Quality Assurance in Neuroscience Research Lab

Neuroscience Research Lab, Department of Neurology, PGIMER, Chandigarh, India

Foreword

The conventional system of running research labs in India was based on no established or uniform method of management relying on individual preferences and experiences. The much-needed quality practices could not be established for a long time in India which resulted in an unorganized data recording and less credible scientific data.

The quest for implementation of such practices led by Neuroscience Research Lab headed by **Dr. Akshay Anand** which for the first time redefined the basic research investigations backed by quality benchmarks. This unique implementation required sustained training of human resources who along with their basic research also practiced Good lab practices, hitherto used in the clinical trial agencies. The team led by Dr. Anand got the support from various distinguished people including **Dr. Sudhir Srivastava, Dr. Sadashivan Pillai**, who periodically trained the researchers.

The development and implementation of such practice in research laboratories require dissemination of knowledge from the established laboratories. Policy changes are also required in the medical as well as basic research institutions to include the Quality Assurance training in the existing curriculum. This module also attracted the institutions such as **quality council of India (QCI)** who also recognized these efforts.

This book compiles the knowledge and experience on benchmarking of basic research investigations under the purview of GLP framework.

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Rahul Tyagi, Ph.D.
Alumni, Neuroscience Research Lab.

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QCI – D. L. Shah Quality Awards-2016

SILVER AWARD

Presented to

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Hari K. Taneja
Trustee, D.L. Shah Trust

R. P. Singh
Secretary General, QCI

Date : 20 August 2016

QCI

D. L. SHAH TRUST
FOR APPLIED SCIENCE, TECHNOLOGY, ARTS & PHILOSOPHY

QCI – D. L. Shah Quality Awards 2014

National Award for Research Services

9th National Quality Conclave

Presented to

Neuroscience Research Lab, PGIMER, Chandigarh

for the case study

Redefining Quality standards in basic research investigations by broadening the purview of Good Laboratory Practices (GLP)

Hari K. Taneja
Trustee, D.L. Shah Trust

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Redefining Quality Standards in Basic Research Investigations by Broadening the Purview of GLP

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Keywords: Quality Research, GLP, IQ, OQ, PQ.

ABSTRACT

Good Laboratory Practices (GLP) has been developed to enhance quality standards, increase credibility, efficiency, transparency and productivity of *research settings*. Our research lab has improvised GLP concept to suit various ongoing research projects, even though none of these projects fall under the purview of GLP accreditation.

The system encourages goal driven, self proposed monthly master schedule of activities in consultation with the Study Director, using the combination of SOPs, DRSs and Master Schedule. The Quality Assurance (QA) conducts periodical audit of the progress, compliance and reproducibility of experiments. The data generated is filed in a defined format using a mandatory raw book, master code, calibrated instruments (with IQ, OQ, PQ), log sheets with continuously regulated infrastructure and room environment providing back up for each facility (including power outrage). This data and samples (if any) are archived in defined shelves or freezers as the case may be. This innovation has led to a system dependent technical and managerial procedures facilitating research audit control, document control, improving purchase and accounting procedures as well as human resource management besides delivery of patient care diagnostic services.

Such benchmarking seeks to fulfil the deficit in the publically funded Medical Institutes by modelling a self regulated and goal oriented quality system which can be followed by others in the country.

Introduction

Neuroscience Research Lab is an integral part of Department of Neurology, Post Graduate Institute of Medical Education and Research, Chandigarh. The mission of the lab is to pioneer therapies for retinal degeneration and dementia, acquire leadership in using invitro and invivo approaches for preclinical evaluation of drugs and biotherapeutics expand molecular diagnostic program for neurological disorders and train graduate students in latest cellular, molecular, electrophysiological and behavioural techniques. Genetic screening of neurological disorders and the risk factors, mouse models of degenerative disorders, manipulation of neural stem cells and molecular diagnosis are the major focus of the Lab.

GLP is a Quality Management System, the original product of OECD convention. Each testing facility innovates its own protocols and managerial processes to suit its activities and goals. The idea of implementing GLP in public funded medical institute, without the objective of seeking accreditation

is novel. GLP adds value to existing ecosystem of research and it also works as an enabler.

The conventional system of running research labs in India is based on no established or uniform method of management relying on individual preferences and experiences. Unfortunately, even the individual medical institutes do not define modules of running research facilities unless mandated by GMP (Good Manufacturing Practices) requirements defined by regulatory authorities. This happens in the case of clinical trials where patient's safety and care is involved. The ability to bring clinical level safety at the basic research investigation (pre-clinical) makes this innovation unique.

Thus aiming to improve and recognise quality in the basic research as well as assuring it through periodic review by Quality Assurance cell, this lab has created a culture of sustainable strategies to maintain the quality of research data. We have periodically improvised these strategies according to the required research conditions in consultation with the external auditors to suit our ongoing research projects.

This innovation seeks to fulfil the deficit in the Govt Departments including Medical Institutes which are devoid of self regulated and goal oriented quality systems in research programme run by public funded medical institutes in India. The implementation of this innovation rubbishes the widely prevalent lackadaisical approach in basic research in medical institutes. This system is run without any funding sources including PGIMER or any funding agencies.

Content

Good Laboratory Practices (GLP) has been developed to enhance quality standards, increase credibility, efficiency and transparency of testing facilities. In India, GLP accreditation is available under Department of Science and Technology, New Delhi for non research related studies. To the best of our knowledge, there is only one public funded Institute (NIPER) whose one project has been accredited to GLP for a certain scope of study. Our research lab has improvised GLP concept to suit all the ongoing research projects, even though none of these projects fall under the purview of GLP accreditation. In this manner our group has raised the bar by enhancing the quality output of biotechnology research projects, thus directly impacting PGIs research output and credibility of data generated.

Research oriented quality system was introduced to the research facility in the year 2007-2008, which is then periodically nourished by the continuous development. Timeline of Lab's development is depicted in **Figure 1**.

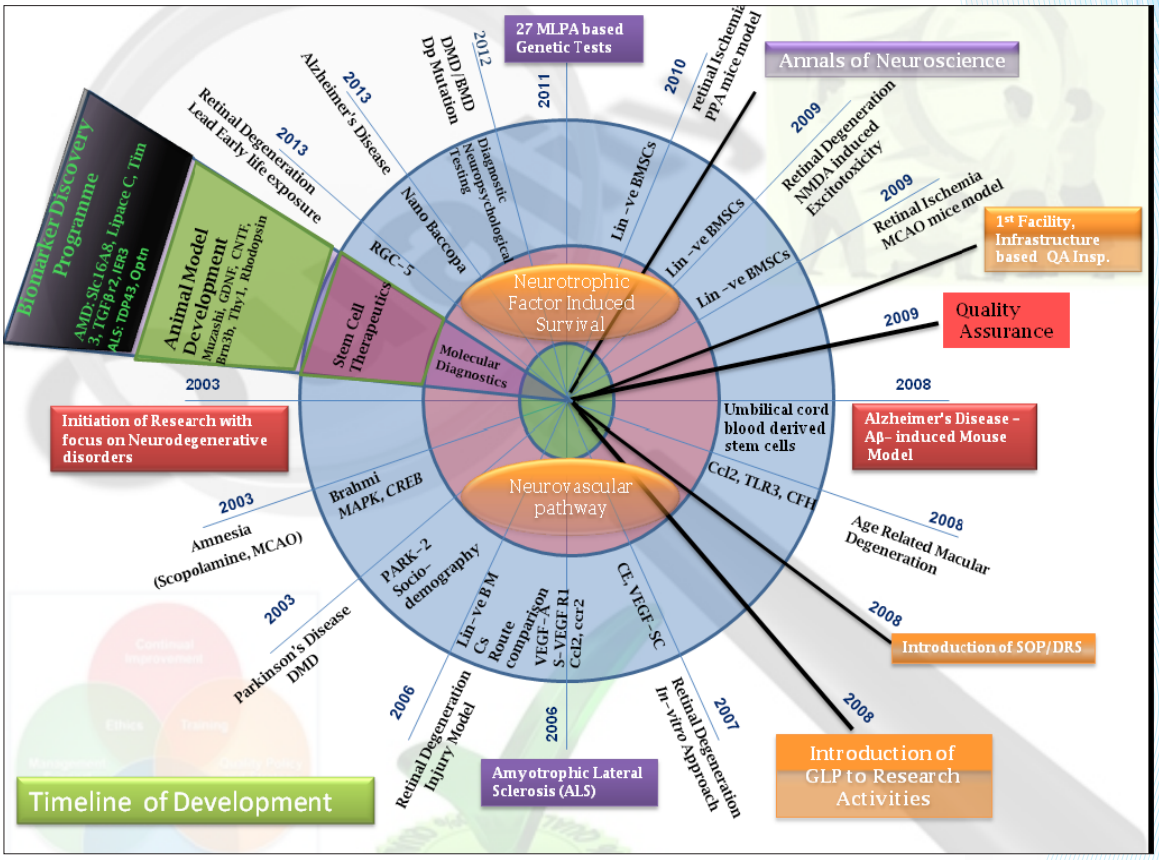

Figure 1: Showing Timeline of Lab's Development

Financial Benefits and Tangible Benefits

Implementation of this concept has led to benchmarking of research projects which are usually considered a soft activity in medical institutes of India, thereby enabling reliable translation of bench to clinic. This innovation has led to a system dependent technical and managerial procedures facilitating research data reproducibility, audit control, document control, improving purchase and accounting procedures and human resource management besides high quality delivery of patient care diagnostic services.

It is generally perceived that GLP accreditation results in enhanced confidence of CROs (Clinical Research Organizations) in launching transnational pre-clinical and clinical trials because of which GLP implementation has been limited to private organizations. Our implementation of GLP transcends the dynamics of profitability thereby redefining quality standards in basic research endeavours in public funded institutes, particularly medical institutions. This innovation of GLP is central theme of the larger research model and the strategy of the lab without which no basic research or diagnostic procedure is operationalized.

Impact of the Projects on Product/Services

Implementation of this innovation system caters to environment safety and saves contamination from hospital based research facility. Because waste management practices, fire safety, first aid are part of this system, it indirectly helps preserve the environment and health of research personnel. It helps in eliminating the hospital or research facility based contamination.

The Neuroscience Research Lab under the Department of Neurology has expanded and strengthened the molecular diagnostic services by introducing 27 advanced and novel genetic diagnostic tests based on MLPA-based genetic testing. The inventor of technologies Dr Jan Shouten from MRC, Holland had recently visited the research facility, sparking the launch of these tests. The commencement of these tests for various diseases including Dystonias, Muscular Dystrophy, Ataxias, Alzheimer's disease, Parkinson's disease, Retinitis Pigmentosa and AMD has also resulted in generation of rapid, accurate genetic information boosting studies defining the prevalence of genetic defects in the population in this region and benefiting hundreds of patients with new, advanced, accurate and affordable diagnosis.

Until now, these tests were available in private labs and hospitals in Delhi and Mumbai at exorbitant prices. But at the hospital, these tests cost half the price and also give accurate and reliable results under the quality assurance guidelines like:.

- Customer/Stakeholder Satisfaction
- Enhanced international discounts are being obtained by international vendors who also participate in other projects in this lab.
- Newly launched 27 advanced and novel MLPA-based genetic tests for diagnosing several neurodegenerative disorders has resulted in generation of rapid, accurate genetic information and gene defects in the population in this region thus benefiting hundreds of patients with new, advanced, accurate and affordable diagnosis.
- Social benefits (Poor patients are granted full waiver for the genetic testing facilities at our facility. Reports which are being generated from the lab ensure credibility and reliability because of stringent GLP module which strives towards attaining accurate results using appropriate internal auditing and proficiency testing).
- Scalability in terms of potential for growth & replication:

This innovation has great potential in both, basic research as well as clinical research in medical institutions. More research in this may lead to new models and legislations for implementation in the entire country. Since biomarker discovery programme is part of the patient related research, it has wider application for community. Community based research is also undertaken by including Geno-demography association.

The driving force of this innovation is its inherent sustainability while long term impacts include creation of innovation system thus enabling discovery, patents resulting in stimulus to knowledge economy.

Research staff is able to easily obtain attractive positions or training facilities around the world without confronting technology gap or changes in work environment. Additional research leadership positions and assignments that require quality output have been offered to lab PI. For example Editorship of one of the journals was awarded to Principal Investigator (PI) of this lab. More and more international scientists are enthusiastic in collaborating with this research facility for gene association studies or drug discovery programs.

