there is an abundance of oncologists so finding a physician that specializes in oncology typically does not require much effort.

A meta-analysis qualitative studies conducted by Phadtare et al. in 2010 concluded that patients in India participate in clinical trials for the benefit of healthcare, access to available treatments and free medication, physician referrals, and financial incentives.

Breast cancer subjects in the U.S. and India increase enrollment not only through physician recruitment but also through various avenues such as media advertisements, flyers, and posters are the clinical trial site, as well as an independent database search for a local clinical trial. Figure 7 is an example of a flyer promoting a domestic and

international breast cancer clinical trial that is actively enrolling, the Brocade 3 study. The official title is "A Phase 3 Randomized, Placebo-controlled Trial of Carboplatin and Paclitaxel With or Without Veliparib (ABT-888) in HER2-negative Metastatic or Locally Advanced Unresectable BRCA-associated Breast Cancer"**.** The Brocade 3 study is a phase III clinical research study evaluating the safety and effectiveness of an investigational drug combination, Veliparib (ABT-888) in combination with Carboplatin and Paclitaxel compared to the combination of Carboplatin and Paclitaxel with placebo. Enrollment includes subjects with HER2 negative metastatic or locally advanced BRCA-associated breast cancer for which local therapy (surgery or radiation) is not appropriate.

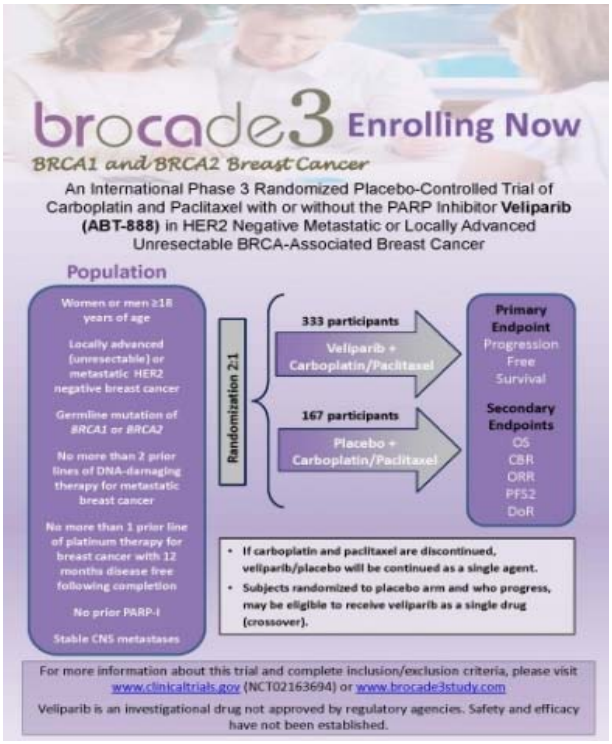

Figure 8 Brocade 3 Flyer

Clinical trials like Brocade 3 use advertisements (Figure 8) at the clinical trial sites, on the facilities' websites, and through other means of media such as social media and newspapers or related journals.

Breast cancer patients interested in participating in breast cancer trials can locate trials via databases such as the WHO International Clinical Trials Registry Platform Search Portal. Clinical trials registered within the United Nations can be found on this database, allowing individuals to search clinical trial registration information from various countries' registries. ClinicalTrials.gov is a U.S. database used to search clinical trials domestically and internationally. It is a government-sponsored database of publicly and privately supported clinical trials that is maintained by the NIH NLM (clinicaltrials.gov). Breast cancer trials conducted in India and the U.S. can be found on this site. For patients in the U.S. that want a more disease specific search, www.breastcancertrials.org is a database that can be utilized to find a current breast cancer trial.

Informed Consent

Informed consent is ethically essential in clinical research involving human subjects. Recognized globally, the informed consent process is the cornerstone of protecting subject's autonomy where full disclosure of, including but not limited to, the risks, benefits, and alternatives to the clinical trial, is given to the potential subject by the research investigator and/or appropriate study team member. Comprehension of this information by the potential subject prior to enrollment is essential. The subject must be able to make an informed decision based on his/her understanding of the treatment plan and procedures, the purpose behind the treatment plan and procedures, alternative

treatments, and risks and benefits of refusing and accepting treatment. If a potential subject does not have the capacity to make an informed decision, a legally authorized representative can sign for him/her. The decision to enroll in a clinical trial must be strictly voluntary, without pressure or coercion. The willingness to participate, the capacity to make a decision, disclosure of information, comprehension, and the decision to enroll are the criteria of the informed consent process (Beauchamp 2011.).

The achieved level of understanding can determine the quality of the informed consent process. A subject's lack of appropriate knowledge can be impactful on the decision to participate. Developing countries typically have a higher illiteracy rate, lower level of formal education, and limited access to health care (Diemert *et al.* 2017).

The informed consent requirements for the U.S. can be found in the FDA's regulations of Protection of Human Subjects, 21 CFR part 50, Common Rule, 45 CFR 46-B-E and ICH-GCPs. Per 21 CFR part 50, "no investigator may involve a human being as a subject in research covered by these regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents

from liability for negligence" (21CRFpart 50). The informed consent is an essential document and requires IRB approval prior to use. It must fully explain the study with the appropriate comprehension level of the research subject. The consenting process must be without coercion or influence and provide a subject adequate time to make an educated decision whether to participate. The informed consent can be in short form where the requirements are presented orally, this can occur in the event of a language barrier. The full informed consent must be provided to the subject to read and understand before signing.

In India, Informed consent requirements are laid out in the IN-GCP, ICMR Guidelines and Schedule Y (NIAID 2016). The informed consent must obtain EC approval prior to use for a study. The investigator is required to provide all study information to the subject, legal representative, or guardian as well as a witness in written and oral form. If a subject is incapable of providing a signature, a thumb impression is acceptable. If a thumb impression is not possible, verbal consent can be used via audio-video. The informed consent form (ICF) content is required to be brief and easily understood and without coercion or influence to enroll in the clinical trial (NIAID 2016).

