CLINICAL TRIALS' BOTTLENECKS AS CRITICAL IMPEDIMENT TO TRANSLATIONAL MEDICINE

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INTRODUCTION

Translational medicine has made impact and have come to be accepted (Dai, et al., 2013) as a global medical strategy for improving Medicare such that, funding of translational medicine globally has increased, it is treated with priority and many institutes for translational studies have been established, (Zhang, 2012). Demonstrating this critical significance of translational medicine to modern medical practice is the emphasis by the World Medical Association (WMA Ethics Manual, 2009), that 'physicians must know how to interpret research results and apply them to patients'.

However, as noted by Zerhouni, (2007) and Qian et al., (2012), a lot remains to be understood and lessons need to be learned on the best strategies for translational medicine which may not be unconnected with observed issues of clinical research bottlenecks. Mankoff, et al., (2004), had earlier identified "three major obstacles to effective translational medicine". The first two revolves around the subject of clinical research; – "the challenge of translating basic science discoveries into clinical studies", and "the translation of clinical studies into medical practice and health care policy". This second issues hinges on the core challenges of the practical conduct of clinical research. Sung, et al., (2003) opined that the two "translational blocks can be removed only by the collaborative efforts of multiple system stakeholders"

Essential for research translation is data generated from clinical research. Clinical trials operations require cooperation among a diverse group of stakeholders including research sponsors (industry, academia, government, non-profit organizations, and patient advocates), clinical investigators, patients, funders, physicians, and regulators. This was aptly captured by Dai, et al., (2013), who noted that "enormous collaborative and multidisciplinary work is required prior to when the results of scientific research can be translated into effective clinical practice". Each stakeholder offers a different set of tools to support the essential components of a clinical trial. These resources form the infrastructure that currently supports clinical research (English, et al., 2010). Time, money, personnel, materials (e.g., medical supplies), support

systems (ICT as well as manpower), and a clear plan for completing the necessary steps in a trial are all part of the clinical research infrastructure.

Significant time, energy, and money from the different collaborators are spent on bringing the disparate resources together. Because these resources are not streamlined, clinical trials infrastructure pose challenges to investigators working on new research questions and most times must start afresh without drawing on existing resources. This imminent lack of harmony and disparate clinical research resources imposes bottlenecks that constitute impediments on the planning, execution and outcome of research which by implication either slow down or prevent translation outright.

CLINICAL TRIAL BOTTLENECKS

The main bottlenecks which borders on broad systemic issues in clinical trial organisation can be broadly classified under the technicalities of research itself, medical practice and trial site conditionality. Specifically these include:

- ✓ Defining clinical research questions in order of priority,
- ✓ Identifying gap between clinical trials and medical practice
- ✓ Meeting up with the modern reality of global sitting of clinical trials.
- ✓ Satisfying regulatory conditions

The others areas centres on the logistics of conducting clinical trials such as financing and research incentives to trial subjects and researchers of various categories. These later challenges become obvious if we consider the dwindling expert in clinical trials across the globe in the face of increasing need to acquire evidence bases for use of medical interventions, the intricacies of clinical trial administration in the light of non-uniform regulatory requirement across the globe and the ever increasing difficulty of recruiting trial subjects to participate in studies.

DEFINING CLINICAL RESEARCH QUESTIONS IN ORDER OF PRIORITY

The Institute of Medicine in its publication, (IOM, 2007), observed that research grant peer review was conservative and not usually awarded to innovative ideas in subject areas with minimal scientific knowledge even though recognising that less than half of all the medical treatments delivered today is evidence based. The implication of this attitude to clinical research is the fact that there is serious knowledge gap such that new research lacks the necessary prior research outcomes to base its hypothetical framework. This become clearer if we consider that to formulate relevant innovative research hypotheses, it is critical and important to focus potential research questions on day-to-day clinical experience with patients rather than on the interest of the pharmaceutical industries on:

- ✓ Gaining regulatory approval

- ✓ Obtaining market authorisation for new drugs or its new indication

Trial designs satisfying these simple criteria have too narrow objectives to provide the needed and most convincing evidence on the drug's benefits and risks required for translation.