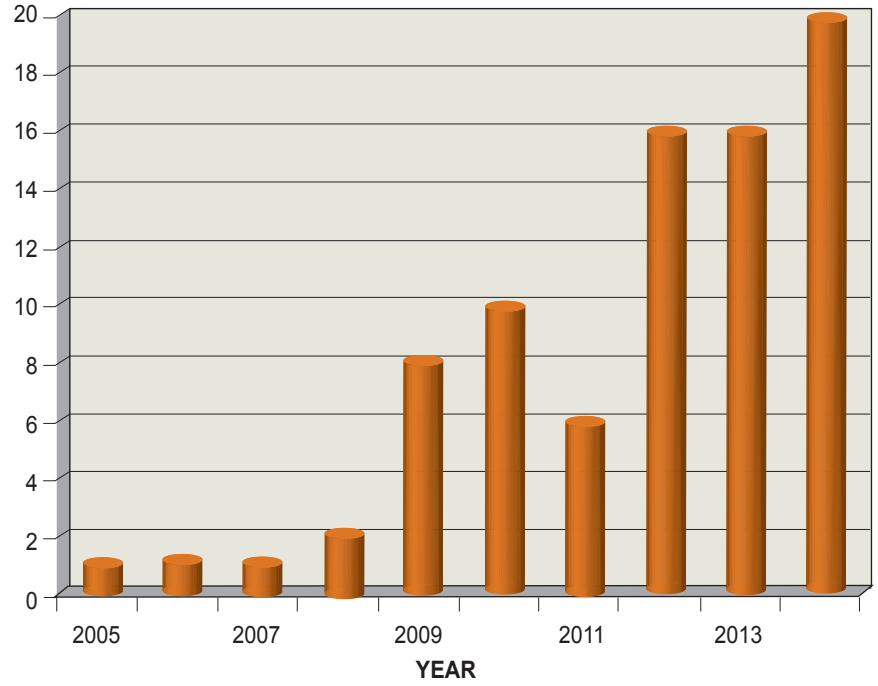

Figure 2: Showing Frequency of Published Paper Increased to One Paper per Month.

Diagnostic Approach

On Solving The Problem Including Tools Used Based Upon Factors Like (But Not Limited To)

- Methods of identifications of the problem
- Degree of efforts employed
- Tools used for identification
- Involvements of the people
- Collection of Data and analysis

Commitment

Neuroscience Research Lab is dedicated towards accuracy of the molecular diagnostic services for patient care. We are committed to providing research output and diagnostic services with international benchmarks.

Methods of Identifications of the Problem

The responsibilities for all the activities such as policy making, administrative, documentation and testing etc. are evenly distributed among the staff. The problems in all respects are identified by the concerned staff in that activity and document in the deviation sheet. It is also informed to the Study Director immediately and the concerned steps are taken to solve it and documented thereafter in structured sheets called Data Recording Sheets (DRS).

There is a three tier Problem Identification System involved in the study, at each level of staff personnel:

- Study Director
- QA Personnel
- Technical Staff/ In-life observer

The log sheets and log books maintained for the entire chemical, refrigerated reagents and all sophisticated instruments are used for documenting usage. These are useful for troubleshooting not only the technical problems but also in ensuing timely re-ordering and re-procuring.

Degree of Efforts Employed

A. Personnel are trained to acquire competence to perform the tests to ensure the credibility of results.

B. Minimum requirement for personnel is graduation/Post Graduation or/with adequate experience to perform the tests. Management maintains records of the relevant educational and professional qualifications, training and experience and competence of all personnel.

C. Laboratory personnel routinely undergo 6 months training on all the techniques and tests performed in the laboratory and special training from collaborator institute is arranged whenever required.

D. Personnel hold the certificates to prove the eligibility and competence to perform the tests. It is the sole discretion of the Study Director to appoint and select the competent personnel.

E. Duties and responsibilities to perform, validate and report the tests are defined by job descriptions for the staff to maintain the quality of results.

F. Study Director is involved in Policy Making, Professional Decision Making, Planning, for Scientific and Advisory Implications.

G. QA is an independent authority under the purview of Study Director.

H. Personnel involved in Quality Assurance have the responsibility of document control, periodic review which includes personnel, facility, and study based inspections.

Tools Used for Identification

We have created our Quality Control Location where all the documents are issued, verified, stored and re-issued whenever necessary. Any deviation from the standard operating procedure is immediately documented in our data recording sheet and brought to the notice of the QC personnel and Study director.

a) This innovation aims to enhance the reproducibility and error reporting of research data and bring quality system in research practices, thereby facilitating a higher sincerity of purpose for research in Medical Institutes in India.

b) This innovation also seeks to bridge the credibility chasm that exists between data generated from India and that from the West, because of which the best research from India is rarely patented or reproduced, the implementation of this innovation has led to more visible and tangible output of research funded by various funding agencies. The research papers provide enough data that shows this innovation has improved the credibility of data generated from a medical institute in India. This is expected to boost in new discovery and products by transforming the innovation landscape,

c) Installation of GLP compliant computers aided by live cams ensures optimal utilization of resources including document control. These are periodically monitored by computer as well VPN based smart phone access.

Involvement of the People

The responsibilities for all the activities such as documentation and testing etc. are evenly distributed among the staff. Study Director is the head of the facility reported by the QA personnel. People are free to provide their suggestions through suggestion boxes.

Collection of Data and Analysis

a. There are dully filled Informed Consent Forms, Patient Information Sheets and Questionnaire for Documentation, duly signed by the patients. In case of minors, the consent forms are signed by the guardians. Electronic Entries, Palm Photographs are documented for future research use.

b. Consent Forms are duly attested by a third party witness, physicians involved and Principal Investigators on the same day.

c. Patient information sheets are signed by the participant and a copy is provided to them.

d. The above documents are piled together with the requisition form and the receipt.

e. Sample arrival, processing and report dispatch status are traceable from the register.

f. Patient records are kept in the cabinets systematically and archived whenever required.

g. Electronic data is kept in the secured domains of server based networking system installed at Neuroscience Research Lab.

h. There is online entry and reporting of the patient samples through **'e - sushrut'**, PGIMER's online **Patient Information System** with two stage validation of reports.

Experimental Documentation

a. All the experiments are preceded by approved Standard Operating Procedures (SOPs) and intervened by approved Data Recording Sheets (DRSs).

b. Experimental usage of consumables and instruments are documented in the respective log sheets.

Methodology adopted for arriving at solution including its validation based upon factors like (but not limited to):

- Planning approach to solving the problem
- Extent of Quality Tools used
- Degree of Data collection and analysis
- Involvements of the people
- Testing of the outcome
- Systematization of the benefits

Planning Approach to Solving the Problem

Policy

There is an existing laboratory's policy on corrective action when nonconforming work or departures from policies and procedures in the management system or technical operations are identified.

Responsibility

There is one in life observer responsible for planning, implementing and monitoring appropriate corrective action for individual instruments and administrative duties. The in Life observer is solely responsible for maintenance, calibration, breakdown and their proper reporting/Documentation for individual instruments.

For procedural/technical errors, the experimenter is responsible for proper reporting and documentation. The QA personnel reports this to the Management and any deviation or amendments in the protocols is finalized after thorough discussion between experimenter, QA personnel and the Management.

Procedure

A. Sources of Information for Identification of Problems:

For every single procedure there is an inbuilt SOP, DRS and Rawbook available. Any experimental procedure performed in the laboratory thoroughly adheres to respective SOP and properly documented in its respective DRS and Rawbook. Any deviation is reported in DRS as well as raw book which could be the source of information for identification of problems.

For every single instrument there is a logbook, instruction sheet and equipment maintenance file available and each instrument has a back up in the lab. Any experimental procedure performed through these instruments in the laboratory is thoroughly followed through their respective instruction sheets. Any deviation is reported in the log book as well as instrument maintenance file which could be the source of information for identification of problems.

B. Cause Analysis

Source of information for identification of problems is discussed among the experimenter, QA personnel and the Management to evaluate the cause of deviation and is documented in respective DRS and equipment maintenance file.

C. Selection and Implementation of Corrective Actions

It is the sole responsibility of management to select the corrective action according to the type of deviation and it is implemented by the experimenter or In-life observer. The corrective measure is also documented respectively and informed to the QA personnel.

D. Monitoring of Corrective Actions

Corrective actions are monitored through respective log sheets, maintenance sheets and through periodical QA reviews. If the deviation is still not rectified, it is documented and immediately reported to the QA personnel and Management.

E. Additional Audits Where Non-conformities/Departures Cast Doubt.

1. Additional audits for instruments are performed by periodical calibrations and preventive maintenance.
2. Study based auditing is performed in three layers of inspections:
   a. Weekly inspection by the in Life observer/experimenter.
   b. Monthly QA review of study based, infrastructure based and personnel based inspections.
   c. Monthly inspection by the Management.

Test Methods and Calibration

1. Test method is selected from the standard international references widely in practice or already existing validated standard operating procedures (SOPs).
2. Instrument calibrations are performed by certified organisations from government authority in annual basis.
3. All outsourced test methods are performed in a certified organisation.
4. Sustainability of the project application
   - Sustainability of the results
   - Involvement of people

   A. The driving force of this innovation is its inherent sustainability while long term impacts include creation of innovation system thus enabling discovery, patents resulting in stimulus to knowledge economy.

   B. The short term risks arising from implementation:

      i. Time that is spent in establishing the system could be discouraging for new investigators and research personnel.

      ii. Potential errors emanating from research investigators cannot be masked and can therefore be a risk for less serious investigators who treat research casually.

      iii. Research workers may find the documentation difficult in their day to day research experiments.

Formats

A. SOP for Thesis Writing

Restricted Circulation **Photocopying Prohibited**

STANDARD OPERATING PROCEDURE

Title: SOP FOR PhD THESIS WRITING				
SOP No.	Edition No.	Effective Date	Review Date	Document Controller (Signature/Stamp)
Copy No.	Date of Issue	Location (Unit/Division)		

SOP for PhD thesis writing

1. 3 copies of bound thesis to be submitted in Training Branch. These copies should not contain signed certificates; instead they should be separately submitted.
2. Thesis should be submitted to the Guide and Co-guides for corrections at least 2 months before the submission deadline.
3. Copies of thesis: 3 copies to Training Branch to be dispatched to external examiners, 1 copy each for guide and co-guides and one personal copy. Generally external examiners return the copy to the institute during viva-voce and these copies are submitted to institute library.

B. SOP for Purchase of Equipment Between 15-50 Lacs

Restricted Circulation **Photocopying Prohibited**

STANDARD OPERATING PROCEDURE: PURCHASE OF EQUIPMENT BETWEEN 15-50 LACS

Title: CTC-B/PRIVATE GRANT (PURCHASE Between 15 to 50 Lacs) EQUIPMENT IMPORT/INDIGENOUS				
SOP No.	Edition No.	Effective Date	Review Date	Document Controller (Signature/Stamp)
Copy No.	Date of Issue	Location (Unit/Division)		

*Note: Case more than 10 Lacs will be sent as a tender and vatting step will be excluded from the list

Purchase of equipment beetween 15 Lacs to 50 Lacs would require following steps:

1. **Identifying the item to be purchased.**
2. **Preparing the technical specifications**
3. **Agenda preparing**

Discussion

This innovation has great potential in both basic research as well as clinical research in medical institutions. More research in this may lead to new models and legislations for implementation in the entire country. Since biomarker discovery programme is part of the patient related research, it has wider application for community. Community based research is also undertaken by including geno-demography association studies.

The implementation of the innovation has led to highly cited research papers, grants and even attracted the MPLADS from Local MP.

Implementation of this innovation system caters to environment safety and saves contamination from hospital based research lab. Because waste management practices, fire safety, first aid are part of this system, it indirectly helps preserve the environment and health of research personnel. It helps in eliminating the hospital or research facility based contamination.

The innovation has drastically helped in reducing the research costs and significantly increased the efficiency of Neuroscience Research Lab. These costs have been reduced because of the inherent planning, visibility of available biologicals through log sheets and real time inventories.

Periodical calibration and availability of backup instruments have resulted in fewer breakdowns and lower electricity dues.

The archiving facility coupled with Quality Assurance programme has allowed maintainability of important records and samples, thus reducing the time of both the research personnel as well as patients.

These costs have a direct bearing for the future course of translational outcome. Costs are also saved due to monitoring of log sheets of expensive biologicals. The innovation system greatly enables zeroing to the source of errors thus enhancing the efficiency. It is difficult to provide the proportion of cost or research expenses which may have resulted due to this innovation.

This system ensures back traceability of data, in a format which is auditable, achievable, reliable and reproducible. Implementation of this concept incorporates generation of Standard Operating Procedures (SOPs) for each methodology (whether technical or administrative) which are audited and followed by research personnel at the behest of quality assurance or document controller, who also regulates adherence and compliance to SOP in a periodic fashion. This is done through the control of Data Recording Sheets (DRSs) for respective research personnel without which no experiment can start.

