1.1. Introduction

Medical science and bio-medical technologies has been having a development that is nothing short of astonishing. The field of Bio-medical research, particularly, has enjoyed the full fruits of computerization. The benefits ensued out of therapies, technologies and knowledge from research and development has laid a hand on the entire mankind in general and every person alive in specific.
New biotechnology revolution is now at the threshold of tremendous expansion through abundant innovative products that has already been launched into clinical trials recently. Furthermore, clinical trials have become a global happening as researchers and investors, including the pharmaceutical companies, search for very large sample sizes and empirical results to advance both their studies and the market capturing of their newest products.

The already multifaceted activity of medical research has been further compounded by the intricacy of the organisations and individuals involved. This complexity is evident at various levels. Primarily, the cognitive domain in terms of the knowledge and skills absorbed in the creation of medicines and medicinal equipments are very obscured, as are the tactics used to analyse and examine them. Secondly, the affective element of health professionals in terms of their attitude and perceptions with respect to management of research can range from ready acceptance to vehement objection and rejection. The endeavour required to resolve these professional-managerial conflicts add significantly to the complexity of the work. Thirdly, at the organisational level, the task of implementing and managing both the research activities and the researchers is complicated at the psycho-motor domain in terms of the administrative red-tapism of educational institutions, universities, funding bodies, industry sponsors, regulatory agencies and research centres in the hospitals. The
challenge of learning the clinical research process and its management in such a complex environment raises questions that require systematic investigation.

This introduction provides an overview of clinical research and of academic medical centres. Section one discusses the evolution of clinical research. The point here is that clinical research is a complex activity and that the demand for more human clinical trials is increasing along with the rate of drug discovery and advancements in biotechnology. Section two deals with the evolution of clinical research in India and the role of Schedule Y. Section three discusses the importance of academic medical centres in providing access to patients, facilities, expertise and management for clinical research. Here the point is that many AMCs, in several countries, have undergone recent organisational transformation in response to changes in their operating environments. Section four to seven renders an understanding of the current research process.

1.2. The evolution of clinical research

The evolution of clinical research has a long and interesting journey. The history of clinical research as recorded may be traced back to 500 BC, which is given in the Holy Bible. The route of clinical research moves from dietary therapy as in the use of legumes and lemons to medicinal herbal drugs (Collier, 2009). Following the portrayal of basic approach in 18th century, efforts were made to refine the design and statistical aspects
of clinical trial. These were pursued by changes in regulatory and ethical environments (Collier, 2009).

Clinical trial has been recorded as early as in the “Daniel” of the Holy Bible. This experiment, resembling a clinical trial, was not conducted by a medical person but by King Nebuchadnezzar – a military leader. During his rule in Babylon, Nebuchadnezzar believed that eating only meat and drink only wine would keep them in sound physical condition and ordered his people to take the diet. He allowed the rebels to take legumes and water – but only for 10 days. When his experiment came to an end, the vegetarians appeared well nourished than the non-vegetarians. So, Nebuchadnezzar permitted the vegetarians to continue their diet of legumes (Collier, 2009).

Avicenna (1025 AD) in his encyclopaedic ‘Canon of Medicine’ elaborates some remarkable conventions for the testing of drugs. He suggested that, in the clinical trial remedy should be used in its natural state in disease without complications. He recommended that two cases of contrary types be studied and that study be made of the time of action and of the reproducibility of the effects (Bull, 1951).

The first clinical trial of a new therapy was a serendipitous experiment by Ambroise Pare, a famous surgeon, in 1537 (Collier, 2009). In 1537 he was responsible for the treatment of soldiers wounded in the battlefield while serving with the Mareschal de Motegni. As the number of wounded was high, and the supply of conservative cure –
oil – was inadequate to treat all the wounded, he had to resort to unconventional action. He describes,

“at length my oil lacked and I was constrained to apply in its place a digestive made of yolks of eggs, oil of roses and turpentine. That night I could not sleep at any ease, fearing that by lack of cauterization I would find the wounded upon which I had not used the said oil dead from the poison. I raised myself early to visit them, when beyond my hope I found those to whom I had applied the digestive medicament feeling but little pain, their wounds neither swollen nor inflamed, and having slept through the night. The others to whom I had applied the boiling oil were feverish with much pain and swelling about their wounds. Then I determined never again to burn thus so cruelly the poor wounded by arquebuses” (Bull, 1951).

James Lind is treated to be the first physician to have conducted a controlled clinical trial of the modern era. Dr Lind (1716-94), whilst working as a surgeon on a ship, was appalled by the high mortality of sailors due to scurvy. He planned a comparative trial of the most promising cure for scurvy. His vivid description of the trial covers the essential elements of a controlled trial (Collier, 2009; Bull, 1951; Twyman, 2004; Dodgson, 2006).