IDENTIFYING GAP BETWEEN CLINICAL TRIALS AND MEDICAL PRACTICE

The critical role of translational medicine is to bridge the gap between research and medical practice and this is a critical goal of clinical trials. To conduct relevant clinical trials meeting the demand of medical practice, clinical practice should actively participate in the trial process. It is widely observed that research questions and protocol design falls short of meeting the required context of clinical practice hence its outcome might not be easily incorporated into clinical practice.

The institute of medicine notes that there is limited involvement of community practice physicians in clinical trials hence a reduction of patient referrals by physicians to participate in clinical trials. This also contributes to lessening the volume of trial experts and experience. Also, research findings from academic medical centers are less likely to be adopted by doctors in daily medical practice. This is reflected in the study by McGlynn et al., (2003), in which adherence to 439 indicators of health care quality for 30 acute and chronic conditions and preventive care were examined. Results indicated that American adults receive on average of only 54.9 percent of recommended care (McGlynn et al., 2003). Inability to translate trial outcome to clinical practice is an obstacle to further clinically demanded trial.

The specific nature of the issues surrounding gaps between clinical trials and medical practice could be categorised as challenges facing:

a) Investigators in Academic Health Centres

b) Community Physicians

c) Patients

A. CHALLENGES FACING INVESTIGATORS IN ACADEMIC HEALTH CENTRES

Such challenges include funding, satisfying established Institutional Review Board's (IRB) appraisal system and obtaining their approvals, undergoing multiple review cycles, fulfilling essential conditions for the establishment of clinical trials and material transfer agreements between sponsors and the academic medical centres, patients recruitment challenges, administration of informed consent agreements, obtaining and complying with research timeframe in line with medical school timelines, and other associated works.

Califf, (2009), identified the following as challenges which could be faced by clinical researchers:

- Time and financial demands;
- Shortage of specific diseases specialists;
- Complexity of regulatory conditions and climate;
- Complexity of contracts;
- Lack of local supportive infrastructure;
- Inadequate research training;
- Less enjoyment from participation (e.g., increasing business aspects, contract research organization pressures); and
- Data collection challenges (medical records, reimbursement, quality control, pay for performance).

B. CHALLENGES CONFRONTING COMMUNITY PHYSICIANS

Physicians in community practices face challenges of busy patient consultation, billing and reporting which is time consuming and constrains their research capacity. Most community practice centres lack clinical research infrastructure and is financially and administratively non-supportive of research.

C. CHALLENGES FACING PATIENTS

A core function of a successful clinical trial is finding patients who fit the predetermined eligibility criteria and getting them to participate. The issues that affect patient enrolment in trials can vary according to features of the disease. Patients are often unaware of, or it may be difficult for them to locate clinical trials to which they may be eligible for. When they are aware of such trials, the challenge may be their living far away from study site leading to significant travel costs and time loss hindering their participation.

Also, Patients' preconceived notions about trial participation could pose a barrier to clinical trial enrolment. The socio-economic status, education, access to health care services and the network of social support patients have affect their connection to the medical system and their interest in clinical research.

Patients may also be hindered by eligibility criteria excluding them on various grounds such as age, concomitant diseases, use of some concomitant drugs or advancement of disease etc. Informed consent procedures could constitute a bottleneck or patient may not adequately trust motives of trial researchers enough to be willing to enrol even though desirous of the benefit. When patient recruitment is impeded, the trial is delayed, sometimes by years, until the number

of patients required by the study protocol can be enrolled. Patient enrolment directly affect trials output.