The system encourages goal driven, self proposed monthly master schedule of activities in consultation with the study director, using the combination of SOPs, DRSs and Master Schedule. The Quality Assurance (QA) conducts periodical audit of the progress, compliance and reproducibility of experiments. The data generated is filed in a defined format using a mandatory raw book, master code, calibrated instruments (with IQ, OQ, PQ), log sheets with continuously regulated infrastructure and room environment providing back up for each facility (including power outrage). This data and samples (if any) are archived in defined shelves or freezers as the case may be.

The entire system operates under a moral obligation for biannual external audit by senior quality assurance expert. This innovation encompasses periodic training of research personnel and staff to not only engage in academic activities but also bio waste management, sanitation, fire extinguisher safety, animal handling, and development of *IQ (Intelligence quotient), SQ (Spiritual quotient), EQ (Emotional quotient)*, through periodic orientations which is essential for mentoring of independent neuroscience leaders for tomorrow. This system does not exist in any research or medical institute funded by the government of India.

This innovation aims to enhance the reproducibility and error reporting of research data and bring quality system in research practices, thereby facilitating a higher sincerity of purpose for research in Medical Institutes in India. It also seeks to bridge the credibility chasm that exists between data generated from India and that from the West, because of which the best research from India is rarely taken seriously, the implementation of this innovation has led to more visible and tangible output of research funded by various funding agencies. The various research papers provide enough data that shows this innovation has improved the credibility of data generated from a medical institute in India. This is expected to boost the new discovery and products by transforming the innovation landscape.

Conclusion

Modified GLP module has found to be effective to safeguard the accountability, back traceability of the research data and management of human resources. We are striving to create a module which can be followed by other basic research facility in India. New Policies can be formulated for the basic research settings using our quality module in this country.

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Editorial

Policy research into Quality Assessment of Published Data from Medical Institutes Can Increase the Authenticity of Translation

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SAGE

Saurabh Kumar[1], Priya Mehra[1], and Akshay Anand[1]

Scientific misconduct in basic and clinical research is increasingly being reported at an alarming rate.[1] According to a study, more than 40% of the researchers that were surveyed were aware of the malpractice but they did not report it. Similarly, a study conducted by Sheehan et al in 2005 reported that 17% authors of clinical trials were aware about their fabricated data.[2] India stands third in queue in terms of highest number of publications after the USA and China.[3] But, it is embarrassing that many scientific researchers have fraudulent publications, and this is supported by huge number of recent cases. It is reported that several papers published in reputed journals contained duplicate, fabricated, or reused images. As of now there are 980 manuscripts from India that have been retracted, out of which 33% was due to plagiarism, and in 13% of the cases image duplication or fabrication was seen[4]; there were very few out of genuine quest for authorship. According to a report published in *Nature India*, most of the retracted cases in 2017 were reported from India.[4] Recently in 2019, we witnessed about 130 papers published by researchers from CSIR-Indian Institute of Toxicology of Research, Lucknow, which were found to be problematic. Similarly, 31 publications from Central Drug Research Institute, Lucknow, while 35 papers from Bose Institute, Kolkata, were found to be duplicate or manipulated.[5] In some cases, it has been seen that the published work was not approved by the ethical committees. Therefore, the key question is: Why this is happening? What is the need of research misconduct?

Most research labs funded by different funding agencies (DST, DBT, CSIR, ICMR, AYUSH, DAE, etc.) do not maintain raw data after research work is over. In order to overcome these drawbacks, a policy research can be initiated in different Institutes across the country that can validate (a) whether the published work contains ethical clearance statement from the respective ethical committees (clinical trial registered on CTRI), (b) whether the published work is plagiarized or not, (c) whether the results from various funding agencies projects have been acknowledged in the published manuscripts, (d) whether the published graphs and tables in the manuscripts match with the raw data available. Files/raw data and other project-related work can be reviewed. Editors of the journals can be approached to provide the details of the published work by contacting the academies who run these journals. Additionally, whether the bench work has been carried out according to the Good Laboratory Practice (GLP) guidelines or not can also be assessed.[6]

At the institution level, there are various rules and guidelines for responsible conduct of research.[7] This includes ethical orientation and guidance for researcher, instituting plagiarism check before submission, availability of data in the repository system, supervision of research being conducted, data ownership, data retention, and long-term storage in the form of e-copy besides early reporting of any such misconduct, etc. Besides, an assessment of whether administrative actions have been taken by the host parent institute or not can also be documented. This may include retraction of all the published articles, suspension, removal from the particular project, ban on getting future projects or strict supervision on other projects, ban from any future publications, probation, and termination from the Institute. Besides this, the publishing journal itself has strict guidelines (retraction of article, ban from future publication, penalty, etc.) to counter any such misconduct. Despite of having these strict guidelines, there is a lack of nationally organized framework for handling scientific misconduct which makes basic and clinical/ scientific research more susceptible in medical institutes than anywhere else. It is important that the research being

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conducted poses some benefits to the mankind. Therefore, it is important for us to follow GLPs. Any malpractice not only affects those that are directly involved but also poses a threat to science and technology, and humanity in general.

The solution to any such scientific misconduct is the urgent need for quality control. A quality policy at the institutional level is also required for doctoral programs. This can be achieved by introducing methods to render raw data auditable, back-traceable, and verifiable. In this way, efficient working environment can be created. This will enable efficient productivity and instill scientific temperament.[7] This study will enable the funding agency to implement or impose strict sanction on the PI or researcher that undertook such scientific misconduct. Financial benefits, reliable translation to the society, improved products and services are the outcomes of implementation of good research practices.[8] Based on the data generated from such policy research initiatives, funding decisions can be linked to mandatory implementation of GLP guidelines.[9]

Declaration of Conflicting Interests

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A UNIQUE DATA VALIDATION PROCESS BY INTERNAL AND EXTERNAL QUALITY ASSURANCE SYSTEM AIMED TO COMBAT RESEARCH MALPRACTICE.

Neurology

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ABSTRACT

Research fabrication and data fraud are one of the major concerns worldwide which are rising and evident from increasing number of retractions in peer reviewed Journals. If not checked, this can impact the reputation of a research organisation as well as the costs of translation of research data. In basic research extremely publicized cases of falsification of data have been reported and it is possible, that there are many unreported or undetected cases. In order to improve the quality standards, the validation processes were implemented for data quality at Neuroscience research lab in India for verifying PhD thesis results. Good Laboratory practices could be implicated in every research institute so that data impostures were prevented. We aimed to establish superior data quality by randomly verifying raw data in multiple projects funded by national agencies before publication of results at Neuroscience Research Lab.

KEYWORDS

Quality Research, GLP, Validation, Neuroscience, Intra-laboratory validation, Standard Operating Procedures, checklist.

1. INTRODUCTION

Since 1976, Good Laboratory Practices were implemented which determined to establish accurate documentation, quality check and undeviating data. GLP was introduced to monitor the compliance of non-clinical safety testing of drugs at first in the USA in order to regulate the generation of fraudulent data and unethical practices(Carson & Dent, 2007). GLP principles were formulated by Organisation of Economic Co-operation and Development [OECD] for global compliance of testing facilities(Kiranmai) but not research facilities.

The evidence based practice were soon acquiring a tremendous amount of significance in research based laboratories where cross sectional studies generate research data which remains non-validated even after publication, due to lack of routine checkups, recall of record maintenance etc. (Wassie, Zeleke, Dachew, & Kebede, 2017). Scientists believe that Good Clinical Laboratory Practice [CGLP] basically ensures compliance to the control of disastrous effects in the field of research and how to implement good science. On the contrary, these systems provide for an evidence based validation of studies to ensure the audit of data thus enhancing the transparency of work. However, in the last 60 years, Research and Development have gained many breakthroughs in instrumentation which may have a positive impact on quality and quantity of research (Jena & Chavan, 2017) as validation improves the scientific quality of data. The case of testing laboratories adopting the implementation of GLP results in the effectiveness of results thus making the patients more confident about the quality of the diagnostics and treatment (Horvath, 2013)

As mentioned above, the basic research investigations were never monitored by the GLP systems or any other alternative quality assurance module (Carson & Dent, 2007). Quality assurance is a challenging task for implementation in research ecosystem for developing countries because it requires consistency, manpower and resources without Institutional incentive for its implementation because the data duplication, plagiarism and cases of data theft are major factors which brought the research from developing countries under the radar. These factors partly prevented the research from developing countries to be published in reputed journals.

The Neuroscience Research Lab at PGIMER, Chandigarh, India [hereafter denoted as NRL] have voluntarily implemented GLP in basic research lab, hitherto never implemented in world, to meet the globally accepted quality standards and in order to bridge the chasm that exists between the quality systems in labs from developing and developed countries. The initial implementation included creation of validation documents, procedures and an independent review mechanism through a quality assurance unit in order to meet the quality requirements of research studies. As a result the facility was recognized by Quality Council of India [QCI] under Research category for this case study "Redefining Quality standard in basic research investigations by broadening the purview of Good Laboratory Practices" (Horvath, 2013) and later "Digital research lab for enhancing capability: Towards skill development and community outreach" (Neuroscience Research Lab & Medical Education and Research, 2016). The recognition of these systems has made it convenient to expand the systems and implement the tools for backtracing the data resulting in a PhD thesis, as a case study.

1.1 Requirement of Thesis validation:

Truthfulness and morality are basic principles of research. Adoption of these principles is important for the development of science and

community awareness. Any deviations from these ethics are considered fraud or scientific misconduct. We therefore, intended to extend the available GLP module for validation of compliance to data generation scheme of GLP including compilation processes, digitizated storage, data analysis, cost audit and publication through various procedures and modules (fig1). This is consistent with other corporate houses and certain testing labs(Paszko & Turner, 2001)

Equipment like autoclaves, pipettes, water bath, gel doc, microscopes, and refrigerators, PCRs were often validated for adherence to annual calibration and daily use entries as per established norms (Panel, 2012). Whether the process of experimental set up correlates with accurately labelled and periodically adopted Quality Assurance procedures by QA in-charge, was determined along with periodic audits in testing labs(Sickles, 1992). Similarly, the corresponding use of chemical and reagents sample log was verified with proper labelling of reagent bottle used for the purpose, like good labs(Cushman, Cornell, Howard, Bovill, & Tracy, 1995). The documentation of test facility was checked for accuracy. These were evidenced properly and quality assurance whose protocol has been approved by the Study Director.

2.METHODS

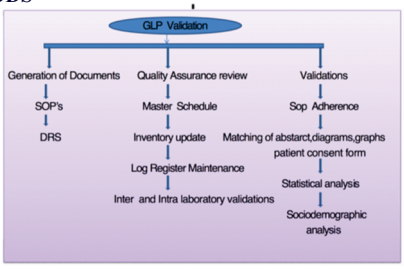


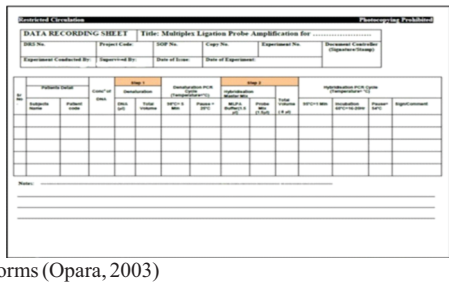
Fig 1.Flowchart showing the methods of research data validation

2.1.Validation of documents for Data Acquisition

The documents pertaining to data acquisition, verification and validation were prepared by the PhD students according to the Plan of Thesis, in consultation with the Study Director. The documents were got verified and finally submitted to the Quality Assurance cell(Hancock & Algozzine, 2016). These documents included Standard operating Procedures[SOPs] for each experiment, Data Recording sheets [DRSs] for all experiments, Raw Book, checklists, Monthly Master Schedules [MS] throughout the duration of PhD, Log registers of chemicals used in experiments, indexed PhD result folders, Sample logs for sample used, documents for inventory management, server storage records of digital data etc(Refaeilzadeh, Tang, & Liu, 2016)

2.1.1. DRS [Data Record Sheet]

Data recording sheets were filled for the real time documentation of correctness/deviations as per GLP rules (Haider, 2001) . DRS were issued through Quality Assurance [QA] cell for stipulated time duration. In the event of change in the experimental procedures, DRSs were modified with compliance to the QA approval. DRSs were coded as per master coding used in the established GLP module [fig 2]. These DRSs provided an important tool to verify and validate the experimental dates with chemical log sheets and the corresponding experiments. A typical DRS would contain the step by step information regarding the experimental protocol performed regularly/periodically at NRL [fig2]. The DRS also recorded the materials and equipment used in the experiment in order to maintain back traceability of the usage in their respective usage log books as per estab

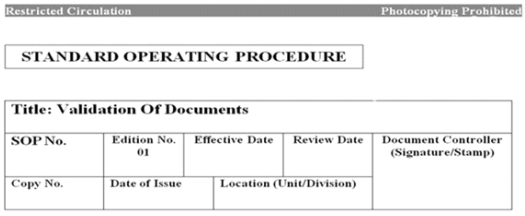


lished norms (Opara, 2003)

Fig.2 Data recording sheet

2.1.2. SOP's [Standard Operating Procedures]

Standard Operating Procedures were documented protocols and the backbone of Good Laboratory Practices. These were periodically used to work for maximum safety and operational efficiency and to reduce the chance of errors(Hartmann-Fritsch, Marino, & Reichmann, 2016) To validate the experiment protocols, the SOPs pertaining to the PhD Thesis plan [fig 3], were formulated by the researchers followed by validation by Study Director. SOPs, for thesis 1 including experimental [Morris water maze, cDNA and RNA synthesis, DNA isolation, ERG, Stem cell isolation, Laser Doppler, Immunohistochemistry, MLPA Plasma isolation, Tunnel assay etc.], academic [Journal club, DC, DDC, Seminar], SOP's for thesis 2 [SNP genotyping, ELISA, Total protein estimation [By Bradford method] linear range, Flow cytometry of mononuclear lymphocytes, DNA isolation, Separation of lymphocytes and serum] and administrative [Ethical clearance, ordering material, Joint grant requirements, accounts] procedures were formulated. Each SOP was master coded as per GLP module by the personnel of the Quality assurance cell. Format of SOP was obtained from SOP of SOPs.