While he was resident in Edinburgh and a Fellow of the Royal College of Physicians, Lind’s Treatise of 1953 was written, which contains not only his description
of controlled trial showing that oranges and lemons were dramatically better than the other treatments for scurvy, but also a systematic review of previous literature on the disease (Chalmers et al, 2008). The publicity and popularity of the James Lind Library has made 20th May to be designated International Clinical Trials Day, because James Lind's celebrated controlled trial began on that day in 1747 (Chalmers et al, 2008).

The word placebo first appeared in medical literature in the early 1800s (Collier, 2009). Hooper's Medical Dictionary of 1811 defined placebo as “an epithet given to any medicine more to please than benefit the patient.” However, it was only in 1863 that United States physician Austin Flint planned the first clinical study by comparing a dummy remedy to an active treatment. In 1886, Flint described the study in his book ‘A Treatise on the Principles and Practice of Medicine’, that instead of an established remedy, he treated 13 patients suffering from rheumatism with an herbal extract which was advised (Collier, 2009).

In 1943 the Medical Research Council (MRC) of United Kingdom carried out a trial in order to investigate treatment for the common cold with patulin – an extract of Penicillium patulinum. This was the first reported double blind comparative trial with concurrent controls in the general population in recent times. It was also one among the last trials with non-randomized method of data collection (Hart, 1999).
Although the idea of randomization was introduced in 1923, the first randomized control trial was carried out in 1946 by MRC of the UK in the use of streptomycin for pulmonary tuberculosis (Hart, 1999). This trial was a model of meticulousness in design and implementation, with systematic enrolment criteria and data collection compared with the ad hoc nature of other contemporary research (Yoshioka, 2008).

The ethical framework for human subject protection has its origins in the ancient Hippocratic Oath, which specified a prime duty of a physician – to avoid harming the patient. However, this oath was not much respected in human experimentation and most advances in protection for human subjects have been a response to human abuses e.g. World War II experiments.

The first International Guidance on the ethics of medical research involving subjects was the Nuremberg Code which was formulated in 1947. The Nuremberg Code highlighted the essentiality of voluntariness of the informed consent for participation in research, although informed consent was described in 1900. In 1948, Universal Declaration of Human Rights (adopted by the General Assembly of the United Nations) reported its concern on the rights of patients subjected to involuntary maltreatment. (Indian Council of Medical Research, 2006).

The brush with thalidomide tragedy helped the U.S. to pass the Kefauver-Harris amendments of 1962 that fortified omission of drug testing and included a requirement
for informed consent. In 1966, the International Covenant on Civil and Political Rights specifically stated,

‘No one shall be subjected to torture or to cruel, inhuman or degrading treatment or punishment. In particular, no one shall be subjected without his consent to medical or scientific treatment.’ (Indian Council of Medical Research, 2006)


1.3. Evolution of Clinical Trials in India

Although India has been recognized as an attractive country for clinical trials only recently, the country's journey in clinical research field has a long history. India has a rich heritage of traditional medicine – Sidha and Ayurveda. The classic medicinal texts contain detailed descriptions and observations on diseases and profound assistance on remedies. It is presumed that these descriptions are based on direct observations made by ayurveda experts of that times. However, recorded empirical documentation is not
available in the ancient texts of any such clinical experiments. Hence, one has to fall back on current history of medical research in India.

The major historic milestones of the Indian Council of Medical Research reflect, in many ways, the growth and development of medical research in the country over the last nine decades (Bhatt, 2010). First meeting of the Governing Body of the Indian Research Fund Association (IRFA) was held on November 15, 1911 at the Plague Laboratory, Bombay, under the Chairmanship of Sir Harcourt Butler. At the 2nd meeting of the Governing Body in 1912, a historic decision was taken to start a journal for Indian Medical research. Between 1918 and 1920, several projects on beriberi, malaria, kala azar and indigenous drugs were initiated. In 1945, a Clinical Research Unit – the first research unit of IRFA attached to a medical institution- was established at the Indian Cancer Research Centre, Bombay. In 1949, IRFA was redesignated as the Indian Council of Medical Research. Over next 60 years, ICMR established many national research centers in the fields of nutrition, tuberculosis, leprosy, viral disease, cholera, enteric disease, reproductive disorders, toxicology, cancer, traditional medicine, gas disaster, genetics, AIDS etc. (Indian Council of Medical Research, 2006)

The Central Ethical Committee of ICMR on Human Research constituted under the Chairmanship of Hon'ble Justice (Retired) M.N. Venkatachaliah held its first meeting on September 10, 1996. Several subcommittees were constituted to consider ethical issues in specific areas e.g., Epidemiological Research; Clinical Evaluation of Products to
be used on Humans; Organ Transplantation; Human Genetics, etc. The committee released Ethical Guidelines for Biomedical Research on Human Participants in 2000 which were revised in 2006 (Indian Council of Medical Research, 2006).