Informed consent is one of the most important notable challenges in India due to the substantial ethical concerns including lack of comprehension, enticement, and coercion. The literacy rate of both countries was evaluated to review possible informed consent comprehension differences; the U.S. had a 99% literacy rate compared to India's 73% literacy rate in 2011 (Mallath *et al.* 2017). In 2013, the Center for Information and Study on Clinical Research Participation (CISCRP) conducted a mock trial to compare the informed consent process in the Asia-Pacific region and the U.S. In the Asia-Pacific

region, 69% of the subjects found the informed consent to be difficult to understand compared to 12% in the U.S. (Mahajan *et al.* 2015). A similar study in India showed only 30% of patients who consented had a poor understanding of the informed consent (Mahajan *et al.* 2015). Consenting without full comprehension contributes to unethical practices. In 2013, the Indian Supreme Court ruled on cases that emphasized the lack of comprehension regarding the informed consent process and the trial as a whole. As a result, the Indian Supreme Court recommended that the informed consent process be audio-video recorded (Grady *et al.* 2017). This process is included as a draft rule in the Gazette of India notification dated 7th June 2013. (Kulkarni *et al.* 2014). As of July 31, 2015, the G.S.R 611 (E) states "investigator(s) must obtain an audio-video (AV) recording of the informed consent (IC) process for vulnerable participants in clinical trials of New Chemical Entity or New Molecular Entity, including the procedure of providing information to the participant and his/her understanding of the consent. This AV recording should be retained in the investigator's files. In cases where clinical trials are conducted on anti-Human Immunodeficiency Virus (HIV) and anti-Leprosy drugs, the investigator(s) must only obtain an audio recording of the IC process. The investigator(s) is also required to retain the audio recording for his/her records" (Gazette 2015).

Post Market Access

The evaluation of post market access to the breast cancer drugs provides answers to whether a clinical study population's welfare was at the forefront of the stakeholders' minds or a financial advantage. Post marketing access to a research drug is not always available in India and, if so, a majority of the population cannot afford it. A recent study

provided evidence that less than 1% of Indian breast cancer patients with HER2 positivity received trastuzumab, a monoclonal antibody approved to treat this type of breast cancer. (Gyawali *et al.* 2017).

Another study "A global comparison of the cost of patented cancer drugs in relation to global differences in wealth" provided information regarding the cost difference and affordability of 8 FDA approved cancer drugs in 7 different countries including the U.S and India (Goldstein *et al.* 2017). The breast cancer drugs bevacizumab and trastuzumab were 2 of the 8 FDA approved cancer drugs evaluated (Goldstein *et al.* 2017). The results concluded that these particular cancer drugs cost more in the U.S. than India, however they are less affordable in India than in the U.S. (Goldstein *et al.* 2017). The 4 weekly cost of trastuzumab was $2761 in India compared to $6849 in the U.S; yet this is still too expensive for the average Indian salary to afford (Goldstein *et al.* 2017). The average salary in India is equivalent to $19,774 whereas the U.S. is $80,085 according to the Average Salary Survey platform.

Next, the current FDA approved breast cancer drugs were review, Table 9 provides a list of all the FDA approved breast cancer drugs. The table is separated in accordance to the application; drugs approved to prevent breast cancer, drugs approved to treat breast cancer, and drug combinations approved to prevent breast cancer**.** The majority of the FDA approved drugs listed are drugs to treat breast cancer. India participated in breast cancer trials that led to FDA approval of a number of products including Lapatinib, Trastuzumab, Neratinib, Soraenib, and Bevacizumab, for the treatment of breast cancer as well as other cancers.

To gain perspective of post market access, the 93 Clinicaltrials.gov-registered breast cancer trials in India were reviewed in regard to the study agents evaluated. Table 10 lists the drugs involved within the 93 registered trials. A majority of the drugs in the registered trials are currently FDA approved, while others are investigational agents. Unfortunately, the information regarding access and affordability of the approved breast cancer drugs listed was not readily available from a reliable source.

Drugs Approved to Prevent Breast Cancer	**Drugs Approved to Treat Breast Cancer**	**Drugs Combinations Approved to Prevent Breast Cancer**
1) Evista (Raloxifene Hydrochloride) 2) Keoxifene (Raloxifene Hydrochloride) 3) Nolvadex (Tamoxifen Citrate) 4) Raloxifene Hydrochloride 5) Tamoxifen Citrate	1) Abemaciclib 2) Abitrexate (Methotrexate) 3) Abraxane (Paclitaxel Albumin-stabilized Nanoparticle Formulation) 4) Ado-Trastuzumab Emtansine 5) Afinitor (Everolimus) 6) Anastrozole 7) Aredia (Pamidronate Disodium) 8) Arimidex (Anastrozole) 9) Aromasin (Exemestane) 10) Capecitabine 11) Clafen (Cyclophosphamide) 12) Cyclophosphamide 13) Cytoxan (Cyclophosphamide) 14) Docetaxel 15) Doxorubicin Hydrochloride 16) Ellence (Epirubicin Hydrochloride) 17) Epirubicin Hydrochloride	1) AC (Doxorubicin, Hydrochloride, Cyclophosphamid) 2) AC-T (Doxorubicin, Hydrochloride, Cyclophosphamid, Paclitaxel) 3) CAF (Cyclophosphamid, Doxorubicin, Hydrochloride, Fluorouracil) 4) CMF (Cyclophosphamide, Methotrexate, Fluorouracil) 5) FEC (Fluorouracil, Epirubicin, Hydrochloride, Cyclophosphamide) 6) TAC (Docetaxel, Doxorubicin, Hydrochloride, Cyclophosphamide)

Drugs Approved to Prevent Breast Cancer	Drugs Approved to Treat Breast Cancer	Drugs Combinations Approved to Prevent Breast Cancer
	18) Eribulin Mesylate 19) Everolimus 20) Exemestane 21) 5-FU (Fluorouracil Injection) 22) Fareston (Toremifene) 23) Faslodex (Fulvestrant) 24) Femara (Letrozole) 25) Fluorouracil Injection 26) Folex (Methotrexate) 27) Folex PFS (Methotrexate) 28) Fulvestrant 29) Gemcitabine Hydrochloride 30) Gemzar (Gemcitabine Hydrochloride) 31) Goserelin Acetate 32) Halaven (Eribulin Mesylate) 33) Herceptin (Trastuzumab) 34) Ibrance (Palbociclib) 35) Ixabepilone 36) Ixempra (Ixabepilone) 37) Kadcyla (Ado-Trastuzumab Emtansine) 38) Kisqali (Ribociclib) 39) Lapatinib Ditosylate 40) Letrozole 41) Lynparza (Olaparib) 42) Megestrol Acetate 43) Methotrexate 44) Methotrexate LPF (Methotrexate)	

Drugs Approved to Prevent Breast Cancer	Drugs Approved to Treat Breast Cancer	Drugs Combinations Approved to Prevent Breast Cancer
	45) Mexate (Methotrexate) 46) Mexate-AQ (Methotrexate) 47) Neosar (Cyclophosphamide) 48) Neratinib Maleate 49) Nerlynx (Neratinib Maleate) 50) Nolvadex (Tamoxifen Citrate) 51) Olaparib 52) Paclitaxel 53) Paclitaxel Albumin-stabilized Nanoparticle Formulation 54) Palbociclib 55) Pamidronate Disodium 56) Perjeta (Pertuzumab) 57) Pertuzumab 58) Ribociclib 59) Tamoxifen Citrate 60) Taxol (Paclitaxel) 61) Taxotere (Docetaxel) 62) Thiotepa 63) Toremifene 64) Trastuzumab 65) Tykerb (Lapatinib Ditosylate) 66) Velban (Vinblastine Sulfate) 67) Velsar (Vinblastine Sulfate) 68) Verzenio (Abemaciclib) 69) Vinblastine Sulfate 70) Xeloda (Capecitabine) 71) Zoladex (Goserelin Acetate)	