Restricted Circulation Photocopying Prohibited

STANDARD OPERATING PROCEDURE

Title: Validation Of Documents				
SOP No.	Edition No. 01	Effective Date	Review Date	Document Controller (Signature/Stamp)
Copy No.	Date of Issue	Location (Unit/Division)		

Fig.3 An example of Standard operating procedure generated for a method regularly practiced in the laboratory

2.1.3. Data archiving

In the lab continuous monitoring systems were used for the storage of data with proper coding. The archive storage conditions had been predefined to maintain the integrity and sustainability of data, all environmental monitoring procedures are implemented within archive storage with defined standard operating procedures in the designated area of storage. Access to the archive is only controlled by and restricted to the QA and the Study Director(Crouse, Coverston, & Cychosz, 1998) A researcher had generated a request to the QA to obtain the archived data with a QA log mentioning date and sign at the time of issue and return.

2.1.4. VPN [Virtual Private Network]

Internet access is primarily associated with GLP to access data remotely for analysis and maintaining confidentiality of such data is achieved by VPN which is used in Neuroscience Research Lab for secured networking for remote access, storage and transferring online data(Corti, Van den Eynden, Bishop, & Woollard, 2014; Furht & Escalante, 2010). Each staff and student in Neuroscience Research Lab is assigned a server domain to store the confidential data with the remote access by Principal Investigator. VPN storage locations are also mentioned in the DRS to link the result data to its respective experiment and also for future access. The Firewall internet security is maintained which creates interface between other network and lab network.

3.QUALITY ASSURANCE REVIEW

Quality assurance cell was established independently to verify the quality and deviations of procedures providing the support for carrying out the validation processes as cited in various articles(Taylor & Tranter, 1987) In NRL, QA analysis was carried out for every individual by the Quality In Charge at the end of every month which includes experimental details, adherence to self -declared Master Schedules, Purchase benchmarks, Inventories checking etc, as an adaptation to new amendments. The QA report also records the accomplishments and deviation from the Master Schedule and an explanation from the researcher to justify the deviation and include any unfinished work to be assigned into the next master schedule.

3.1 Master Schedules

Master schedules was working timeline of every individual research scholar typically for a month which was needed to be self-declared before starting of the month to QA under intimation to the Study Director(Evans & Lindsay, 2013). The master schedule helps the researchers to plan their work schedule, book any high work load equipment, if needed and maintain their inventory required for the procedures, in advance and useful for effective planning and efficient

execution QA evaluated the progress of every staff at the end of every month and made a report of the ongoing things and work which is not completed yet.

3.2 Inventory update

All inventories of lab were divided among the students who look after the usage of every material. Lab materials like reagents, pipettes, and glassware are placed on different shelves and refrigerators. A Concerned student in-charge of the inventory is responsible for proper usage of materials and periodic procurement through wish lists whenever items reach their critical level. Master inventory sheets are placed in the front of every shelf, cabinet and fridge for easy access. It was mandatory to update these sheets quarterly by the responsible student and should thereafter be reviewed by Quality Assurance in charge. These were also used by the validation processes.

3.3 Checklists

Checklists were prepared with lists of do's and don'ts for every task, ranging from seminar presentation to thesis writing, in order to ensure the completeness of the task without unreported deviation. Other examples include checklist for synopsis preparation, synopsis approval, seminar and Journal club presentation, Ethical clearance, manuscript writing etc. It helps to create a system dependent approach(Hooijmans, de Vries, Leenaars, Curfs, & Ritskes‐Hoitinga, 2011) which is another media for assessment of adherence profile of a student undergoing validation.

3.4 Log register maintenance

Sustenance use of log registers was mandatory task for every research scholars in the lab to maintain his/her record related to research activities. A log register maintains the record of Journal clubs presented and attended, leave records, literature search records, SOP records, workshops attended, record of personal discussion with PI and lab meeting attended etc. These records help to maintain the progress and evaluation of individual scholar at NRL.

4.MIDTERM REVIEW

In midterm verification Inter and Intra laboratory validations were done quarterly to ensure the efficacy of work. It was done by internal Quality Assurance in charge and outside laboratories like CDFD Hyderabad, India [fig 4].

Fig 4. Copy of an Intra laboratory validation report for one of the procedures regularly used in the laboratory

4.1 Physical verification

Biannual audit of test facility by physical verification of inventories, sample log, a log book was also carried out by external auditors to verify the GLP compliance of the students. Thus, it was mandatory for every scholar to update all the required data from time to time. Whether these procedures were followed or not it was also not analysed by the person who carried out the validation.

5.Validation of acquired and analysed data before Thesis submission

Validation of thesis was done in a curative way to analyse the thesis for its authenticity. A team of students were made by Principle Investigator to cross verify the data and some of the procedures explained above(Herr & Anderson, 2014). The data was analysed on the basis of the following criteria: raw data and excel sheet, patient data to informed consents, Patient details to physical location and amount of sample left and so on.

5.1. Checking of Thesis Format –For writing a thesis, a proper protocol with guidelines was followed in a particular sequence which are- Abstract, Introduction, Review of literature Hypothesis, aim, objectives, result, conclusion etc. All these sections were reviewed for adherence to the format.

5.2. Diagram and figures validation- Various graphs and illustrations, if any, were matched with relevant data which was cross checked to ensure that no irrelevant data was found filed. Citations were cross verified. The figures were closely matched with their respectively recorded DRS copies, raw book entries and VPN data archives to validate their authenticity and accuracy.

5.3. Socio demographic analyses – In socio demographic analyses, the telephonic verification was done by calling every individual patient and controls to match his/her data with excel sheet. For example, cross validation of the patient sleeping time, water intake capacity, diet, parent's education level and income etc. were cross checked.

5.4 Physical verification of samples-Each sample was verified for its log, proper location, storage and coding to ensure if it was maintained properly and matched patient's details and date of sampling. It was also ensured that it was properly entered in its respective inventory.

5.5 Sample coding- Sample coding was carried out to code the sample for blinding and tracing the location and to maintain the sample log**.** The sample coding of various samples was verified as per established norms (Grant & MacDonald, 1986)

5.6 Genetic result matching-The reports of genetic data and mutations of specific genes of patients on excel sheets were cross checked with hard copies. Results obtained from the capillary electrophoresis were also cross verified. Result verification of genetic data of patient with Dystrophin gene and other genes like APP, PSEN was enumerated and matched the hard copies with excel sheets in PhD thesis 1 and in another PhD thesis the same data of patients with Age related macular degeneration were analyzed and matched with hardcopy.

5.7 Consent form- Informed consent forms along with audio visual consents, Patient information sheets, Patient records were cross verified for validation along with signatures of witnesses(Paasche-Orlow, Taylor, & Brancati, 2003)

5.8 DRS [Data Record Sheet] -All DRS of experiments was cross examined to check if they were filled concurrently with the experiment. The process was done for locating any discrepancy or deviations in the experiment.

5.9 Neuropsychology of Patients – Neuropsychological assessment data was cross checked in the patient, control and follow-ups of a particular time period before archiving the data after coding. The data was tallied with attached consent form along with videography record.

5.10 Genetic result verification –Result verification of genetic data of patient with Dystrophin gene and other genes like APP, PSEN was enumerated and matched the hard copies with excel sheet.

5.11. Blinding sheet – Blinding sheet was prepared during data acquisition and analysis with every set of experiment. We checked if blinding sheets were attached with every data and the same was recorded.

6. RESULTS

A final report was prepared after PhD Thesis validation. The concerned Quality Assurance personnel wrote a GLP compliance statement indicating assurance for the validated data. A final master validation sheet was prepared with proper recommendations for errors.

6.1 Documentation analysis

The adherence to SOPs, matching of raw data to excel sheets, accuracy of raw data and statistical analysis of the data was done independently by using validation SOP. It was found that indexes were not made. Some discrepancies were found which were recorded and updated as per GLP compliance.

6.2 Telephonic verification of patients

In PhD thesis 1- The data acquisition dates in records were matched with those obtained telephonically by contacting individuals recruited in the study data. The data of 90 male patients with an average age of 10-11 years were telephonically verified. In continuation to the validation process, the socio-demographic data verification was carried out by matching of hard copies with excel sheets corresponding to the telephonically obtained information including water intake, physical status, educational qualification, parents income, ambulation

age, use of electronic devices, time of Neuropsychology and their follow ups etc. It was reported that 5 of the DMD cases had expired while telephone numbers of 9 patients did not match with records after 4 years of recruitment. Other minor errors were also found in the data which were included in the master validation sheet for further compliance and necessary correction [Fig5].

In PhD thesis 2- 280 AMD patients and 200 controls were recruited in the study. The study consisted of participants [both AMD patients and controls] falling in the age group of 50 and above. During collection of Socio-demographic data, information pertaining to smoking habits, drinking habits, night sleeping hours, physical activity, yoga practice, history of surgery, co-morbidities etc was gathered. To cross validate the collected data, participants were contacted at their telephone numbers given by them during data collection. Patients were again asked similar questions on phone call. Cross-checking was done to match this data with already existing information. In addition, validation exercise also helped in checking whether participants have voluntarily participated in the study or not. A sheet was made enlisting number of patients who attended the call, 12 of them who didn't respond the call and 6 patients had died and 9 patients had invalid contact number [Table1].

6.3 Neuropsychology Record

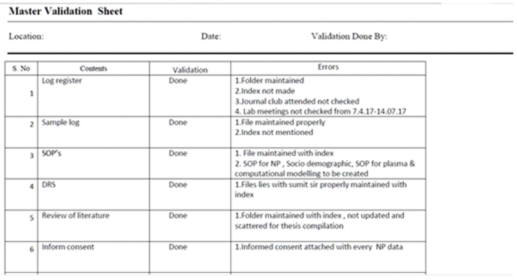
In PhD thesis1- The Neuropsychology data was validated by preparing name wise patient list. Consent forms of patients attached with forms was checked individually. Consent forms were found to be attached with every questionnaire duly signed by witness.

6.4 Matching of Experimental data

In PhD thesis 2 - The experimental data comprised of ELISA and SNP genotyping data. The results were maintained in form of excel sheet. The samples were matched with raw data; Data recording Sheet [DRS] was checked to verify the validity of experiments [Fig 6].

6.5 Result Validation and sample location

Genetic result data was verified by following different steps. All the genetic data [coafflyser report, soft genetics reports] was attached with Neuropsychology data as analysed in Fig 5.

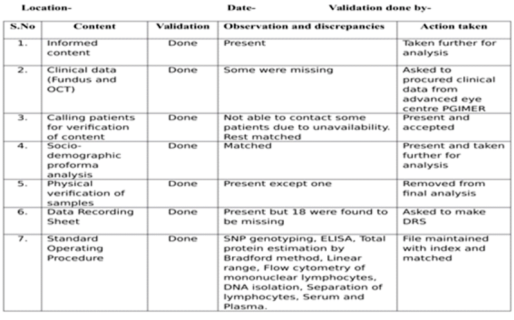


Master Validation Sheet

Location: Date: Validation Done By:

S. No	Contents	Validation	Errors
1	Log register	Done	1.Folder maintained 2.Index not made 3.Journal club attended not checked 4. Lab meetings not checked from 7.4.17-14.07.17
2	Sample log	Done	1.File maintained properly 2.Index not mentioned
3	SOP's	Done	1. File maintained with index 2. SOP for NP , Socio demographic, SOP for plasma & computational modelling to be created
4	DRS	Done	1.Files lies with sumit sir properly maintained with index
5	Reviewv of literature	Done	1.Folder maintained with index , not updated and scattered for thesis compilation
6	Inform consent	Done	1.Informed consent attached with every NP data

Fig 5. Thesis- 1 A copy of Master validating sheet reporting errors identified in a scholar's thesis data.