Schedule Y of Drugs and Cosmetics Act came into force in 1988 and established the regulatory guidelines for clinical trial (CT) permission. The schedule did force the industry to conduct Phase III clinical trials for registration of a new drug and supported growth of a predominantly generic Indian pharmaceutical industry. However, this schedule only permitted clinical trials at a phase lower than its global status. This phase lag obstructed integration of India in global clinical development (Bhatt and Sewlikar, 2007).

The next major step has been revision of Schedule Y in Jan 2005. As compared to Schedule Y 1988, which had narrow and restrictive definitions of clinical trial phases, the amended Schedule Y 2005 provided pragmatic definitions for Phase I to IV. The definitions and guidelines for clinical trial phases are broad and rational. The earlier restrictions on number patients and centers in early phases stipulated in Schedule Y 1988 were removed allowing the sponsor company freedom to decide these in relation to protocol requirements. The phase lag requirements gave way to acceptance of concurrent Phase II-III as part of global clinical trials (Bhatt and Sewlikar, 2007).
Schedule Y 2005 legalized Indian GCP guidelines of 2001 (Bhatt and Sewlikar, 2007). This schedule stipulated GCP responsibilities of ethics committee (EC), investigator and sponsor and suggested formats for critical documents e.g. consent, report, EC approval, reporting of serious adverse event. These amendments in Schedule Y have been a major step forward in direction of GCP compliant trials and have provided the much-needed regulatory support to GCP guidelines (Bhatt and Sewlikar, 2007).

1.4. **The importance of clinical research**

Clinical research is fundamentally important for improving human health. The general aim of clinical research is to produce knowledge applicable to human illness and to translate that knowledge into new clinical applications (Blumenthal, Campbell, & Weissman, 1997). Clinical research has long been regarded as an integral component for the delivery of health care that is based on good science (J. K. Iglehart, 1995; Pettus, Dodd, & Murray, 1999). Over the past 50 years, the volume and scope of medical and health research conducted on human beings has increased dramatically (Nauert, 1995; Paugh & Lafrance, 1997; Pickett, 1996; Reuter & Gaskin, 1997). Clinical research also has the potential to improve the cost effectiveness and health outcomes of health service delivery, and hence the utilisation of scarce resources (J. Iglehart, 1994). It is estimated that the annual healthcare savings resulting from health and medical research in the United States was almost US$70 billion in 1995. In contrast, the total 1999 research budget for the National Institutes of Health (NIH) was only US$15 billion.
Clinical trials are also thought to be important in stimulating an ethos or culture whereby health professionals question their clinical practices and develop robust methodologies that systematically test their assumptions (Dobson, Coleman, & Mechanic, 1994; Pettus, 1996). However, there is still enormous variation in treatment practices and clinical outcomes. In many instances there is only anecdotal evidence that any particular medical treatment is efficacious in the ways intended. Clinical research informs health policy, priorities and strategies that promote effective practice (Paterson, 1996). Research is needed to test, measure, compare and report clinical practices and their outcomes in order to inform the development of practice guidelines or protocols (Sceats, 1997). Patients who enrol in clinical studies may also benefit from the often more intensive clinical observations and assessments that are made under a research protocol. Indeed, it has been observed that some patients participating in clinical trials have better outcomes than those who do not, although the ailment and the treatment may be the same. Various explanations have been put forward to explain this observation, such as the placebo effect and the more extensive monitoring of the research participants (Levene & Cohen, 1974; Stiller, 1994).

Clinical research covers a broad range of medical and health-related studies, including trials of pharmaceuticals, medical devices and procedures. These activities represent an expanding industry, which is having a dramatic impact on human health. In real economic terms, commercial investment in clinical research has expanded steadily
since the 1980s, mostly in response to developments in biomedicine and genomics (Paugh & Lafrance, 1997). In 1988 pharmaceutical companies spent more on research and development (R&D) in the United States than the entire US National Institutes of Health (NIH) budget. By 1994 pharmaceutical R&D expenditure increased by a further 40 percent. A 1996 survey of companies belonging to the Pharmaceutical Research and Manufacturers of America (PhRMA) found that there were 284 biotechnology drugs in human trials, an increase of 21 percent over the previous year (Paugh & Lafrance, 1997). A 1999 review of the Pharmaprojects database reveals that the number of products in clinical development worldwide was 6046, up from 5930 the previous year. In addition to larger pharmaceutical giants, there are a number of smaller biotechnology companies moving their newly discovered products into clinical trials, particularly as the human genome and rapid small-molecule screening assays open up new foundations for drug discovery and application (Moser, 1999).