Table 9 FDA Approved Breast Cancer Drugs

Lapatinib	Capecitabine	Tamoxifen	Alpelisib	Cemcitabine
Trastuzumab	Doxorubicin	Y353381	Vinorelbine	Carboplatin,
Neratinib	Paclitaxel	Triptorelin	Sunitinib Malate	Cisplatin
Soraenib	Nanoxel	Exemestane	EndoTAG-1	Anastrazole
Bevacizumab	HERMyl	Letrozole	AG-013736	LEE011
Endoxifen	Taxotere	Pazopanib	Goserelin	SPARC1210
Pertuzumab	Docetaxel	SAR439281	Ribociclib	Epoetin Alfa
SPARC1613	A-EP2006	Fulvestrant	HKI-272	INCB007839
Reference1210	Neulasta	Bosutinib	Vinorelbine	Ixabepilone
Denosumab	Myocet	Reference1613	Sevoflurane	Fulvestrant
Vinflunine + Capecitabine	Depot Hydroxy-Progesterone	Celecoxib + Exemestane	Capecitabine + cyclophosphamide	Trastuzumab Emtansine
LEP-ETU	Progesterone	Afatinitb	Cyclophosphamide	Capecitabine
Abemaciclib	Anastrozole	AMG 386	Atezolizumab	Everolimus
Trabectedin SID530	Aromatase Inhibitor			

Table 10 Drugs listed in Clinicaltrials.gov for Breast Cancer trials in India

DISCUSSION

Regulatory requirements implemented and proactive steps taken by India

The regulatory requirements for breast cancer clinical trials in India are comparable to the U.S. The governing regulatory authorities practically mirror each other in playing a key role in ensuring human subject protection in clinical research. The CDSCO is equivalent to the FDA whereas the DCGI is much like the review divisions within CDER that grants permission to start a clinical trial involving a new unapproved drug (Saxena *et al.* 2014). The regulatory authorities provide several laws, regulations, and guidelines to plan and monitor breast cancer trials in a safe and ethical way. Schedule Y and the CFR describe the details of the application process for conducting the clinical trial and the responsibilities of the sponsor, investigators, and the ethics review process. Prior to beginning the trial, protocol approval is required from the EC or IRB, as well as mandatory registration of the trial. In theory the regulatory requirements are practically the same, therefore implementation and compliance of the regulatory requirements and guidelines could be the issue regarding allegations of unethical practice.

Maintaining the highest ethical standard is essential for public confidence and participation in clinical research. Allegation of unethical practices resulted in a decline of clinical research in India. In the face of criticism, India has made an effort to mitigate the regulatory uncertainty and address the concerns of the public and stakeholders through recent amendments to Schedule Y. Rule 122 DAB, of Schedule Y is the most significant change in regulations and one that has faced criticism from sponsors that conduct clinical research in India. Under Rule 122 DAB, the sponsor is required to cover medical costs for any injury during the clinical trial for as long as required, regardless of whether the

injury is related to the trial. The sponsor is also required to financially compensate if injury is related to the clinical trial based on the following criteria, “Adverse effect of investigational product (s) (IP); Violation of the approved protocol, scientific misconduct or negligence by the sponsor or his representative or the investigator; Failure of IP to provide intended therapeutic effect; Use of placebo in a placebo-controlled trial; Adverse effects due to concomitant medication excluding standard care, necessitated as part of approved protocol; For injury to a child in-utero because of the participation of parent in a clinical trial; Any clinical trial procedures involved in the study”. These are fairly broad criteria and could deem very expensive for a sponsor of a breast cancer trial. This is uncommon to global practice and standards. The U.S. does not have regulatory regulations for compensation due to injury or death. This amendment is clearly in favor of the subjects participating in the clinical research, which could provide confidence in the public regarding participation in clinical research. However, such broad criteria could result in increased expenses from the sponsor of breast cancer trials, ultimately steering sponsors away from India as a clinical trial site. Efforts to be more standardized to global practices should be considered. The 122 DAC and 122 DD amendments are aligned more with global standards, thus not receiving the same criticism as122 DAB.

IRB and EC

IRB and ECs are established primarily to protect human subjects and promote ethical clinical research. The review of the IRB and EC did not provide significant differences that would contribute to unethical practices. This could be due to the recent amendment to Rule 122 DD in India. Rule 122 DD describes the requirements and process of registration on an EC, also stating that no EC can review a study protocol

without prior registration with the CDSCO. This was a major milestone for ECs in India; the registration requirement led to more than 1000 ECs being registered with CDSCO (Thatte *et al.* 2017). These new regulations are expected to positively impact subject protection and safety. A proficiently functioning accredited EC provides accountability and confidence that all necessary safeguards are met for conducting clinical trials and publishing data.

Regulatory Harmonization

GCP is a set of international ethical and scientific standards for conducting, designing, documenting, and reporting clinical trials that involve human subjects (ICH). These standards derive from the Declaration of Helsinki, the cornerstone document of human research ethics (WMA 2013). GCP compliance assures that clinical trials are conducted considering the rights, safety, and well-being of the subjects as well as providing credible clinical trial data (ICH). In efforts to harmonize the GCP standards, the regulatory authorities from the U.S., European Union, and Japan developed a unified standard to facilitate mutual acceptance of clinical data submitted (ICH 2016). ICH-GCP E6 guidance, the core guidance document for GCP, was released in 1996 (ICH 2016). The Indian version of GCP, based on the ICH-GCP, was released to the public in December 2001 (Bhatt 2014). India hoped that compliance to these standards would further provide assurances that human subject protection and well-being is central in conducting human clinical trials. Globalized ethical standards can ultimately minimize human exposure to investigational product and provide reliance in the data collected during the trial (Vijayananthan *et al.*). However, the differences noted in Table 4, an overview of how IN-GCP do not completely represent ICH-GCP. For instance, the

qualification standards for investigators noted in Table 4 stated that the investigator is not qualified unless recognized by the MCI. Implementation of this provision could become an obstacle for the sponsor when selecting investigators (Bhatt 2015). Another example that could be burdensome to investigators is the IN-GCP provision that holds investigators responsible for all data analysis. As per ICH-GCP, the investigator has to provide the EC with a summary of the outcome of trial upon completion. The IN-GCP requires the investigator to sign and forward all data from the study to the sponsor and EC upon completion of the study. Usually data analysis is the function of the sponsor not the investigator (Bhatt 2015). It would be beneficial if IN-GCP was more aligned with ICH-GCP, which would further increase global regulatory harmonization, ensuring that the goals and vision of the ICH are being met.