Location- Date- Validation done by-

S.No	Content	Validation	Observation and discrepancies	Action taken
1.	Informed content	Done	Present	Taken further for analysis
2.	Clinical data (Fundus and OCT)	Done	Some were missing	Asked to procured clinical data from advanced eye centre PGIMER
3.	Calling patients for verification of content	Done	Not able to contact some patients due to unavailability. Rest matched	Present and accepted
4.	Socio-demographic proforma analysis	Done	Matched	Present and taken further for analysis
5.	Physical verification of samples	Done	Present except one	Removed from final analysis
6.	Data Recording Sheet	Done	Present but 18 were found to be missing	Asked to make DRS
7.	Standard Operating Procedure	Done	SNP genotyping, ELISA, Total protein estimation by Bradford method, Linear range, Flow cytometry of mononuclear lymphocytes, DNA isolation, Separation of lymphocytes, Serum and Plasma.	File maintained with index and matched

Fig6. Thesis 2- Master validating sheet reporting errors and action taken identified in a scholar's thesis data

Table 1 Thesis 2 Validation of various parameters and action take

Parameter	According to concerned person	Observation	Correction made	Outcome
Calling patients	All the participants had voluntarily participated and socio-demographic data was correctly entered	Some patients didn't pick up the phone some were dead but for those we were able to talk Socio-demographic data entered was correct	Consent forms were checked for voluntary participation of patients and it was made sure that those forms had signature of participants	Finally those participants were recruited who had matched socio-demographic data or signed consent forms
Physical verification of samples	All samples recruited in study are physically present	Sample 259 not found	Wrong data entered by mistake was removed	Samples except 259 was included
Clinical data matching	Clinical data record was maintained	Clinical data record of some patients was missing	Asked to procure clinical records	Patients recruited only after getting clinical records
Consent form matching	All consent forms were present	Consent forms were present but some didn't have signature of PI or Ophthalmologist	Incompleted	Incompleted
Matching of Experimental data	Experimental data matches the excel entries	Matched	Matched	Matched entries included

7. DISCUSSION

Cross validation of PhD Thesis by recording various parameters like telephonic verification, record of chemical usage with dates of experiments, thesis format, result cross verification, genetic data validation ensured validity and accuracy of the Thesis which was reassuring for both student and the Supervisor. The thesis of both PhD scholars were submitted after all compliances and corrections and Quality practises had been conducted. This instil a sense of responsibility and enhances accountability of data (McLachlan, 2017). Error reporting at the time of thesis validation, after following Quality practices, enhances the translation value of the research without further need to repeat experiments. Good Laboratory Practices and such Quality checks necessitate the research scholars to maintain the records including sample logs, master sample location chart etc. Format checking of Thesis showed the occurrence of proper algorithm which also reduces the time taken by supervisor to ensure minimising the deviations in the GLP compliance. DRSs, however, are a good source of real time deviation identifier along with proof of experimentation and corresponding utilization of chemicals. These are often installed in other establishments to ensure transparency and increase cost effectiveness(Best & Kahn, 2016). Similarly, master schedules are used to steer the performance of researcher in a planned manner ensuring real time monitoring. Using VPN networks, the working of staff to becomes system dependent thus enhancing efficiency(Kerzner & Kerzner, 2017). Socio-demographic data validation provided a proper record of patients with change in their habits over the time which necessitates follow ups for prospective studies. The critical aspect of Good Laboratory Practices requires proper audits and verifications which is used to empower data accuracy leading to valuable research. It is difficult to state whether this degree of compliance could be found in other labs not following GLP for the sheer reason that no lab in India and perhaps world follows GLP in the research settings(Organization, 2010)

These findings provide support to the current ideas suggesting the benefits of Good Laboratory Practices for the PhD thesis validation. Documentation in research is aimed to maintain the record of research for Quality Assurance thereby addressing of questions that may be asked under the Right to Information, a right given by all Indians constitution. The validated data enables accurate reporting of data

manuscripts to various Journals, attracting high citations, awards, grants and national projects especially when no lab in the country follows similar benchmarks implemented.

8. CONCLUSION AND FUTURE PROSPECTS

Today research misconduct and data falsification is a serious threat to the credibility of science. The manipulated research publications can disrupt the basic scientific honesty and can mislead a research group. It may also wrongly extrapolate the data for community. A 2009 report published by the Office of Research Integrity [ORI] of the US Department of Health and Human Services mentioned a large number of research misconduct analysed from opened cases from 2007-08 publications. A majority of the cases were found to be involved with image manipulation(Mayer & Steneck, 2007). A gradual increase with a significant degree of concern of "falsified images" were identified in published articles over a period of 20 years [1989-2008] in a 2 yearly based analysis(Wright, Titus, & Cornelison, 2008). Another ORI report disclosed a case of research misconduct by a research coordinator from Emory University in a NHLBI and NIH funded grant in 2009(Jamieson). It was observed and simultaneously acknowledged by the research coordinator that patient information was fabricated to increase the number of enrolees in the study while they never existed on ground. Such kinds of scientific misconduct must attract severe penalties. There should be a regulation to identify such frauds and a unified approach should be applied for internationalization of data quality as well as authenticity of research data published.

In Medical Institutes, GLP compliance could be crucial aspect of bringing robustness to data especially when data generated in such Institutes in generally considered soft. Thus, it is necessary for the basic scientists to implement the validation protocols for quality thesis outcome. It will reinforce the quality of research data acceptable to the international standards.

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Development and implementation of ZED-YOG quality module: *Niyantrita Madhumeha Bharata skill* development initiatives

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KEY WORDS

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ABSTRACT

Background: Government initiatives and schemes for global healthcare improvement require efficient implementation which can transform the quality standards. We redefined the purview of Good Laboratory Practices (GLP) in the basic research investigations in order to create a benchmark of quality standards for conducting translational research.
Methods: We propose *Zero effect-Zero defect Youth Oriented GLP* (ZED-YOG) as a management tool for funding agencies to monitor data generated in labs funded by them.
Summary: This strategy can not only promote enhanced data scrutiny, validation but also health awareness.
Key message: *YOG* will ensure the communication of audited research data generated from publically funded national agencies

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Introduction

In the twenty-first century, the global healthcare management has been transformed through policy reforms and innovative technological interventions. A qualitative and quantitative assessment of clinical research and laboratory settings is crucial as their decisions influence the critical care of patients. Data fabrication, falsification of research data, authorship disputes are among the prime cause of research misconduct reported throughout the world, not only in biological sciences but also in other scientific disciplines [1]. Human errors have brought down million dollar Mars mission in the past as a result of failure in checks and regulations [2]. Similarly, recent stem cell research related incidents of misconduct have contributed to a change in society's opinion regarding science and its harmful effects. This necessitates applicability of quality module and quality assurance in order to ensure the credibility of processes, services, management, research and health care. Similarly, establishing the quality driven research facilities will ensure a competitive translational research among faculty driven research projects [3]. Various institutions have implemented or mandated one or other regulatory norms including Good Laboratory Practices (GLP), International Organization for Standardization (ISO), National Accreditation Board for Testing and Calibration (NABL), National Accreditation Board for Hospitals & Healthcare Providers (NABH) etc. for specific healthcare sectors. However, there are no mandatory policies for implementation of quality standards in the basic research as well as national public health initiatives for improved public health and research practices.

GLP was developed by Organisation for Economic Co-operation and Development (OECD) to regulate clinical trial and pharmaceutical studies but not the basic research. The Neuroscience Research Lab (NRL), PGIMER, Chandigarh, India transformed the quality management system to regulate the basic research laboratory based on requirements of day to day research conducts. Therefore, GLP was introduced in 2008 for creating a scaffold for quality management. GLP was later redefined by this group for implementation in the basic research investigations without diluting the core principles of GLP or research. It fulfilled the needs of research functioning as well as the needs of research personnel for their professional and personal development alike.

In the under-developed and developing countries, various government flagship initiatives have been launched but systems of data monitoring is lacking. There is also dearth of compliance to quality standards in the public funded government initiatives involving massive human research and epidemiological data. The major two national initiatives focusing global health were International Yoga day (Global wellness) and Niyantrita Madhumeha Bharat (Diabetes control movement). Another national initiative, Zero effect zero defect (ZED) was a recent implementation of Government of India which focuses on error free manufacturing capabilities with minimal environmental impact. ZED was proposed as the effective to change the dynamics of economy by focusing on manufacturing as an engine to sustained growth.

We, therefore, sought to acquire processes involved in implementing ZED scheme with integration towards Quality driven skill development and empowerment of youth in the Government of India's (GOI) yoga-based intervention initiatives. We propose the term ZED-YOG (Zero effect zero defect -Youth Oriented GLP) which inspires propagation of the integration of youth driven implementation of quality standards in the management of these government programmes by mandatory integration of Yoga research activities in offices and healthcare organizations.

We discuss our effort to align the Government of India's initiatives with existing quality management research systems in order to provide an organized and successful outcome of the initiatives. Government of India has launched three significant initiatives which were implemented to transform the gamut of Health and manufacturing sectors in India. We mobilized and channelized the youth to complete two mega programs of GOI through ideologically similar ZED programme. This has been accomplished through existing GLP module of the NRL, importantly, by training more than 100 student in this maiden effort. These students were trained by the experienced lab personnel with expressed purpose of skill and leadership development. We emphasized the documentation of minimal error rate, penetrence of standardized yoga protocols in work place, periodic monitoring through digitization efforts defined as zero defect. In line with ZED effect in the "Make in INDIA" concept of manufacturing sector, the research sector could also be driven by ZED policy. Simultaneously, NRL's community outreach programme, encouraged by Government's Swachh Bharat Abhiyan (cleanliness drive) was also linked to the camps. Yoga camp activities were followed by Swachh Bharat activity at the camp site. We define this to be "Zero Effect" as the biomedical waste generated at camp sites is safely disposed according to the standard biomedical waste segregation protocol.

Prime Minister of India, Narendra Modi asked the world leaders to adopt an International Yoga Day, emphasising changing lifestyle as means to lead healthy life advocating policies for climate change. Addressing the 193-member UN General Assembly in United Nations, Prime Minister Modi said "Let us work towards adopting an International Yoga Day," Noting that Yoga is "an invaluable gift of our ancient tradition", he said: "It is not about exercise but to discover the sense of oneness with yourself, the world and the nature." "Yoga embodies unity of mind and body; thought and action; restraint and fulfilment; harmony between man and nature; a holistic approach to health and well being," he said, adding "By changing our lifestyle and creating consciousness, it can help us deal with climate change." During the 2nd International day of yoga (21st June 2016) held at Chandigarh, The Indian Prime Minister gave a clarion call to all Yoga institutions to focus this year, on taking up several programs to promote yoga for Diabetes. NRL took to the call and analysed the effects of Yoga protocol on biochemical, anthropometric and molecular changes in persons practising Yoga, and integrating it with ongoing research projects. Niyantrita Madhumeha Bharata (NMB) is an ambitious national project for controlling Diabetes through yoga intervention. National Diabetes Control Program (NDCP) routed through Central Council of Research in Yoga and Naturopathy, New Delhi, and implemented by the Indian Yoga Association (IYA) (IYA is an association that has members from all major traditional yoga *paramparas* of the country). NRL took up the project and has analysed the results from the 3-month intervention on prediabetic and diabetics screened from house to house survey in North India.

This paper discusses the methodology adopted to carry out the NMB programme to enhance the credibility, back-traceability of the data obtained from a facility following GLP quality module. We integrated two different concepts ZED and YOG (Youth Oriented GLP) for seamless implementation of the abovesaid program.

Methods

Yoga protocol for NMB

Quality Council of India, in coordination with AYUSH, Government of India, developed yoga protocol for pan-India diabetes control. More than 9000 individuals were selected pan-India for participation based on the IDRS score. We focused on North Indian region (Chandigarh) for implementing NMB initiative.

Orientation to Yoga Instructors

Orientation classes were provided to all Yoga volunteers for diabetes management (YVDMs) regarding the NMB program and different phases of entire regimen. Methods of administering the questionnaire were explained along with demonstration of measurements of anthropometric variables and precautions. Orientation class regarding hands on training of screening procedures with mock drill of screening session was carried out.

YOG (Youth Oriented GLP) Module

Basic research investigations and procedures are dynamic in nature and need several rounds of modifications. Therefore, sustainability of the module was maintained by continuously improving this module through student-oriented protocols. One of our improvisations was to regulate and improve the functioning of basic research investigations through digital processes. We digitalised the procedures for GLP compliance, human resource skill development, environment safety, Intelligence, Emotional, Spiritual Quotient (IQ/EQ/SQ) of researchers, communication skill development, Security of research data and premises, economic viability and productivity which were helpful to formulate new policy changes for better regulations in this field.