Concurrent to this increase in clinical research activity has been an increase in the rigour and complexity of the regulatory requirements for clinical trials. International regulatory standards, generally referred to as ICH-GCP (International Committee for Harmonisation - Good Clinical Practice), have been developed with regard to data, privacy and research on human subjects. As the rate of new drug and medical applications has soared over the last decade, the US Food and Drug Administration (FDA) has also responded by restructuring its approval processes and policies,
particularly with regard to the protection of human subjects participating in clinical trials. These regulatory statutes, standards and guidelines are frequently updated, which adds to the complexity, and hence cost, of compliance by the investigative site.

The scope of clinical trials, like the regulatory environment, has also expanded in the last decade. In order to improve statistical power for analysis, clinical trials are designed to recruit greater numbers of participants. For example, multi-national clinical trials may require 10,000 participants in order to generate data adequate for meeting their research objectives. A trial such as this might involve the identification, coordination and management of over 100 investigative sites, local investigators and research associates in several countries. Each site is responsible for the accurate and timely execution of the research protocol, such as obtaining ethical approval, recruiting participants, conducting the research procedures and completing the required study documentation. Moreover, human genome research has prompted the pharmaceutical industry to recruit participants from genetically varied populations to study drug-linked polymorphisms.

Undertaking research on this scale and at this level of complexity is a monumental task of organisation and logistics. In response to the increasing scope, volume and complexity of clinical research, specialised clinical trial project contractors, called Contract Research Organisations (CROs), have emerged. Pharmaceutical companies and medical manufacturers engage CROs to manage a range of activities
associated with clinical trials, such as statistical, diagnostic, regulatory and logistical assistance, such as the identification, initiation and management of various clinical research sites. Thus, while clinical research is important for the advancement of cure and prevention of human illness and disease, it has also become a multi-billion dollar global industry, comprised of funding bodies, commercial sponsors, CROs, regulatory bodies, ethics committees, investigators and clinical research facilities. As the demand for research increases, these investigators and clinical research facilities, such as AMCs, are faced with managing an increasing number of complex clinical trials and other health-related studies.

Research is a traditional function of academic medicine (Blumenthal et al., 1997; Colloton, 1989; Dobson et al., 1994; Epstein, 1995). Therefore, a large proportion of clinical research takes place within facilities that are associated with a medical school or other academic programme. Academic medical centres are unique and complex organisations, many of which have undergone significant structural transformation over the last twenty years. These changes are largely due to pressures from the economic environment in which AMCs operate, and are governed to a large extent by national health policies affecting medical and nursing education and healthcare funding. AMCs bring together the facilities, expertise and patients required for clinical care, education and research. An understanding of the structure of these institutions and the contextual factors that influence them are therefore critical to our understanding of clinical
research in academic medical centres. The following section describes the structure, function and environment of academic medical centres and discusses the relationship between the environmental context of AMCs and the management of clinical research.

1.5. Academic Medical Centres

Academic medical centres serve a tripartite mission. They are clinical care, teaching and research. These organisations are usually comprised of a university and a hospital, or other clinical care facilities where training and research are conducted alongside the provision of health-related services. These complex tasks are usually co-ordinated between a university and one or more clinical facilities, such as hospitals. The university is responsible for the advancement of knowledge in medicine through research, and for teaching clinical skills and professional norms. The hospital provides an enabling environment for the application of those skills, norms and research to patient care.

Since the 1960s US federal government funding for research and education in AMCs has declined substantially in real economic terms (Korn, 1996). State budget cuts also have progressively removed pools of discretionary funding that were frequently accessed by AMCs for research (J. Alexander, 1988). A decisive change came to the US healthcare sector in 1983 when federal policy adopted the Prospective Payment System for Medicare (Mechanic & Dobson, 1996). This change shifted the funding mechanism from retrospective reimbursements to prospective payments, based on diagnosis. Laws
were passed that enabled Medicaid and commercial insurers to contract selectively with
groups of physicians and hospitals, thus fostering cost competition among providers,
including AMCs. To make economic matters worse, in 1995 the United States Congress
reduced additional Medicare payments received by AMCs for treating the most
complicated injuries and illnesses as well as the indigent poor (Anonymous, 1996). In
addition, academic medical centres in the United States have been under an enormous
financial strain as other purchasers, such as managed care health plans, also demand
lower costs. In parallel with these market changes, academic medical centres have
adopted a more corporate-like business demeanour (Golembesky, 1995). In response to
these policies, healthcare facilities in the US moved toward "managed care" practices
aimed at containing and reducing their costs, which resulted in price-based competition
between hospitals and other healthcare facilities (Zajac & D'Aunno, 1997). In the eyes of
some health care purchasers, value has become a function of effectively managed care,
high service levels and quality outcomes. At the same time, the relevance of teaching
and research in the managed-care environment has become obscured (Burnett, 1996;
Nauert, 1995).