Sponsors and Investigators

The roles and responsibilities of the sponsor and the investigator are virtually identical in both countries. Upon review of the 21 CFR Part 312 in the U.S. and the guideline in IN-GCP and Schedule Y, there were only a few notable differences in sponsor responsibilities. Noted above in Table 4, in India the sponsor is required to store records for a minimum of 3 year per regulation where as in the U.S. it is 2 years or institutions policy, whichever is longer. The IN-GCP sponsor responsibilities refer to compensation for participation in section 2.4.5 (CDSCO 2014). This corresponds to the recent amendment to Schedule Y Rule 122 DAB, in efforts to resolve the controversy surrounding deaths reportedly related to clinical trials participates in India. As mentioned previously, this is a significant difference in sponsor responsibilities, as the U.S. does not have this responsibility. Indian investigators are limited to 3 clinical trials at a time while

their U.S. counterpart does not have a federally mandated limit. This could restrict investigators from other research opportunities, especially considering clinical trials are conducted over years. The reasoning behind this limitation could be to ensure that the investigator provides the amount of time and attention necessary to conduct safe and ethical research.

SAE Reporting

SAEs are defined under the ICH E6 guidelines; reporting compliance from investigators in the U.S. and India are standard. There is a noted difference between the countries regarding SUSARs reporting requirements. U.S regulation defines SUSARS and there reporting requirements but in Schedule Y, SUSARs are not distinguished. Schedule Y also refrains from specifying expedited reporting requirements, there is no reporting priority for events that are suspected to be life threatening due to the study agent or the occurrence of unexpected death. The U.S. reporting requirements are found in 21 CFR 312. 32 and state that SUSAR are to be reported within 7 calendar days to the proper regulatory authorities in the event that they appear to be fatal or life-threatening.

India being a key player in globalized clinical trials needs to consider revising Schedule Y to incorporate SUSAR definitions, standards and reporting timelines. This will allow for more consistency with the U.S. and avoid any confusion in the event of a SUSAR during a multinational clinical trial.

Trends of Breast Cancer and Breast Cancer Clinical Research in the U.S. and India

The values obtained from GLOBOCAN 2012 (Table 4) present the U.S. with a higher incidence of breast cancer. The CDC reports that in the U.S. “While rates of cancer diagnoses and cancer deaths continue to decline each year, the number of new

cases and deaths is going up. This happens because the size of our population is growing and aging each year" (CDC 2017). While in India, as shown in Figure 4 the incidence of breast cancer has increased, surpassing cervical cancer as the most common cancer in women. Increasing westernization of lifestyle, environmental factors, geographic variation, genetic variation, socioeconomic status, utilization of screening mammography, paucity of diagnostic aids, stage of disease at diagnosis, and the availability of appropriate healthcare are among the many contributing factors to the increasing incidence and overall outcome of breast cancer in India (Manoharan 2017).

The results clearly show that the U.S. presents a higher rate of breast cancer; however, the percentage of mortality in India is nearing 50%, more than double that in the U.S. This higher mortality rate could be a result of lack of awareness. Culturally in India, breast cancer is viewed as taboo and thus not frequently acknowledged or discussed. This avoidance or lack of awareness could result in a later diagnosis. In addition, the scarcity of oncologists in India adds to the problem. The lack of oncologists can result in delays in diagnosis, proper treatment, and poorer overall outcome of a breast cancer patient. A significant difference between the U.S. and India is how breast cancer in Indian women presents nearly a decade earlier than in women in the U.S. (Forouzanfar *et al.* 2011). Developing breast cancer at a younger age often results in a poorer prognosis and decreased survival rate, with contributing factors consisting of, but not limited to, higher incidence of invasive ductal carcinoma (IDC), larger tumor size, higher number of metastatic lymph nodes, and ER-negative tumors (Das et al. 2015). One resource that the U.S. has that India does not is the mammography breast screening programs commonly available to the population. The use of these screening programs

could contribute to the higher median age at diagnosis in the U.S. compared to that in India (Manoharan 2017).

There were limitations with the review of CTRI. The inconsistency of the database search did not allow for a clear view of registered breast cancer trials in India. Therefore, Clincialtrials.gov was the only platform reviewed. Results from the Clinicaltrials.gov database search were as expected; the U.S. not only conducts more breast cancer research than India, but it is responsible for more than half of breast cancer research worldwide. The pharmaceutical industry funds most of the U.S. and Indian breast cancer trials. This is not surprising because pharmaceutical companies are in the business of developing drugs whereas a government entity is not, there is also a large market for breast cancer treatment; discovering and developing a new and effective blockbuster drug for breast cancer can generate significant profit for a pharmaceutical company.

According to this review of breast cancer clinical trials registered via ClinicalTrials.Gov, the majority of breast cancers trials conducted in the U.S. are Phase II clinical trials, while in India Phase III studies are more common with Phase II at a close second (Table 6). High enrollment rates and cost savings are factors that may explain why Phase III breast cancer clinical trials are more prominent in India.

The breast cancer research trends correlate with the increased incidence of breast cancer in India. The bibliometric analysis study shows that while the U.S. contributes the majority of publications on breast cancer research, India's contributions to breast cancer research is growing rapidly (Ram 2017).

Breast Cancer Trials

U.S. government funded trials are required to follow all the stringent rules and regulations enforced by the FDA. Pharmaceutical companies that seek FDA approval of their products must also follow these guidelines and regulations. Globalized breast cancer trials in India must comply with the rules and regulations from both India and the U.S. The following section will focus on recruitment techniques, informed consent processes, enrollment trends, and post-market access per country.

Recruitment and Enrollment

Recruitment and enrollment trends as well as informed consent process were also evaluated via scholarly articles. Notable differences are as follows; recruitment and enrollment rates appear to be higher in India vs. the U.S. Higher recruitment and lower screen failure rates decrease the cost of the clinical trial if the subjects remain enrolled for the duration of the trial. As discussed previously, higher recruitment rates in India attract global pharmaceutical companies that are interested in outsourcing clinical trials for the potential cost benefit. The DCGI promotes India as a site for clinical trials claiming the cost is cheaper than the U.S., claiming cost saving in recruitment rates being among the highest if not the highest internationally (Srinivasan *et al.* 2010). India's selling proposition focuses on the fact that large amounts of Indian people do not have access to routine medical treatment; this fact alone make them more willing to participate in a clinical trial than people from the U.S. (Srinivasan *et al.* 2010). Although high recruitment rates are a great selling point, Indian people should not be so desperate for medical treatment that they overlook the risks of the clinical trial. Multiple surveys have suggested that main contributors of poverty in India are medical expenses (Parth 2013).