Methods of Identifications of the Problem

The responsibilities for all the activities such as policy making, administrative, documentation and testing etc. were distributed among the staff. The problems in all respects were identified by the concerned staff in that activity and document

in the deviation sheet. It was ensured that the Study Director was kept informed and the concerned steps were taken to implememnt data capturing sheets called the Data Recording Sheets (DRS). There was a three tier Problem Identification System involved in the study, at each level of staff personnel:

- Study Director
- QA Personnel
- Technical Staff/ In-life observer

Policy

Measures for corrective actions were formulated when non-conforming work or departures from policies and procedures in the management system or technical operations were identified. Responsibilities for the actions were centred around the in-life observer who was responsible for maintenance, calibration, breakdown reporting/documentation for individual instruments. For procedural/technical errors, the experimenter was responsible for reporting and documentation. The QA personnel reported this to the Management and any deviation or amendments in the protocols was finalized after thorough discussion between experimenter, QA personnel and the Management.

Adherence of national initiatives to the Quality module in NRL as "Zero defect Policy"

Master Schedule

Each research staff mandatorily proposed a weekly plan of the work to be completed in a month to plan the entire month. Master schedule was to be submitted to Quality Assurance **(**QA) cell before the beginning of the month. Master schedule of NMB camps were also prepared as per Figure 1. QA reviewed the progress of the research and technical staff at the end of the month through one to one interaction. Students prepared a draft in the Microsoft word document and mailed it to the Quality Assurance personnel to reduce the paper work. Master schedules were kept in a format by QA personnel in an electronic format.

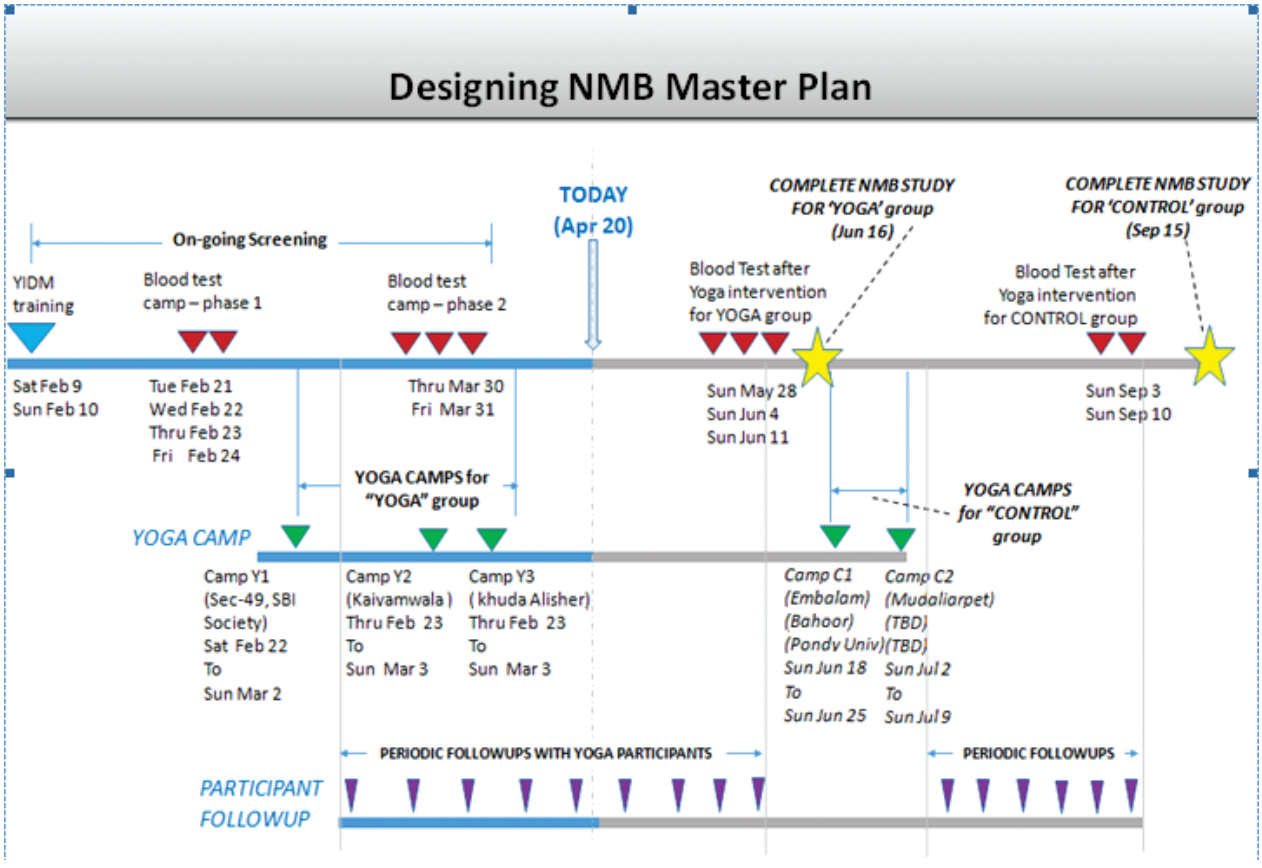

Fig. 1: Master Schedule of date wise NMB Camps.

Standard Operating Procedures (SOPs)

Experimental and administrative procedures performed in the laboratory adhered to the corresponding SOPs in order to streamline lab experiments and related procedures including purchase procedures, cleanliness drive, publication of Annals of Neurosciences (PubMed indexed Journal published from the lab), project writing, grant writing, thesis writing etc.

Using similar quality modules, SOPs were developed to streamline entire NMB yoga camps as explained in Figure 2.

Standard Operating Protocol (SOP)

NMB Camps

Neuroscience Research Lab, PGIMER, Chandigarh-India

Niyantrit Madhumeha Bharat (NMB) is the Yoga initiative from AYUSH and SVYASA for controlling diabetes in India via Yoga. Under NMB, blood testing camp to check diabetes were carried out across India. This protocol represents the structure of management to handle the blood testing camps.

The whole camp activities were divided into following activities which was done in serial order:

1. Token Distribution: Token number is distributed to people coming to manage crowd and chaos.
2. Master Coding: Each person is assigned with a unique master code which is exclusive for him only and this code is written on all the forms and vials in which blood is collected.
3. Registration Form: Registration form filled for each person by indicating master code on top of the form.
4. SRL Form: SRL form is filled for each person by indicating master code on top of the form.
5. Height/Weight/Waist Circumference/Hip Circumference: measurements are taken by using weighing machine and measuring tapes. After that write that on form.
6. Blood Pressure: measure and write on form.
7. Blood Sampling: Blood sample taken by SRL team.
8. Glucose Drink: Glucose is given to prediabetic person only. Diabetic person should take regular food
9. Form Filling: Detailed Neuropsychology form is filled after person give the blood sample
10. Photography/Crowed Management/Swachh Bharat: These activities are keep running with other activities during camp.

Fig. 2: Standard Operating Protocol of NMB camp.

Data Recording sheet (DRS)

To minimize the procedural errors, DRS were formulated along with SOPs for the real time monitoring. This was prepared in consultation with Study director and consisted of the columns for identification of SOP, along-with control of the document through Quality Assurance (QA) cell. DRS was issued only at the time of conducting the experiment and re-submitted to the QA after attestation from the Study Director. Data recording sheets were followed in all procedures of NMB data analysis.

Quality Assurance Review

Independent review of infrastructure and facility-based QA audit was carried out once in a month. Study based QA review encompassed the review of the work planned by the research scholars as per their master schedule. Deviations from the master schedule were documented and carried forward for the next month. Independent verification of experiments was carried out to check the compliance to SOP. QA review sheets were prepared in the Microsoft word document.

Log Sheet and Log Books

The log sheets and log books maintained for the entire chemical, refrigerated reagents and all sophisticated instruments are used for documenting usage. These are useful for trouble-shooting not only the technical problems but also in ensuing timely re-ordering reagents.

Checklist Based Management

Checklists were developed to ensure the completeness of the task assigned to students which compensate for the human limitations. Checklists were formulated for all the academic or administrative lab procedures including, synopsis preparation and its approval through Dean Doctoral Committee (DDC), presentation of the progress of research through Doctoral Committee (DC), PhD viva, grant writing, seminar presentation, human and animal ethical clearance, visa application for travelling for conferences, manuscript writing etc. Checklists were stored in the common domain of the lab networking system. Thus, it could be used among the closed user group for guidance without having the need to approach a senior/Study Director. This created a system dependent guidance system for the trainees for implementation with respect to NMB project execution.

VPN based servers for digital data accessibility and storage

Server based virtual private network (VPN) in the secured network is installed in the Neuroscience Research Lab for the storage, security and remote accessibility of research data. Usually, in industries or IT sectors the server-based access and storage are available; however, introducing it to basic research facility in a Medical Institute is challenging. The server spaces were utilized to import the data obtained from NMB camps. Server domain was allocated to each student and staff to store the confidential research data. Only study director was authorised to access all domains. Besides having personal drive, every computer was allocated with official user domain among closed user group where research data is fed in the form of SOP, DRS and master schedule. This domain represented a personal and common drive in which research data could be accessed in a secure fashion by the study director in order to restrict the access of intellectual property and common administrative procedures, respectively. Network security system, through firewall, was created as a barrier across internal network. Another network was geared up to provide security of confidential research data that protects the server against various threats from public networks. Remote access through virtual private network provided secured access to data from anywhere through internet and ensured safety of lab assets by real time surveillance.

Real Time Monitoring (CCTV)

NRL was kept under the surveillance of CCTV camera and real time monitoring was enabled through VPN system. It acted as a deterrent for any unforeseen security lapse thus it also provided a secure environment to the female members of the lab and monitoring of the research activity in lab.

Master Coding of Individuals And Samples

Participants were provided a unique code according to the ongoing GLP led quality management system of NRL. This maintained confidentiality of participants, data blinding and management of the crowd. Samples obtained were coded for blinding and kept according to the existing quality standards. Data was digitised through new team under the supervision of experienced personnel.

Personal Discussion and Lab Meeting

A day was allocated to every student for personal discussions regarding the research problems, progress and purchases with the study director. Every experimental and purchase procedure was structured into indent, benchmark checking, and assessment of log sheets maintained to see the previous purchase.

Administrative documents

(Log books, Log sheets, Inventory sheets, temperature sheets)

Inventory Sheets and Master inventory

Lab reagents, Kits and glassware were kept in various shelves and refrigerators. These inventories and their management were distributed among students who looked after the exchange of material. Inventories were submitted monthly to QA, who prepared a master inventory. Master inventory was used to check the location and available stock of any chemical or kits. Quarterly, the hardcopy of the inventory sheets was updated with freshly updated quantity of the stock. To reduce the paper burden on this task, the quarterly review of inventory was carried out and electronic records of the inventories were sent by the students to the QA and Master inventory was maintained by the QA personnel.

Zero Effect Supporting Initiatives

Bio Medical Waste Management

Rigorous biomedical waste management training was provided to the students with periodic orientations to the trainees. Biomedical waste was segregated in four different polybags. Black containers were used for general waste, Yellow containers for soiled infected waste, Blue containers involved sharps and red containers included plastic wastes.

Printer/Paper Usage

Printers were linked to each computer/Laptop in the NRL. Printer log was monitored for each research personnel in order to save resources.

Swachha Bharat Abhiyaan (Clean India Mission)

Zero effect programme was also encouraged by Swachha Bharat Abhiyaan (SB) led by Neuroscience Research Lab. Volunteers from the NRL devoted two hours each week for continuation of cleanliness drive continuously for 203 weeks till date. The activities were also submitted to government portal Mygov.in and propagated through Facebook and WhatsApp groups. Government officials from scientific, academic and social backgrounds were mailed and chal-

lenged to propagate the cleanliness drive further in an ice bucket challenge mode.

Educational Programmes

Scientific symposiums were carried out to disseminate the importance and challenges in implementing quality standards. Research projects and thesis works were connected to quality assurance programme in order to orient the researchers about implementation of quality standards. These trained researchers further oriented the yoga teachers and volunteers of NMB national initiative for integration of quality parameters in the execution of NMB. Researchers were oriented to adopt the quality parameters from experts in the field.

Validation of NMB Data

Entire set of NMB documents and data were validated by trained personnel. Each participant was telephonically identified, excel files were cross checked for manual errors in digital entries and the statistical data was also validated by an independent investigator.

Results

In 2014, Quality Council of India (QCI), recognized NRL for D. L. Shah National award for "Redefining Quality standards in basic research investigations by broadening the purview of Good Laboratory Practices (GLP)" under research category. In 2016, Quality council of India again recognized this effort and awarded the NRL for "Digital Research Lab for Enhancing Capability: Towards Skill Development and Community Outreach". For the first time, this award was constituted to create a special category to accommodate the unique initiative.