Burnett (1996) regret the plight of AMCs in this way:

"For decades the intricate web of relationships that exists across and within the
clinical and research components of academic medical centers has gone unrecognised
and unquestioned. Space, personnel, protected time, travel, salary supplements and a
host of other forms of support for researchers have often been provided or subsidized by hospital, college of medicine, departmental and sectional clinical dollars. How this support flows within the academic medical center has sometimes been explicit, but it is often implicit. Mounting financial pressures are prompting the development of fund-flow analyses at academic medical centers. As a result, traditional perquisites that support clinical research will be identified, quantified, and subjected to investment criteria similar to those applied to other uses of funds." (Burnett 1996:90)

As the vital level of financial accountability has increased, the clinical faculties and facilities of AMCs have become more exact in defining and costing their teaching, research and patient care activities. Thus, funding support for each has become more clearly identified and standards of productivity built up, making it more difficult for clinical staff to switch their time and resources to research activities, mainly when those activities have no defined funding source (Marwick, 1997). This has created a dilemma for clinical investigators and funding agencies, which have come to expect some level of institutional support for research.

Unfortunately the costs and revenue associated with clinical research are often co-mingled with other costs and revenue. In a study of AMC financial systems, Lound (1995) concluded that the highly integrated and complex relationships that exist between clinical and research activities is a barrier to the establishment of robust accountability systems (Lound, 1995). This finding suggests that there may be structural
issues related to how well AMCs are able to unbundle and manage their clinical research activities. The evidence suggests that some AMCs have addressed the mixing of clinical and research costs and revenue by establishing separate organisations, such as research institutes, which are dedicated to the management of clinical research.

In order to be competitive in the managed care environment, many US AMCs have had to undergo significant changes to their governance and/or managerial structures (B. Alexander, Davis, & Kohler, 1997; J. Iglehart, 1998). Since the 1980s, industry journals have reported numerous examples of mergers, acquisitions and restructuring in US AMCs (Abdelhak, 1996; B. Alexander et al., 1997; Andreopoulos, 1997; Barnett, 1995; Doyle, 1996; Epstein, 1995; Goldsmith, 1999; Japsen, 1994; Johnson, 1995; Nauert, 1995; Pickett, 1996; Reuter & Gaskin, 1997; Serb, 1997). In an effort to drive out competitors in this environment, many health service providers have integrated or merged with others, creating large health systems, some responsible for twenty or more hospitals. However, to compete on price is more difficult for academic medical centres, which have traditionally carried the costs of treating the poorest and sickest patients while also some of the costs associated with research. Taken together, these activities are estimated to increase the operating costs of AMCs by 30 to 40 percent, which may explain why some health care plans shun contracting with AMCs for providing health services to their members (Abdelhak, 1996; Anderson, Greenberg, & Lisk, 1999; Andreopoulos, 1997). Some authors have worried that the shift to a
competitive marketplace under managed care seriously erodes the clinical research mission of AMCs (Goldman, 1995; Gottlieb, 1997) and that AMCs may be forced to alter or abandon research in order to maintain profitability (Anderson et al., 1999).

These changes have generally resulted in more price-based competition for health services contracts. In order to compete and maintain financial viability AMCs have had to address their relatively high cost structures including those associated with research. However, research costs may be difficult to identify if there is a low level of accountability or transparency in the research management systems. At the same time, though, the opportunities for generating revenue through commercially sponsored clinical trials have increased dramatically as investment in biomedical research and the rate of new clinical applications increase.

AMCs in the US also compete with non-academic and other private clinical facilities for commercial clinical trials (Hudson, 1997). These private institutions compete with AMCs on price, since they do not bear the additional costs associated with teaching, research or caring for the indigent poor (Capper & Fargason, 1996; Hudson, 1997; Pardes, 1997; M. Porter, 1980).