MEETING UP TO THE MODERN REALITY OF GLOBAL SITTING OF CLINICAL TRIALS

The increasing trend towards conducting clinical trials globally means that regulatory agencies question the extent to which the results can be translated to local clinical practice. The applicability of foreign trials results depends on the disease being studied and the state of current clinical practice in that area. There is also the issue of the time it takes to bring the trial site into regulatory compliance. Aban et al. (2008), reported that "the mean time for non- U.S. centers to achieve regulatory approval was significantly longer (mean 13.4 ± 0.96 months) than for U.S. sites (9.67 ± 0.74 months; $p = 0.003$, t-test)".

English, et al., (2010) in paraphrasing Califf, (2009), indicated that "the difficulties inherent in conducting clinical trials in the United States have contributed to the relative decline of clinical trials in U.S". Califf further opined that while globalization has an overall positive trend for clinical trials, it is unsustainable. The overall cost associated with gathering the necessary resources to conduct a clinical trial is an important factor in the choice of a trial site. In India and many other countries, the charges to clinical trial sponsors for conducting a clinical trial with physician involvement are lower than they would be in the United States. However, would multicentre trials in these places be acceptable to the U.S. FDA?

❖ Cost of Clinical Trials

Clinical trial costs can vary widely depending on the number of patients, the number and location of research sites, the nature of the trial protocol, and the reimbursement provided to investigators. English, et al., (2010) suggest that the total cost can be between $300−$600 million to implement, conduct, and monitor a large multicenter trial to completion.

❖ Incentives for Participation in Clinical Trials

Private practice physicians have disincentives to refer their patients to clinical trials. The fewer physicians are involved in developing and implementing clinical trials, the less scientific the practice of medicine will be. Participation of Community-based physicians in clinical trials have a positive effect on patient recruitment; engagement of community in research; and influence change in practice behaviour by physicians and strengthen the trend toward evidence-based medicine.

❖ Shrinking Clinical Research Workforce

Research involving human subjects has become an increasingly complex environment in which to work and be successful. The clinical investigator workforce is plagued by high

turnover. Lane (2009), indicate that the overall decrease in intramural investigators is due in part to the fact that more researchers are turning to laboratory work because publishing results from this work is easier, and the difficulties of getting a clinical trial protocol approved can be avoided.

Many trials teams are constituted as need arises since future trials are not foreseen. The implication of this is that the trial team is trained onsite and not based on previous experience hence leading to variation in trial execution across sites and sometimes variation in data outcome. There is hardly a trial expert whose full time responsibility is to plan and ensure successful execution of specific trials hence such variations are expected. Califf, (2009), noted that clinical investigators are often not supported by their academic institutions and are left largely to their own devices to design a trial and gather the necessary resources. Califf (2009), further explained that, while investigators who are leading large, multisite trials predicted to have a major impact on clinical practice enjoy respect, this is not the case for those conducting less visible work or just starting out in their research careers.

BOTTLENECKS POSED BY REGULATORY PROCEDURES

The internal requirements of an academic institution, regulatory agency, or pharmaceutical company for reviewing multiple aspects of a clinical trial can significantly delay its initiation. When academic institutions conduct clinical trials for industry sponsors such as a pharmaceutical company, or a federal agent like the NIH or FDA, the internal review processes of both organizations are usually involved. In addition to such internal requirements, other state regulatory requirements affect the conduct of the trials. Adhering to these many requirements constitute significant challenges and bottlenecks for investigators. Such bottlenecks, delays and lost time constitute added cost of trial and decrease overall trial efficiency.

INSTITUTIONAL REVIEW BOARD APPROVAL

According to Lane's survey of intramural NIH investigators (Lane, 2009), the top four barriers to clinical research are:

- Ethical/IRB approval,
- Scientific review/protocol approval,
- Interaction with industry and issues with technology transfer, and
- Adequacy of resources.

He further noted that there is often a lack of clarity among investigators regarding the roles and responsibilities of different oversight bodies. Investigators often do not know or understand what the IRB expects of them, and the IRB decision-making process can be lacking in timeliness and

accountability. A key concern is that IRBs are accountable only to their own institution and not to the greater public good.