Financial and tangible benefits of the quality module

The research chemicals upto the scale of microlitres were laboriously documented for as per daily use. Purchasing time was streamlined through availability of chemicals and correspondingly documented in the log sheets. Experiment wise documentations ensured auditability of experiments. Digital scrutiny encouraged improvements in the purchase and accounting procedures. Intra and Inter laboratory auditing of various grants were carried out to ensure auditability.

Storage and Security of the research Data

Large data saving capacity makes this server unique in the basic research settings. Server automatically updates the storage capacity after one year. Thus, the data can be extracted from the server within this time-frame. Server is also used as a data backup device. The security of crucial research data, which is a requirement in the basic research settings, is stored under the control of firewall which disables any possible hackers efficiently. Network layout plan is described in figure 3.

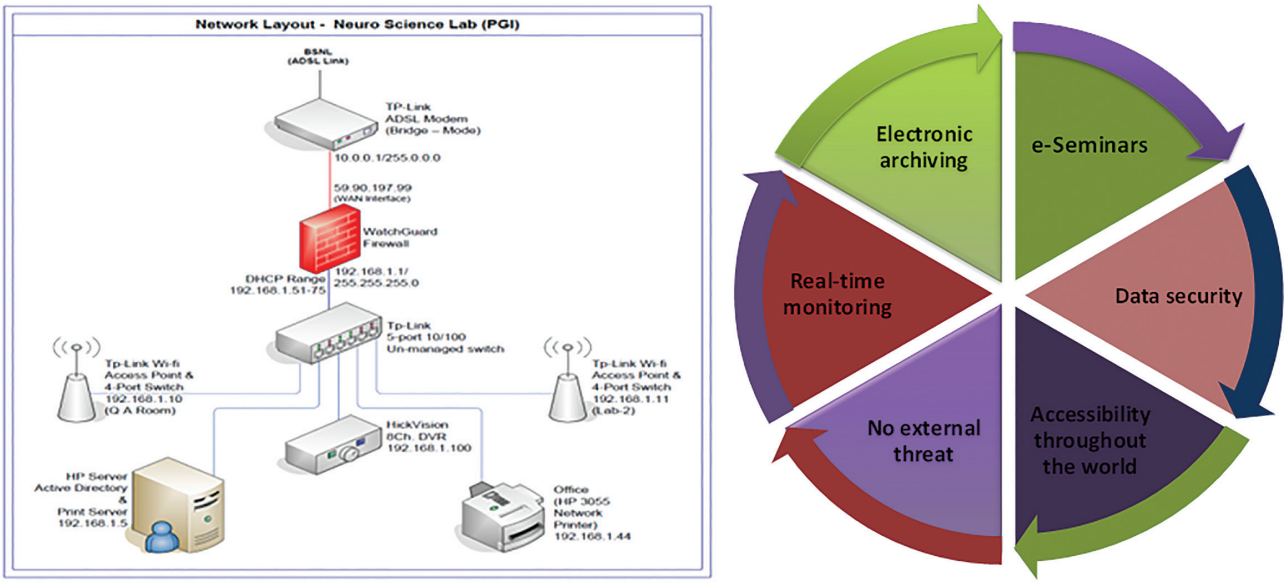

Fig. 3: VPN based Network layout plan.

The Server based networking system encourages controlled utilization of papers as it keeps the log of printer usage for each personnel. In this way the system is kept environment friendly as it is important in the smooth functioning and saves time. NRL became the first entity to finish 100 hours of SB in India. It trained youth to participate in the "Swachha

Bharat Activities" through the camps NMB and International Yoga Day. After each of such camps, the completion youth driven *Swachhata Abhiyaan* were carried out for orientation of staff towards ZED-YOG.

NRL Social networking

NRL team enhanced its efficiency through WhatsApp group chats. Professional guidance's, suggestions, sharing ideas and instructions were facilitated through the WhatsApp group. It reduced the communication gap between the study director and other research staff. NRL's activities, achievements, future programmes are projected through a separate Facebook page. Implementation of quality module has increased the credibility of data published through the scientific fraternity. Benefits of such quality module in various research areas is depicted in Figure 4.

Fig. 4: Benefits of ZED-YOG quality module.

Discussion

The student/youth driven GLP module enhanced the reproducibility of data and error reporting of research data and internalised the quality system in research practices, thereby facilitating a higher sincerity of purpose for research in Medical Institutes in India (paper in communication). It also sought to bridge the credibility chasm that exists between data generated from India and that from the West, because of which the best research from India is rarely published in top Journals. The implementation of this module has led to enhanced visibility in the research. Research papers written from NRL provide sufficient data which shows that this quality module has improved the quality of data generated [4–6].

The redefined GLP system encourages goal driven, self proposed monthly master schedule map of activities in coordination with the study director, using the combination of SOPs, DRSs and master schedule applicable for various research projects. The Quality Assurance (QA) unit in NRL conducts periodical audit of the progress, compliance and reproducibility of experiments. The data generated filed in a defined format using a mandatory raw book, master code, calibrated instruments (with IQ, OQ, PQ), log sheets with continuously regulated infrastructure and room environment provides the necessary back up for data retrieval. The data and samples which are archived in defined shelves or freezers, as the case may be, can be seamlessly used for future experiments saving precious resources. The current system is rare in any research settings specifically in the medical institutions. In view of the increasing government participation for global health programs, the implementation, backed by quality standards, is necessary. Ideological integration of governments quality module, ZED and our youth oriented GLP (YOG), provides a robust organizational system for success of science policy implementations in govt funded research labs. Manufacturing & Design capabilities, Quality/Environment/Safety assurance systems, People development and engagement systems, Standardization and measurement systems for quality and environment, Learning and improvement systems, Legal compliances are the key features of ZED which are being integrated with the GLP core principles.

SOPs facilitate the robustness of the system and enhances productivity of students and staffs thus reducing the scope of errors. It also results in internalising the quality principles in the youth. More than 100 volunteers working in various streams have been trained to work in a ZED-YOG fashion by adapting the NRL module of GLP and minimizing medical waste through Swachha Bharat Activity. The scientific analysis of the samples obtained from International Yoga Day (IYD) and Niyantrita Madhumeha Bharata Abhiyaan (NMB) camps were similarly evaluateds according to the existing quality management system developed by NRL. Successful implementation of government programmes such as IYD and NMB camps generated crucial authenticated data backed by Quality standards thus, necessitating implementation of quality standards in all government programs.

Conclusion

Modified GLP module has been found to be effective to safeguard the accountability, back traceability of the research data and management of human resources. NRL strives to create a module which can be emulate by other basic research facilities in India. New policies can be formulated for the basic research settings using the quality module. ZED-YOG has capacity to develop a new generation of basic scientists striving towards quality-oriented environment with effective research output. The national initiatives with focus on global health research standards can consider adopting the ZED-YOG protocol in their work places.

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Commentary

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National Medical Commission Set to Replace Medical Council of India after Gorakhpur Episode: A Case for Quality Assurance

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Non-medicos (scientists) joining the national medical commission (NMC) is likely to facilitate scientific advancement in medical practice in India by propelling indigenous research. This is likely to result in affordable tests and therapies, as doctors in India are unfortunately not trained for research unlike those in West (as curriculum of MBBS, MD/MCh, DM, etc., does not include basic research syllabus). This bill was likely to be tabled in Monsoon session on Indian Parliament but this case for quality assurance appears to have been delayed. This will impact expansion of genetic testing services nationwide whose revenue would have been re-invested in training of medical graduates and generation of genetic database for cure of genetic disorders. The adoption of NMC will accelerate translational research and improve the provision for integrated health care which may provide solutions of incurable disorders as well as innovative means to address Gorapkhpur like episodes. Further, inclusion of Ayurveda, Yoga, and other alternative medical approaches in health care delivery will reduce patient rush and generate comparative data between modern medicine and alternative medicine, thus paving the way for regulation of costs of healthcare and save the precious lives.

Engagement of individuals from quality assurance in NMC is likely to ensure patient feedback and check outsourcing of investigations/tests through installation of treatment, testing, and patient cost audit protocols something, which could have been easily prevented in Gorakhpur episode in which more than 36 children died. This will ensure continuous monitoring of patient services through clinical audit, thereby improving the quality of patient service.

Patient cost audit will further ensure reducing "out of patient" expenses of patients as health economists have also been included in NMC which can evaluate the effect of private practice. This can additionally be achieved through audit of company sponsored conferences generated from unnecessary investigations/branded prescriptions that are suspected to be ploughed into conferences kitties for fun and frolic.

One example (of role of non-medicos in NMC) is to install IT tool enabled provision for surgicals, in house tests through the institute inventory management system, as also developed by Dr. Wakhlu of King George's Medical University (who won the SKOCH platinum award for his innovation and implementation of IT tools) thus saving costs of treatment for patients and empowering rural healthcare such as in Goraphpur. The resources saved can be earmarked for rural healthcare development and prevention of spread of infectious brain diseases.

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With the help of inclusion of patient advocacy groups in NMC, it will establish the quality process so that (by engagement of patients engagement in NMC) rapid changes in practice of medicine benefits the patients, not doctors or scientists.

NMC must also include Yoga and alternative medical practitioners in ensuring its seamless integration and patient cost reduction in health budget. This can compensate for weak rural healthcare system for villages. It is only possible by integration of the role of non-medicos (patient advocacy, quality assurance, health economists, and scientists) in reallocating over staffed medical institutes to rural postings in rotation.

The importance of generation of evidence from comparison of treatment outcomes between modern medicine and traditional medicine can be generated through integral healthcare, which was impossible with medical members of MCI.

Disclosure Statement

The views expressed in this article are personal and not that of any organization. The names and situations described in the article are imaginary and any resemblance to anyone is purely coincidental.

Commentary

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Policy Research for Assessment of Quality Assurance Practices in Skill Development of Doctoral Programs in Medical Institutes

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Introduction

Doctoral programs in India are focused around empirical laboratory and field studies with theoretical and computational explorations aimed at addressing fundamental issues in the field of science. PhD students are often motivated to pursue the PhD by scientific curiosity, the desire to contribute to the academic and social community, and/or personal development. However, in the absence of basic research administration and because of overemphasis on patient treatment, the quality research of ecosystem in medical institutes remains soft [1].

DST recently started the Policy Research Fellowships to promote policy-related investigations. Since Science and Technology is now recognized as playing a significant role in advancing human, social, and economic development and addressing the aspirations of citizens across the world, the need to integrate quality assurance tools in Doctoral programs cannot be over-emphasized. An analysis of the nature of biomedical research in India indicates that most of the research has primarily been of academic nature and has rarely assessed the methods in research with any policy implications [2]. Along with "fabrication" and "falsification," plagiarism is one of the "big 3" crimes of the research fraud rising in India [3]. Therefore, a need for quality control is urgent. A quality policy is required in Institutes for Doctoral Programs. This can be done by incorporating methods to render raw data verifiable, back-traceable, and auditable.

Introduction of a policy management system for doctoral programs in medical institutions can help in linking research with quality assurance so that the resources, time, and efforts can be utilized in an efficient way for enhanced productivity, innovation, translation, and skill development. Such assessment tools can enable the establishment of a quality system. This can ensure and validate the uniformity, consistency, reliability, reproducibility, and quality in research data. It is possible to analyze this by 4-tier assessment: (i) by way of measuring the time spent by students in PhD program, including regular laboratory hours, (ii) what are the quality tools used/created by them, (iii) their number of publications, patents published during the course, and (iv) whether any quality statements were inserted in their respective research publications. The student's skill development program can also be gauged by the number of their visits to national and international workshops and conferences as well as their participation in social outreach activities. The costs involved in completing PhD degree can also be documented.

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Such analysis can also include the number of principal investigators in the department and their qualifications, ongoing projects and those completed, amount of funding and the number of invited talks to national and international conferences, including ones on quality and management meetings. Their awards, grants, and leadership roles in the launch of social outreach programs for training of PhD students must also be measured. It is also possible to map the number of national and international collaborators, with interdisciplinary teams, if any, and the time spent by faculty with students on bench must also be assessed.

Similar quality audit at the administrative level can be done by assessment of administrative record keeping, file tracking, monitoring and documentation processes engaged by the administrative staff including efforts to continue providing guidelines, institutional independence to faculty, students and managerial support for procurement, and quality programs with allocation of various portfolios to various Deans etc.

The quality assessment must not exclude the funding agencies' commitment to implement quality audit of experimental facilities funded by them. Even the publishers or societies can make a commitment to periodically assess the journals, wherein all data regarding number of manuscripts submitted for publication, efforts to recall raw data from authors could be open to public eye. The retraction policies for articles must be matched to number of retractions executed by them.