One indicator of this shift away from AMCs is the number of academic staff acting as investigators in industry-sponsored trials. In 1989, academic staff comprised 82 percent of the investigator pool for commercial trials, whereas by 1993 this percentage
had decreased to 68 percent. In the five years from 1991 to 1996 the percentage of US clinical trials performed in academic medical centres fell from nearly 80 percent to 43 percent. Independent research centres, which are not burdened by the administrative and overhead costs of an AMC, have been found to perform this work faster and more cheaply (Hudson, 1997). One example is the Howard Hughes Medical Research Institute, which operates independently from, yet has alliances with, dozens of investigators, hospitals and universities (www.hhmri.org). However, private hospitals have also been accused by the pharmaceutical industry of delaying the enrolment of participants into clinical trials (Dexter, 1994). Non-US universities and clinical facilities also compete with those in the US for commercial trials. In the period 1979-1994, the percentage of first-in-human clinical trials conducted in the United States decreased from 61 percent to 36 percent.

The decline in market share for contracted research has had a negative financial effect on many US AMCs (Burnett, 1996) and raises questions as to the cause. This erosion may be an indication that AMCs have been ineffective in meeting industry expectations with respect to the management of clinical research at investigative sites. One possible explanation is that AMCs lack robust policies, structures or mechanisms for managing these activities. High-performing study sites are sought by hundreds of biotechnology and pharmaceutical companies (Silverstein, Garrison, & Heinig, 1995). During the time that Investigational New Drugs (INDs) are in clinical trials, the key
performance indicator for the pharmaceutical industry becomes the drug's time to market. These companies become frustrated by delays to their clinical research, as delays impede the registration and marketing of new drugs. The 'burn rate', a term used to express the cost of these delays, can be US$1 M per day by the time a drug reaches the clinical trial stage. Delays in clinical trials are frequently blamed on investigative sites at academic medical centres, a perception that casts AMCs as a fragmented group, with variable experience and approaches to both the conduct and management of clinical research (Maloff, 1999). These frustrations may explain why pharmaceutical companies frequently engage Contract Research Organisations (CROs) and Site Management Organisations (SMOs) to liaise directly with investigative sites and to establish functional relationships with researchers and their institutional management.

Modern clinical studies are conducted at global proportions as researchers design more highly powered studies that require thousands of research subjects and involve AMCs in several countries. As in the US, AMCs in other countries have also experienced economic pressures and changes to their national health policies. For example, during the 1980s and 1990s the publicly funded health systems of the UK, Canada, Australia and New Zealand were restructured as more market-driven principles of health care delivery were introduced. In the public health systems of these countries, the role of health service purchasers (government) and health service providers (hospitals) have been separated, creating conditions for price-based competition between providers.
Similar to the US, AMCs in these countries face additional cost burdens with respect to their teaching and research missions, compared to private clinical care facilities (Blumenthal & Meyer, 1996; Capper & Fargason, 1996; Gale, 1997; Hagland, 1996; Hudson, 1997; J. Iglehart, 1994). Many AMCs in these other countries have also been forced to curtail research activity perceived to be impacting on clinical care costs (Colloton, 1989; Dobson et al., 1994; Epstein, 1995; Hellerstein, 1998). This trend has been identified as a factor in the increased competition for external research funding of clinical research (Gale, 1997; Naylor, 1999; Neutze, 1995; Williams & Rowell, 1999); Australian Ministry of Health and Aged Care, 1999; (J. Iglehart, 1994; Rogers, Snyderman, & Rogers, 1994).

In summary, clinical research is a complex activity and one for which demand is increasing as new therapeutic agents and devices are presented for human testing. Once conducted primarily in US AMCs, clinical research has become a global enterprise, involving a multitude of international investigative sites. The loss of AMC market share in commercial clinical research raises questions with respect to how these organisations manage clinical research. The frustrations experienced by sponsors suggest that some US AMCs, and perhaps AMCs in other countries, tend to have poor processes for managing clinical research and that this contributes to delays in the initiation and progress of clinical trials. This chapter has described some of the economic, regulatory and commercial factors that might affect the management of clinical research in AMCs.
The global nature of clinical research means that questions relevant to US AMCs might also be relevant to non-US AMCs, particularly in countries such as Canada, Australia, New Zealand and the United Kingdom. This key assumption is based on the commonality of language, training, literature and professional norms that are shared between these five countries.

It is important that AMCs understand their clinical research management processes in order to maximise the potential for improving health outcomes and for generating revenue while minimising the associated risks. This thesis aims to facilitate that understanding. Given the issues of environment, structure and professional management presented above, the following sections introduce the primary research aims and questions and present a methodological framework for pursuing these objectives.