This causes concern if the government is promoting clinical trials for a vulnerable population starved of affordable healthcare. Clinical trial research investigators have a duty to conduct a clinical trial guided by ethical principles, with human subject protection as top priority. Health benefits, possible cure of disease, free medication, lack of alternative therapy, and detailed knowledge of the breast cancer clinical trials are motivating factors for the people of India to enroll in breast cancer trials (Avis *et al.* 2006). There has also been some controversy in India claiming that subjects are being influenced by their physicians to participate in clinical trials. This becomes a conflict of interest when the investigator is receiving incentives to recruit trial participants (Srinivasan *et al.* 2010). In the U.S., breast cancer patients receive referrals for breast cancer trials by their physicians. The difference is the investigators in India often receive significant financial benefits for patient enrollment. Breast cancer patients in India have access to few oncologists in comparison to the U.S., which tends to make Indian patients more compliant when receiving advice from their respective physician. The physician has to duty to make the patient's health and well-being their priority. A physician who is receiving a financial incentive may be more inclined to refer subjects that may not be the best candidates for the trial. This should be monitored to ensure that the motives of the physician are strictly in regard to the subject's health.

Recruitment strategies for breast cancer trials vary, depending on the nature of the trial. A patient database, media advertisements, flyers and posters at the clinical trial site, and physician referrals are examples of possible recruitment strategies employed in the U.S. and India (Parth 2013).

Informed Consent Process

As previously discussed, there are concerns of subjects being influenced to enroll and sign informed consent to participate in a clinical trial for which their physician is also the investigator. The Declaration of Helsinki states in paragraph 27 “When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship” (WMA 2013). This does not always seem to be the case in India. Illiteracy rates and poverty are higher in India than in the U.S.; per the results India has a 73% literacy rate compared to the U.S. at a 99%. Poverty stricken and illiterate individuals are typically more compliant research subjects due to the trust they place in their physicians and the perceived healthcare benefits from research. India has a large proportion of sick, poor, illiterate people without access to proper healthcare, sponsors must keep this in mind to avoid subject exploitation (Mallath *et al.* 2017).

Language barriers are also another obstacle worth noting when evaluating proper informed consent, considering not all Indian people speak English, especially in rural areas. Culturally, India is a Hindi-speaking community, but English is often used in day to day communication and management in educational settings, among medical staff, and even by India's judicial and governing institutions, health ministry, regulatory bodies, and ethics committee (Stober 2003). Although English is well known among many there are still a vast amount of the Indian population, especially in rural areas, that only speak their

native tongue. This should be considered during the informed consent process to ensure full comprehension.

As noted in the results, inadequate informed consent processes led the Indian Supreme Court to recommended that the informed consent process be AV-recorded, this has since been adopted into the clinical trial regulations. AV consenting has been in practice for potential subjects that could not sign their consent or give a thumb impression per Indian Council of Medical Research Ethical Guidelines (Kulkarni *et al.* 2014). The draft rule in the Gazette of India notification dated 7th June 2013 states it is mandatory for the informed consent process of all clinical trials to be AV recorded along with the written consent of each trial subject (Goyal 2014). This earlier provision for mandatory AV faced scrutiny due to challenges regarding confidentiality, suitable infrastructure for audio video recording, and refusal of consent due to being uncomfortable being recorded. There was also an increased financial burden on the sponsor and investigators due to the requirements to safely maintain the records (Goyal 2014). The current notification regulations G.S.R 611(E) includes only "vulnerable populations" under the requirement for mandatory AV recording (Gazette 2015). Regardless of the challenges, the transparency will be a step forward for regaining confidence in clinical research in India.

Post-Market Access

Novel anti-cancer treatments approved by the FDA are typically high-priced to recover the financial investment in development. Trial subjects may benefit from the novel anti-cancer treatment while on trial, but the benefit to the society as a whole is null in developing countries, such as India, due to high cost and financial disparities of the

population. Treatment regimens that become the standard of care in the U.S. are only available to the wealthy in India that can afford the high costs of these treatments (Urooj 2017).

Multinational trials for the role of trastuzumab in early breast cancer enrolled a significant number of subjects from developing countries including India. The involvement of the developing countries increased recruitment, which contributed to timely results. The communities contributing to these trials would not benefit from the approved drugs. Cancer patients in India typically pay out of pocket for their treatment due to not having health insurance or having poor health insurance. Expensive therapies like the anti-HER2 monoclonal antibody trastuzumab, marketed under Herceptin by Roche, are unaffordable to the majority of the population in India. Herceptin is a blockbuster cancer drug with global sales of $6.79 billion in 2015 according to FiercePharma. A clinical trial is not beneficial to a host community if the treatment is deemed effective but is not readily available or affordable to the people who live there. This practice is a clear violation of Declaration of Helsinki, "Whereby the research or experiment and its subsequent applicative use are conducted and used to benefit all human kind and not just those who are socially better off but also the least advantaged, and in particular, the participants themselves and or the community from which they are drawn." ICMR ethical guidelines for biomedical research refers to this quote in regard to post-trial access (Usharani *et al.* 2013).

The question then arises, what is the priority of clinical research, the health of the population or financial gain? This can be considered as exploitative. The results of post market access suggest that the medias criticism may not have been exaggerated.

Although not all breast cancer treatments were reviewed due to the limitations of the results. Standard of care method trastuzumab was only received but a small portion of the breast cancer population. Could the reasoning be the affordability of the drug or were patients unaware of this method of treatment. India's high illiteracy and poverty rate could be a key factor to why many patients go untreated. Future studies regarding breast cancer treatment awareness could be beneficial in answering this question.

Clinical trials bring an option of treatment that may have not be available to a poverty-stricken population, this is true for low income regions in both the U.S. and India. Future studies of accessibility and affordability from breast cancer treatments should be considered to evaluate the current scenario and whether the study population is truly benefiting or merely just test subjects. There needs to be an emphasis on providing affordable research drugs once approved for the populations that helped contribute to the data necessary for the drug to receive market approval. India's government has tried to counteract expensive brand therapies by developing biosimilars and generics to provide affordable access to health care treatments for critical conditions like breast cancer as well as economic benefit to the country.

SUMMARY

Based on the increasing incidence of breast cancer in India in combination with the trend of globalized clinical trials and international collaborations, we will likely continue to see an increase in breast cancer trials in India. India was once one of the most sought out global clinical trial sites due to fast recruitment of patients and lower clinical trial costs. However, negative publicity regarding unethical implications caused India to lose its luster and attractiveness as a host for clinical trials, ultimately resulting in the decline of such research in the country. India has since tried to address these concerns by providing transparency and aligning regulatory regulations to global standards via revising Schedule Y to parallel with the FDA guidelines and the internationally acceptable guidelines of ICH-GCP.

India hoped to regain the trust of the public as well as the stakeholders of the clinical trials by addressing the ethical concerns that initially caused the downfall of clinical trials in the country. The thought process being that concentration on the rights, well-being and safety of the trial subjects, as opposed to financial gain, will attract sponsors and make India a competitor once more for clinical research. Unfortunately, the recent amendments to Schedule Y and IN-GCP that were implemented in hopes to resolves the issues were received with some resistance due to the increased financial burden on the sponsor and investigators. Efforts to continue to align with global standards need to be priority.