Because multiple IRB approvals are required for most large, multisite clinical trials, in-consistencies in IRB determinations and standards complicate and delay the process of conducting a clinical trial and can inhibit the ability of investigators to implement the same trial protocol across all study sites and this is a critical factor for developing valid trial results.

INFORMED CONSENT PROCESS

The process of documenting the education of trial subjects on the details of a clinical trial and potentially gaining their consent to participate in the study requires a significant amount of time. This is because, informed consent is central to human subject protection in clinical research, Beauchamp and Childress, (1996) and as variously stipulated by the various regulatory guidelines such as The Belmont Report; 45 CFR §46.111(a)(4); The Nuremberg Code, (JAMA. 1996;276:1691). The informed consent process includes developing appropriately worded consent documents, discussing the documents and the clinical trial process with individual patients, obtaining the required patient signatures on the documents, and keeping track of the paperwork generated throughout the enrolment process.

TIME FROM PROTOCOL APPROVAL TO TRIAL

Lane (2009), noted that many bottlenecks arise internally and are imposed by institutions that are home to the research workforce. Because clinical research relies on substantial human effort that incurs large labour costs, the timeline for a clinical trial affects overall cost. DiMasi et al., (2003) estimated that in 2000, the average cost to develop a new drug was $802 million, and time costs associated with the length of research and development accounted for half of this cost.

Years can elapse from the time researchers begin talking about a study idea to the point at which they assemble the appropriate investigators, develop collaborations, establish study sites, and initiate the trial. For the pharmaceutical industry, protracted timelines increase cost and reduce revenue as medications typically have a finite life before losing patent protection and creating an opportunity for generic competitors. Moreover, when a trial addresses a question important for medical practice, increasing the time it takes to obtain an answer can reduce the impact of the results.

CASE REPORT FORMS

Collecting data for each participant in a clinical trial efficiently and accurately and according to the study objectives is essential for regulatory compliance, as well as the success of the research effort. The Case Report Form (CRF) is the tool used by investigators to collect patient information throughout a clinical trial. A portion of the monitoring costs for a trial is directly linked to the complexity of the CRF developed for that trial. Complex CRFs with many data

points are more expensive to monitor than simpler CRFs. Also, the lack of standardized CRFs and trial procedures can create chaos in the study sites. Another problem is the failure of sites to conduct critical study procedures correctly or poor entry of data required in the study protocol due to poor understanding of the protocol this could lead to morbid and poor data quality.

CONCLUSION

Translational medicine, a research dissemination tool for advancing gains of basic laboratory discoveries to populations via clinical trials, has made impact and have come to be accepted (Dai, et al., 2013) as a global evidence based medical strategy for improving Medicare such that, funding of translational medicine globally has increased, it is treated with priority and many institutes for translational studies have been established, Zhang (2012) and the World Medical Association (WMA Ethics Manual, 2009), insist that 'physicians must know how to interpret research results and apply them to patients'. According to Sun, et al., (2011), translational medicine takes data from laboratory to bedside. Evidence Based Medicine (EBM) thus exploits translational research as tool to facilitate scientific investigation into clinical practice.

Clinical researchers across the globe have adopted wide variety of approach in conducting translational research in response to this emphasis. However, clinical research bottlenecks appear to impede the very purpose for conducting research in the first place. Because these resources are not streamlined, clinical trials infrastructure pose challenges to investigators working on new research questions. This imminent lack of harmony and disparate clinical research resources imposes bottlenecks that constitute impediments on the planning, execution and outcome of research which by implication either slow down or prevent translation outright.

The bottlenecks borders on broad systemic issues in clinical trial organisation broadly classified under the technicalities of research itself, clinical practice and trial site conditionality. It is essential to address these bottlenecks in other to adequately reap the benefits of translation from clinical research.

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