1.6. The present study

The objective of this study is to explore the organisation and management of clinical research in academic medical centres. This investigation is important for both theoretical and practical reasons. Firstly, a description of the organisational context and structure of AMCs and their management of clinical research provides an opportunity to apply organisational theories to the analysis of systematically collected quantitative and qualitative data. It is expected that an analysis of these data will contribute to the body of knowledge on complex organisations in general and AMCs in particular. Secondly, this
study is intended to inform management practice by identifying structures and mechanisms that enable the management of clinical research. It is expected that this will contribute knowledge to assist in the planning and development of clinical research management practices in academic medical centres as well as other professional research organisations.

There is no reported research that specifically describes the management of clinical research in academic medical centres. The observations presented in the previous sections describe AMCs as complex organisations operating in a dynamic environment and clinical research as a complex activity that is conducted by professionals within these organisations. It is important, therefore, that questions related to clinical research management are posed at two levels: the macro-organisational and the micro-organisational. At the macro-organisational level, elements of analysis include national health policies, the economic environment, regulatory and statutory requirements and advances in biotechnology. These factors, which have experienced significant change over the last two decades, are largely external to the AMCs, which have little direct control over them.

In order to understand the role of these external forces the first question in this exploratory study is:

*What is the contemporary context of clinical research in AMCs?*
The study of AMC structures at a macro-organisational level is necessary to understand how the functional processes of clinical research management operate within the structural framework of the organisation. Hence, the second question is:

**What are the formal structures and mechanisms that enable clinical research management in AMCs?**

In order to understand the internal context of clinical research management it is also necessary to explore the interactions between the professional and administrative hierarchies at the micro-organisational level and to identify informal structures or mechanisms that enable clinical research management. That is, in addition to the administrative hierarchy of the organisation, there are also professional hierarchies of doctors, nurses and academics. Researchers are notorious for their subscription to values such as academic freedom and professional autonomy to pursue their research activities with minimal interference from organisational structures and procedures (Pettus, 1996). As professional bureaucracies, AMCs present unique challenges to the management of activities such as clinical research. It is therefore important to explore clinical research management at the micro-organisational level in order to identify mechanisms that enable relationships between the professional and administrative hierarchies. The literature presented in chapter three suggests that these mechanisms might be found within the informal structures of professional bureaucracies.
Hence the third question is:

**What are the informal structures and mechanisms that enable clinical research management in AMCs?**

The three research questions therefore guide this exploration of clinical research in AMCs and description of an organisational structure for AMCs. The following section summaries the key assumptions and constraints and the methodological approaches that have been applied to addressing these specific questions.

1.7. **Key assumptions and constraints**

This thesis is clearly ambitious in its attempt to describe and compare the environment and the clinical research management structures of AMCs in three kinds of structures – Central government, State Government, and Private. There are specific methodological risk issues that have been identified in the development of a research strategy.

Firstly, observations suggest that the environment in which clinical research and AMCs operate is dynamic and complex. This dynamic feature means that a cross-sectional study design might fail to identify patterns and trends. Methodologies such as survey questionnaires are cross-sectional in that they capture a moment in time for the organisation and the individual respondent. A study design that places a strong reliance
on a survey questionnaire might limit the scope of this research through the exclusion of longitudinal and qualitative data needed to identify patterns.

Secondly, the researcher's professional role as Director, Administration in a Dental Institution in Kerala has the potential to bias not only respondents' openness but also the interpretation of results. Experiential data that has been collected as a participant-observer within the AMC in which the researcher is associated have therefore not been presented. However, these observations, with recognition of bias, have been used in the development of the research questions and for the interpretation of some results, particularly with respect to their implications for clinical research managers. Moreover, Kerala has a very small population of academic medical centres and it is doubtful whether the application of the research questions to the AMC in which the researcher is associated with would yield findings relevant to the wider population of AMCs. The research questions have therefore been applied to AMCs in three various AMCs, which share common and similar cultures of healthcare, professional training and health research practices.

Thirdly, there are considerable barriers to both identifying and accessing a robust sample population from AMCs in three different ownerships. The challenge is to identify likely participants for this study from as many academic medical centres as possible in five countries and to establish a means of accessing these individuals. The sample population is loosely comprised of 'research managers' or other decision-makers
involved in the research management process in AMCs. It is expected that this sample will be accessible through the universities, hospitals and clinical research institutes. The generalisability of results from this study is contingent upon the scope of the sampling frame and the scope of the sampling frame is contingent upon whether these individuals can be identified, accessed and have the time and desire to participate.

There is a considerable risk that, given the busy work schedules of AMCs, the sample will be insufficient to permit generalisation of the results.

This potential limitation is acknowledged although the effect does not impact greatly on this exploratory study, which neither tests hypotheses nor aims to generalise the findings. It is expected that some of the barriers to the identification of and access to potential participants might be mitigated to some extent through the use of Internet-based technologies and resources.