The comparison of breast cancer trials in the U.S. versus India revealed far more similarities than differences; consequently, the differences are significant in regard to ethical standard and are not to be ignored. Unethical practices have undeniably occurred,

but according to my research, the vast amount of current clinical research in India is well conducted and compliant with the global standard for ethical research using human subjects. India has a large illiterate and economically deprived patient population. The vulnerability of these patients makes them easy recruitment targets. The benefits of free healthcare alone persuade these individuals to participate in a clinical trial without understanding the potential risks. Question of ethics and conflict of interest surface when a physician/investigator gains incentive to recruit patients, these patients put their trust into their physicians and can easily be coerced into signing the informed consent without full comprehension. This knowledge needs to be taken in consideration when proposing clinical research at a cancer center in India. Ensuring the integrity of the informed consent process contributes to protection of the research subjects, ultimately providing confidence in ethics of the clinical research.

Unfortunately, breast cancer specific information was not always available for comparison. In light of this, cancer trials as a whole were compared with regards to enrollment and informed consent. The notable differences revolved primarily around the vulnerability of the patient population in India and the lack of affordable healthcare. The availability of breast cancer treatments post-market varied; the majority of the brand name treatments were far too expensive for the population suffering from breast cancer. This contributes to the theory that sponsors take advantage of the recruitment numbers available in India but focus on marketing in the U.S. and other developed countries. India's regulatory bodies need to address this issue; easy access to affordable drugs developed through clinical trials in India should be mandatory. The local industry of

biosimilars and generics in India is the only saving grace for more affordable treatments at this present time.

The clinical trial industry in India has the elements necessary to become a favorable location for breast cancer research. The cost savings, availability of skilled English-speaking professionals, and a large diverse treatment naïve patient population are a few contributing factors. Ethical concerns arise when financial gains outweigh the welfare of the patient population - human subject protection must be the ultimate focus in clinical research. India is on the right track by adapting to the global standards of conducts and procedures, but there is room for improvement. Stakeholders must maintain the highest standards when conducting clinical research; the confidence of the public depends on it, as we have noticed in the past. Word of unethical implications results in a decline in clinical research, ultimately halting valuable studies that could benefit individuals who suffer from breast cancer. Research ethics and a regulatory environment that ensures the utmost protection of human subjects need to become priorities in clinical research in India. Regular audits and inspections of the trial sites and the investigators by regulatory bodies would provide transparency and assurance that the trials are being conducted according to global standard. This is a common practice in the U.S. and deemed beneficial in upholding ethical standards and ensuring the quality of the data collected during the clinical trial.

REFERENCES

[American Cancer Society] 2014. Breast cancer. [Internet]. Available from: www.cancer.org/cancer/breast-cancer.html

[American Cancer Society] 2017. Breast Cancer Facts and Figures 2017-2018. [Internet]. Available from: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/breast-cancer-facts-and-figures/breast-cancer-facts-and-figures-2017-2018.pdf

[American Cancer Society] 2017. How Common is Breast Cancer. [Internet]. Available from: https://www.cancer.org/cancer/breast-cancer/about/how-common-is-breast-cancer.html

[ASCO] American Society of Clinical Oncology. 2015. The State of Cancer Care in America, 2015: A Report by the American Society of Clinical Oncology Journal of Oncology Practice. 11:2, 79-113

Avis, N. Smith, K. Link, C. Hortobagyi, G., Rivera, E. 2006. Factors Associated with participation in Breast Cancer Treatment Trials. Journal of Clinical Oncology 24:12, 1860-1867. [Internet] [cited 2018 Feb 14] Available from: http://ascopubs.org/doi/abs/10.1200/JCO.2005.03.8976?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed

Bajpai V. 2013. Rise of Clinical Trials Industry in India: An Analysis. International Scholarly Research Notices; Volume 2013, Article ID 167059:17. [Internet] [cited 2016 Jan 21] Available from: http://dx.doi.org/10.1155/2013/167059

Beauchamp TL. 2011. Informed consent: its history, meaning, and present challenges. Camb Q Healthc Ethics.;20(4):515–23. pmid:21843382 [Internet] [cited 2014 Jun 20] Available from: https://doi.org/10.1017/S0963180111000259

Bhatt A. 2004. Clinical trials in India: Pangs of globalization. Indian J Pharmacol 2004;36:207-8

Bhatt, A. 2014. Clinical trials in India: Way forward. Perspectives in Clinical Research, 5(2), 53–54. [Internet] [cited 2018 Feb 14] Available from: http://doi.org/10.4103/2229-3485.128017

Bhatt, A. 2015. Difference between Indian GCP and ICH GCP [Internet] [cited 2018 Jun14] Available from: https://docslide.net/documents/differences-bw-indian-gcp-and-ich-gcp.html

Brahmachari B, Fernandes M, Bhatt A. 2011. Pharmacovigilance for clinical trials in India: Current practice and areas for reform. Perspect Clin Res 2:49-53. [Internet] [cited 2018 Feb 19] Available from: http://www.picronline.org/text.asp?2011/2/2/49/80366

Burt T, Dhillon S, Sharma P, Khan D, MV D, Alam S, Jain S, Alapati B, Mittal S, Singh P. 2013. PARTAKE Survey of Public Knowledge and Perceptions of Clinical Research in India. PLoS One; 8(7): e68666. [Internet]. [cited 2015 Nov 11]] Available from: https://doi.org/10.1371/journal.pone.0068666

[CDSCO] Central Drugs Standards Control Organization. Ministry of Health and Family Welfare. 2004. [Internet]. [cited 2013 Jan 10] Available from: http://www.cdsco.nic.in/html/GCP1.html (CDSCO)

[CDC] U.S. Cancer Statistics Working Group. 2017. United States Cancer Statistics: 1999–2014 Incidence and Mortality Web-based Report. Atlanta: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute; [Internet]. [cited 2018 Feb 4]

Das U, Lakshmaiah KC, Lokanatha D, Babu G, Jacob L,Babu S. 2015. Breast Cancer in Women of Younger than 35 Years: A Single Center Study. J Mol Biomark Diagn 6:261. doi:10.4172/2155-9929.100026

Diemert DJ, Lobato L, Styczynski A, Zumer M, Soares A, Gazzinelli MF. 2017. A Comparison of the Quality of Informed Consent for Clinical Trials of an Experimental Hookworm Vaccine Conducted in Developed and Developing Countries. PLoS Negl Trop Dis 11(1): e0005327. doi:10.1371/journal.pntd.0005327

Desai, S., Mahajan, A. 2015. Clinical Trials in Oncology: Has India Come of Age? Indian Journal of Medical and Paediatric Oncology : Official Journal of Indian Society of Medical & Paediatric Oncology 36.3: 146–147. [Internet] [cited 2018 Feb 16] Available from: http://www.ijmpo.org/article.asp?issn=0971-5851;year=2015;volume=36;issue=3;spage=146;epage=147;aulast=Desai

[DHHS]U.S. Department of Health & Human Services. 1979. Ethical Principles and Guidelines for the Protection of Human Subjects of Research. The Belmont Report. [Internet] [cited 2015 Jul 18] Available from: http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html

Enfield, K., Truwit, J. October 2008. The Purpose, Composition, and Function of an Institutional Review Board: Balancing Priorities. Respiratory Care, 53 (10) 1330-1336

[FDA-CFR 21] The Food and Drug Administration. 2014a. CFR - Code of federal regulations title 21. [Internet]. [cited 2013 Jan 10]. Available from: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm

[FDA- Drug Development] The Food and Drug Administration. 2014a. The Drug Development Process [Internet]. [cited 2013 Jan 10]. Available from: https://www.fda.gov/ForPatients/Approvals/Drugs/ucm405622.htm

[FDA-IRB] The Food and Drug Administration. 2017a. CFR - Code of federal regulations title 21. [Internet]. [cited 2013 Jan 17]. Available from: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=56.107

[FDA-Guidance] The Food and Drug Administration. 2014. Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics. [Internet] [cited 2015 Nov 10]. Available from: https://www.fda.gov/downloads/Drugs/Guidances/UCM358301.pdf

[FDA-Guidance] The Food and Drug Administration. 2009. Guidance for Industry: Investigator Responsibilities — Protecting the Rights, Safety, and Welfare of Study Subjects. [Internet]. [cited 2013 Jan 17] Available from: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM187772.pdf

Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray, F. 2013. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 Lyon, France: International Agency for Research on Cancer; [Internet]. [cited 2015 Nov 11]. Available from: http://globocan.iarc.fr

Forouzanfar, Mohammad H et al. 2011. Breast and cervical cancer in 187 countries between 1980 and 2010: a systematic analysis The Lancet, Volume 378 , Issue 9801 , 1461 – 1484

Garnier J-P. 2008. Rebuilding the R&D engine in big pharma. Harvard Business Review; 86:68–76. [Internet]. [cited 2014 Oct 29] Available from: https://hbr.org/2008/05/rebuilding-the-rd-engine-in-big-pharma

Gazette of India. 2015. Ministry of Health and Welfare, Notifications, New Delhi. G.S.R 611 (E). [Internet]. [cited 2017 Dec 2] Available from: http://www.cdsco.nic.in/writereaddata/Gazette%20Notification%2031%20July%202015.pdf

Ghoncheh M, Pournamdar Z, Salehiniya H. 2016. Incidence and Mortality and Epidemiology of Breast Cancer in the World. Asian Pacific Journal of Cancer Prevention 17 (S3): 43-6

Gogtay, N.J., Ravi,R., &Thatte,U.M. 2017. Regulatory requirements for clinical trials in India: What academicians need to know. Indian Journal of Anesthesia, 61(3), 192–199. http://doi.org/10.4103/ija.IJA_143_

Goldstein, D. A., Clark, J., Tu, Y., Zhang, J., Fang, F., Goldstein, R., Rosenbaum, E. 2017. A global comparison of the cost of patented cancer drugs in relation to global differences in wealth. Oncotarget, 8(42), 71548–71555. http://doi.org/10.18632/oncotarget.17742

Goyal, S., Bhadu, I., Kapoor, A., Beniwal, S., 2014. New Audio Video Consent Guidelines: Elements for Informed Consent Process for Clinical Trials in India. International Journal of Information Research and Review, Vol 1. Issue 2, pp. 021-023

Gradishar, W. J., Kaklamani, V., Sahoo, T. P., Lokanatha, D., Raina, V., Bondarde, S., Jain, M., Ro, SK., Lokker, NA., Schwartzberg, L. 2013. A double-blind, randomised, placebo-controlled, phase 2b study evaluating sorafenib in combination with paclitaxel as a first-line therapy in patients with HER2-negative advanced breast cancer. European Journal of Cancer, 49(2), 312-322. DOI: 10.1016/j.ejca.2012.08.005 [Internet].[cited 2018 Feb 20]. Available from: http://www.ejcancer.com/article/S0959-8049(12)00630-2/fulltext

Grady C, Cummings SR, Rowbotham MC, McConnell MV, Ashley EA, Kang G. 2017. Informed Consent. N Engl J Med.;376: 856–867. doi: 10.1056/NEJMra1603773

Gupta YK, Padhy BM. 2011. India's growing participation in global clinical trials. Trends in pharmacological sciences; 32 (6):68–76. [Internet]. [cited 2015 Jul 18].

Gyawali, B., Sullivan, R. 2017. Economics of Cancer Medicines: For Whose Benefit?, The New Bioethics, 23:1, 95-104, DOI: 10.1080/20502877.2017.1314885

[ICH]. The International Conference on Harmonization. 2016. ICH guidelines. [Internet]. [cited 2017 Feb 10]. Available from: http://www.ich.org/products/guidelines.html ICH

[ICH]. The International Conference on Harmonization. 2014. About ICH. [Internet]. [cited 2017 Feb 10]. Available from: http://www.ich.org/products/guidelines.html ICH

[ICH] The International Conference on Harmonization. 2014. About ICH. [Internet]. Available from: http://www.ich.org/about/vision.html

[ICH] The International Conference on Harmonization. 2015. ICH guidelines. [Internet].. Available from: http://www.ich.org/products/guidelines.html

Indian Council of Medical Research. 2017 National Ethical Guidelines for Biomedical Research on Human Participants. New Delhi: Indian Council of Medical Research; [Internet]. [cited 2017 Dec 2]. Available from: http://icmr.nic.in/guidelines/ICMR_Ethical_Guidelines_2017.pdf

Imran et al. 2013., Mohammed et al. 2013. Clinical Research Regulation in India-History, Development, Initiatives, Challenges and Controversies: Still Long Way to Go. Journal of Pharmacy & Bioallied Sciences 5.1: 2–9. PMC.

Jackson, E., Dukes, G., Braithwaite, J., Moloney, J.P. 2015. Pharmaceuticals, Corporate Crime and Public Health. Journal of Law and Society, 42: 308–311. doi:10.1111/j.1467-6478.2015.00709.x

Kadam R, Karandikar S. 2012. Ethics Committees in India: Facing the Challenges! Perspectives in Clinical Research 3.2 50–56.