Although these technologies have only been available to mainstream researchers for only a few years, they present a powerful, although largely untested, mechanism for identifying and accessing information about academic medical centres as well as a potential survey sample. It is expected also that the Internet-based methodologies employed in this study may provide useful experience for guiding future study designs.

Fourthly, there are constraints to accessing the sample population, as participation is reliant on the time individuals have available and their desire to
participate in this research. These are mentioned together, as the time available may indeed be small, however their desire to participate in this study may be sufficient for them to justify the time taken. Another barrier is the potential commercial sensitivity of the information that might be revealed in the responses.

Finally, the literature reviewed in chapter two suggests that professional bureaucracies, such as AMCs, place significant reliance on informal organisational structures. As implied in their description, these structures are not formally articulated and unlikely to be identified using quantitative data gathering techniques. The methodologies employed must therefore include the use of qualitative methods that are capable of probing beyond the formal organisational structures and in statistics in order to identify informal structures and mechanisms within these organisations.

The constraints described above have the potential to limit the scope and generalisability of the findings. However, the research questions are exploratory in nature and set in a broad context to identify patterns. In order to delimit the effect of these constraints the strategy adopted in this study is to reduce reliance on any one data source or research methodology. The use of a multi-method strategy is analogous to the construction of a laminated timber beam, where each layer is thin, however the composite structure is significantly stronger than a single thick piece of wood.
This approach is reflexive to the extent that a weakness in any one data element might be compensated or offset by alternative data. Such a 'thin-layer' composite provides a means to delimit constraints to participant access by including data from alternative sources, such as historic data, published resources and other sources of qualitative data extend the exploration of informal organisational structures. It is expected that these layers of data will form a platform on which to build a composite 'picture' of the environment and formal structures.

The research questions that guide this exploratory study seek to identify the context and structures related to the management of clinical research in AMCs. The methodological strategy adopted for this study employs a mixed method approach that endeavours to reduce absolute reliance, and hence risk, on any one method. Moreover, this study is designed to build a composite of both broad contextual data and in-depth data that is reflexive with respect to the research questions. This study is conducted over three phases where each phase is focused on collecting data related to each research question.

In phase one, archival data are collected from a variety of secondary sources, such as industry journals, reports and Internet websites. These techniques are used to establish a breadth of data in order to describe the situational factors and structures of AMCs and to establish levels of comparability within and between AMCs in different countries. The archival data collected in phase one also provides in-depth material that
is used to develop thin case studies of individual organisations. From these background data, a database of organisations and individuals was also assembled as a potential survey sample.

The second phase of this research employed a survey instrument that was distributed to the sample population identified in either an electronic or paper format. The survey generated data that were analysed to develop a profile of clinical research management structures, tasks and practices in the identified sample of AMCs. The survey also explored the perceptions of individuals with regard to factors critical to the management of clinical research.

In the final phase, in-depth data is collected to primarily address the third research question and to confirm the findings from the previous two phases.

**Figure 1.1**

**Overall Research Design**

- **Phase One**
- **Phase Two**
- **Framing Research Question**
- **Collection of Background Data**
- **Collection of Data from Respondents**
- **Primary Data Analysis**
- **Summary of Results**
- **General Categories**
  - Managerial Tasks
  - Environment
  - Structures
1.8. **Scheme of the thesis**

The body of this thesis is organised under seven chapter headings, with a separate appendix containing references, raw data and diagrammatic analyses.

Chapter one presents an overview of the theoretical and conceptual background, the development of research questions, and the research framework behind the research.

Chapter two discusses the literature with respect to the relationship between environment and organisational structures, and between formal and informal
organisational structures. With respect to the latter, literature in the field of professional management is also reviewed. This literature provides a theoretical framework for the application to the three research questions, which relate to these three general areas of study. The literature also provides examples of research methodologies employed in the study of organisations.

Chapter three discusses the methodological issues associated with researching organisations and presents a methodological strategy for addressing the research questions along with a description of the survey instrument development process.

Chapter four provides an outlook of the secondary data collected from the institutions under the purview of the current research and formed the base for data collection in phase two of the research. The findings from this phase are discussed with respect to the research questions and their application to the second phase of research.

Chapter five presents the results from the survey and concludes with a composite analysis of the study findings.

Chapter six provides some excerpts from the interviews conducted with key respondents who could spare time with the researcher.

The conclusions and implications of this study with respect to the research aims and questions are presented in chapter seven, where the findings are discussed in relation to the theoretical frameworks developed in chapter three.
The appendix includes the survey instrument (appendix A), the Interview checklist (appendix B) and References (appendix C).

The following chapter presents an elaboration of review of literature that encompasses the three research questions.