[JHM] Johns Hopkins Medicine. 2015. Breast Cancer & Breast Pathology: Johns Hopkins Pathology. [Internet] Available from: http://pathology.jhu.edu/breast/trials.php

Karwa M, Arora S, Agrawal SG. 2013. Recent Regulatory Amendment in Schedule Y: Impact on Bioequivalence Studies Conducted In India. J Bioequiv Availab 5:174-176. doi: 10.4172/jbb.1000154

Kulkarni, N. G., Dalal, J. J., Kulkarni, T. N. 2014. Audio-video recording of informed consent process: Boon or bane. Perspectives in Clinical Research, 5(1), 6–10. [Internet] [cited 2018 Feb 15] Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3915373/

Kumar M, Kher S. 2007. Regulatory consideration for conducting clinical trials in India. Regul Aff Focus. 12:26–31. . [Internet] Available from: https://www.amarexcro.com/articles/docs/RAPS_Focus_Mar2007.pdf

Mahajan, P. et al. 2015. Reasons Why Patients Fail Screening in Indian Breast Cancer Trials. Perspectives in Clinical Research 6.4: 190–193. [Internet] Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4640011/

Mallath, M. K., Tanuj C. 2017. “nvestigators’ Viewpoint of Clinical Trials in India: Past, Present and Future. Perspectives in Clinical Research 8.1: 31–36. PMC. [Internet] [cited 16 Feb. 2018]. Available from: https://www.ncbi.nlm.nih.gov/pubmed/28194335

Manoharan, N., Nair, O., Shukla, N. K., Rath, G. K. 2017. Descriptive Epidemiology of Female Breast Cancer in Delhi, India. Asian Pacific Journal of Cancer Prevention : APJCP, 18(4), 1015–1018. Available from: http://doi.org/10.22034/APJCP.2017.18.4.1015

Murari G. 2013. Clinical Research and its Condition in India. Journal of Clinical Research and Bioethics;4 (2). [cited 2014 Oct 29]; [Internet] Available from: https://www.omicsonline.org/clinical-research-and-its-condition-in-india-2155-9627.1000146.php?aid=14540

[NABH] National Accreditation Board for Hospitals & Healthcare Providers. 2017. [Internet] Available from: http://www.nabh.co/

[NCI] National Cancer Institute. n.d. NCI Dictionary of Cancer Terms. [Internet] [cited 8 Feb 2018]. Available from: https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=44680

[NIAID] National Institute of Allergy and Infectious Disease, ClinRegs. 2016. [Internet] Available from: https://clinregs.niaid.nih.gov/country/india#_top

Parth, G. 2013. Clinical Trials In India Innovare. Journal of Medical Sciences Vol 1 Issue 1 (April-June) Page: 19-32.

Ram, S. 2017.Indian contribution to breast cancer research: a bibliometric analysis. Annals of Library and Information Studies Vol. 64 99-104

Saini KS, Jagannathan R, Metzger-Filho O, Saini ML, Mistry K, Ali R, Gupta S. 2013. Challenges in launching multinational oncology clinical trials in India. Saini KS, Agarwal G, Jagannathan R, et al. Challenges in launching multinational oncology clinical trials in India. South Asian Journal of Cancer.2(1):44-49. doi:10.4103/2278-330X.105896. Jan-Mar:44–49

Sanmukhani, J., Tripathi C.2011. Ethics in Clinical Research: The Indian Perspective. Indian Journal of Pharmaceutical Sciences 73.2: 125–130. Print.

Saxena, P., Saxena, R. 2014. Clinical Trials: Changing Regulations in India. Indian Journal of Community Medicine: Official Publication of Indian Association of Preventive & Social Medicine, 39(4), 197–202. http://doi.org/10.4103/0970-0218.143018

Shah, J. Y., Phadtare, A., Rajgor, D., Vaghasia, M., Pradhan, S., Zelko, H., Pietrobon, R. 2010. What Leads Indians to Participate in Clinical Trials? A Meta-Analysis of Qualitative Studies. PLoS ONE, 5(5), e10730. [Internet]. [cited 2018 Feb 20]. Available from http://doi.org/10.1371/journal.pone.0010730

Sharma GN, Dave R, Sanadya J, Sharma P, Sharma KK.2010. Various types and management of breast cancer: An overview. J Adv Pharm Technol Res;1:109-26. [Internet] [cited 2017 Dec 10] Available from: http://www.japtr.org/text.asp?2010/1/2/109/72251

Singh, M. 2008. Should Clinical Trials be Outsourced? TIME, August. http://content.time.com/time/health/article/0,8599,1830334,00.html

Somdatta P, Baridalyne N. 2008. Awareness of breast cancer in women of an urban resettlement colony. India J Cancer; 45: 149-53.

Stober, M. 2003. Multinational Clinical Trials: Breaking Language and Cultural Barriers, Applied Clinical Trials, 13 (9). [Internet] [cited 2018 Feb 14] Available from: http://www.actmagazine.com/appliedclinicaltrials/article/articleDetail.jsp?id=79882 [9]

Srinivasan, S. 2010. Patient Protection in Clinical Trials in India: Some Concerns. Perspectives in Clinical Research 1.3: 101–103. Print.

Thatte, U. M., Marathe, P. A. 2017. Ethics Committees in India: Past, present and future. Perspectives in Clinical Research, 8(1), 22–30. http://doi.org/10.4103/2229-3485.198549

[UNESCO] UNESCO Institute for Statistics. 2015. Literacy Statistics Metadata Information Table. [Internet] [cited 19 Nov 2015] Available from: http://uis.unesco.org/

Urooj, M., Husain, G. M., Khan, M. A., & Kazmi, M. H. 2017. Compensation to clinical trial participants in India: A gap analysis. International Journal of Pharmaceutical Investigation, 7(2), 41–46. http://doi.org/10.4103/jphi.JPHI_31_17

U.S. Department of Education and the National Institute of Literacy. 2013. The U.S. Illiteracy Rate Hasn't Changed In 10 Years. [Internet] [cited 5 Sep 2017] Available from: https://www.huffingtonpost.com/2013/09/06/illiteracy-rate_n_3880355.html

Usharani, P., Naqvi, S. M. H. 2013. Post-trial access. Perspectives in Clinical Research, 4(1), 58–60 [Internet]. [cited 2018 Feb 20]. Available from: http://doi.org/10.4103/2229-3485.106391

Vijayananthan, A., Nawawi, O. 2008. The importance of Good Clinical Practice guidelines and its role in clinical trials. Biomedical Imaging and Intervention Journal, 4(1), e5. http://doi.org/10.2349/biij.4.1.e5

Suhag, V, BS, S., Singh, AK., Dashottar, S., Semwal, M., 2015. The Oncology Scenario in India: Lots of Gaps Need to be Bridged. Global Journal of Medical Research. Available from: https://globaljournals.org/GJMR_Volume15/1-The-Oncology-Scenario.pdf

[WMA] World Medical Association. 2013. Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. JAMA. 310 (20): 2191–2194. doi:10.1001/jama.2013.281053. PMID 24141714. [Internet] [cited 24 Jul 2015]