The policy research studies will help in improving the quality of doctoral programs in medical institutes and help in establishing individual quality assurance cells in research laboratories matched to the qualifications of PIs. Such studies will also help in ranking and mapping the labs in a systematic and evidence-based manner so that crucial national projects may be funded to facilitate "Make in India" program a grand success. If successful, it will help in improving research quality, social values, productivity, and skill development of PhD students across the country and world.

The policy scoring may also help in incubating ideas which may result in new tests and therapies, which are invariably imported at the cost of indigenous discoveries which are devoid of quality and benchmarking. Currently, the quality benchmarks are not mandated by funding agencies even though Universities have Quality Assurance Cells.

Recently, DST started policy research fellowships to promote policy research. Ironically, all post-doctoral fellowships were assigned to 5 centers of policy research. Interestingly, junior research fellowships were not provided to anyone which is a self-defeating step.

The periodic rolling out of policy research fellowships will help emphasize the importance of the need for linking release of research grants and fellowships in order to promote Science and Technology in Medical Institutes and universities.

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Eye Genetics: The Road Ahead to Quality Standards

34

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Abstract

The prevailing system of running research labs in conventional set-ups are based on no uniform method of management, relying completely on individual preferences and experiences. Unfortunately, even the leading institutes involved with research in health and medicine fail to incorporate defined modules unless mandated by the guidelines of GMP, essential for clinical translation. The present trend shows the drop in clinical trials presumably due to inherent questionable data and lack of back traceability of information. The ability to bring clinical level safety at the genetic research level facilitates Quality control measures unique, transparent and credible for clinical translation. Good Laboratory Practice (GLP) modules have been developed to enhance quality standards, increase credibility, efficiency and transparency of research settings. The studies in ocular genetics, pathology, pharmacology require similar benchmarks. There have been rapid increase in the cases of eye diseases in Asia but the process of genetic data generation is not uniform and auditable. The studies involving larger populations include meta-analysis and GWAS etc. which require collaborations, need to be supported by a standardized managerial system. Quality standards define such tools ensuring back traceability, verifiability and auditability of data and test systems. These should also address IP conflict management and implementation of standardized protocols. The quality control

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and GLP can lead to benchmarking of research data which are usually considered a soft activity in Medical Institutes where most of the genetic data is generated. The Quality control practices in such large scale research collaborations require testing the source, prevalence and resulting therapies for overall ocular health.

Keywords
Quality assurance • Good laboratory practices • Eye genetics

Around 285 million people over the world live with visual deficiency. Out of these 39 million people are blind, and 117 million are with uncorrected refractive errors [1]. Most of the blindness is curable. India is now home to the world's largest number of blind people with more than 18 million people who suffer from one or other form of blindness. Genetic factors are important in the development of eye diseases. An increasing number of genes have been associated with eye disorders. The delivery of accurate test results is the most serious problem indicator for laboratories. Presently, practice of medicine has been entirely redefined by the developments in genetic testing. Genetic testing is widely used as common tools by research institutions. However, there is extensive and widespread application of genetic testing and analysis after the completion of the Human Genome project. During genetic testing, there is always a possibility that any systematic or random error may occur and put human health at risk. To categorize and to work with eye genetics, we need to build and improve the quality standards with genetic research and services to achieve excellence.

34.1 Quality Throughout the Testing Process

Genome-wide association (GWA) and meta-analysis have accelerated the pace of genetic research in eye diseases. GWA studies are based on analysis of single nucleotide variation in the genome and its association with pathological condition. GWA studies are required to have case and control participants. Case group may be clinically pre-diagnosed, but control group should not have similar disease phenotypes. After the completion of human genome project (HGP) in April 2003, it identified millions of SNP changes in the whole genome which has been deposited in public database "The SNP consortium (TSC)." Two major aspects need to be emphasized in GWA studies, i.e. large population size and large genome coverage. Large population size is important to avoid false-positive genetic association derived by modest p-values for some of the genetic alleles. Similarly, a genotyping array provided by companies (like Illumina, Perlegen, Affymetrix, etc.) does not cover the whole genome. Meta-analysis is quantitative statistical analysis from all the studies done in particular field by combining them all and to draw a precise and effective scientific inference. Meta-analysis shows the presence of heterogeneity by including all relevant studies randomly that could provide impartial and balanced conclusion. Even the studies which have less impact due to less sample size could show up on meta-analysis inference. Meta-analysis studies provide new research question or perspective which assist policy makers to customize new policies/protocols in the research area. Therefore, in both kinds of studies, it is crucially important to have proper guidelines or checklists to improve the quality of such studies, reports, and scientific conclusion obtained from these reports. Here in this chapter, we have discussed some of these issues which should be included while performing such studies.

34.2 GWA Studies in Eye Research and Its Quality Control

GWA studies could provide direct relation between disease and genetic changes, which possess powered study designs. There are some limitations in GWA studies, which result in drawing varying inferences. However, we can enhance the quality of GWA studies by considering following issues in various studies.

1. GWA studies have defined case-control population in which case could be pre-diagnosed before recruiting them in the study, while control population must not have similar disease phenotypes as case population. There should be proper documentation of inclusion and exclusion criteria in verifiable format.
2. Sample size for GWA studies is important since all its inference and conclusion are based on the significant association of SNP variance with disease pathology (p-value). Moreover, there are a few studies which have been retracted from renowned journals due to discrepancies raised by use of different kinds of genotyping arrays. Commercially available high-throughput genotyping array (e.g., *Affymetrix*, *Illumina*, or *Perlegen*, etc.) covers only a small proportion of total SNPs found in human genome. Various arrays used in genotypic analysis have different sets of SNPs, which lead to different inference/conclusions and also have reported various genetic markers in disease pathology. In the Indian set-up, such limitations can be addressed by adopting whole genome sequencing or next-gen seq. method. Additionally, the introduction of statistical imputation analysis in such studies could bridge the gaps for missing genetic links between different study outcomes. The cost of sequencing is now much cheaper and can be made affordable in Asia if quality tools are implemented.
3. The whole genome coverage analysis also provides gene-gene interaction and assortment of different genetic alleles in disease phenotypes.
4. GWA studies also are not able to describe the cross talk between different diseases and their common SNPs. The pleiotropic effect of particular SNP which affects different sets of other disease conditions cannot be analyzed by GWA studies.
5. GWA studies must also have to include some statistical tools that could analyze the gene-environment interaction and epistasis phenomenon in disease phenotypes. Such problems are being solved by introducing genetic linkage analysis and Mendelian randomization approach.

34.3 Quality Control in GWAS

34.3.1 Sample Quality

It is very crucial to code the sample immediately on receipt along with defined gender identifier. The chromosomal structural changes and atypical X chromosome numbers can also influence the end point analysis of GWA studies calculated through software. It is very important to code the sample properly and also introduce basic questionnaire, which includes all the basic points like sex and other sociodemographic details of the participants. By doing so, it could reduce the chance of type 1 and 2 statistical errors in final analysis of the genetic data. However, sample identity and kin relation could also be identified by using PLINK software while analyzing GWAS genetic data. Pairwise dot matching in the dot plot of GWAS data could identify unrelated, parental, or duplicate/twin samples by their scoring as 0, 1, or 2, respectively. The graphical representation of the pairwise data can be done through R software [2, 3]. It is also possible that in such studies, an individual can be involved in more than one center in case GWA studies are multicentric. The common method used to identify the ancestor in a large population is principle component analysis (PCA). Therefore, in such cases, the person has to be excluded after software analysis by which we can reduce the type 1 and 2 statistical errors in final analysis.

Additionally, it is also desirable to assign a defined sex or number of X chromosome of the participant so that it may not increase the copy number variance or the SNP's number of total genome as in case of Klinefelter's syndrome (XXY) or Turner syndrome (XO). The X or Y chromosome numbers can be calculated through probe intensity or log-R ratio which is the ratio of a particular sample to total samples. If the value is less than zero, it is considered as deletion in the chromosome, and a higher than zero value could be signified as the duplication of chromosomal genes or nucleotide sequences throughout the chromosome. Considering these issues, the quality of analysis can be enhanced. Therefore, a good way is to maintain a checklist in a lab and ensure periodic orientation of research staff associated with genetic analysis.

34.3.2 Population Stratification

Population stratification is the major problem of biasness in the population-based case-control study, which has different genetic and phenotype appearance [4]. Therefore, it is advisable that the population must be homogenous in nature in GWA studies. True-false association occurs due to the ancestry rather than the true association of allele to disease. Small stratification in population affects GWAS severely because large population size is required to detect common variant of complex disorders [5]. By combining the samples from multicentric GWA study, the complete analysis could result in population stratification. Population stratification could be detected and adjusted by applying genomic control approach [6, 7]. Tools like Eigenstrat analysis [8] and STRUCTURE [9, 10] could be used to address the biasness raised because of population stratification by combining data from different subpopulations and further linked with the data of cohort GWA studies.

34.4 Meta-analysis and the Contribution in Quality Control

The meta-analysis studies provide scientific clues in a particular field by combining all the relevant articles. It provides the precise and effectiveness of the study which had even shown less significance in an individual study. Hence, such studies are very useful in policy making and initiation of evidence-based treatment [11, 12]. As compared to GWA studies, the heterogeneity in literature selection can play a crucial role in conclusion of the study. Therefore, quality control in meta-analysis is an important component in order to provide impartial, balanced, and effective conclusion of the research done in the particular field.

There are some issues that may prevent biasness from the meta-analysis.

34.5 Random Selection and Independent Literature Search

A good and independent literature search is important to reporting the accurate conclusion in meta-analysis [13]. Literature search should not be confined up to only single database. Literature search and selection of article could be done on different search engines independently like PubMed or MEDLINE or Embase with three independent key words by each individual author.

34.6 Inclusion and Independent Review of Selected Articles

It is also important to isolate relevant article in the study and that should be reviewed by each authors to make their critical comments on inclusion and exclusion of the paper.

34.7 Data Extraction

Most data extraction analysis is based on the question to be addressed by the meta-analysis. Therefore, it is necessary in such studies to extract data independently with multiple individuals. It is useful to compare the results obtained from independent data extraction and resolve any divergence in the results or conclusion.

34.8 Analysis and Conclusion of Meta-analysis Studies

More rigorous and complex analysis is required in such studies, especially when it includes a large number of studies to avoid biasness in the conclusions of study i.e. there must be heterogeneity in data analysis. Heterogeneity is defined by how many variables are analyzed in the studies in order to make a harmonious conclusion. Heterogeneity could happen at the level of mythology, too. Moreover, the type of statistical analysis could also create statistical heterogeneity. Therefore, in any meta-analysis, it is imperative to report what kinds of approaches have been used in interpretation and analysis of data.

There are several guidelines statements being used. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [14] statement defines the guidelines to carry out the meta-analysis especially in clinical trials. Similarly, Meta-analysis Of Observational Studies in Epidemiology (MOOSE) [15] statement has also described the guidelines for epidemiological studies and their conclusions. These essential guidelines and protocols have also been described in "Cochrane Handbook for Systematic Reviews of Interventions" [16]. Recently, the Quality Of Reporting Of Meta-analyses (QUOROM) and checklist of meta-analysis statement provide descriptive protocol to present abstract, introduction, methods, results, discussion, and conclusion of the meta-analysis studies. It also defines the method of searching, inclusion, and selection of articles. It contains the checklist for inference, data assessment, validation, data abstraction, and extraction. By failing to comply to the QUOROM checklist, it could enhance the biasness of meta-analysis study.

34.9 Confidentiality and Security of Eye Genetic Research Data: A Case for Global Quality Control

Emergence of techniques to explore the human genomic information in order to provide the health care services and for the interoperability of information has increased the vulnerability to privacy breach. Patients' genetic data has direct implications on the family members at risk due to which exchange of genetic information needs to be regulated by timely documentation and installation of tools for protection of privacy, ensuring regulated health-care delivery. There is a need to have global law that ensures compliance by signatory nations so that confidentiality of patients is protected.

34.10 Definition of Genetic Research Data

Nucleic acid information includes targeted diagnostics, where a single gene or a polymorphism is evaluated; population-based newborn screening by MLPA, NGS, or PCR; and large scale microarray techniques which screen multiple genes and polymorphisms constituting genetic data. Analyzing human DNA, RNA, and banding patterns that aid in providing diagnostic and prognostic information about an individual or a patient needs regulation because more and more eye-related disorders are being discovered that have genetic basis [17].

34.11 Consent for Sharing

Most informed consent forms for data collection state that the information obtained will remain confidential, and it is made sure that disclosure is done with precaution. Though genetic information

constitutes medical information for individuals and families, there is a conflict between maintaining confidentiality with the family [18].

34.12 Storage

Most of the genetic information is preserved in the form of electronic data, which must be kept in server-based storage, and data accessibility should be strictly through virtual private network (VPN) in the secured network. Server domains are required to be allocated to the staff so that personal confidential data can be stored with restricted accessibility and back traceability.

34.13 Good Lab. Practices

Implementation of GLP principles has the potential to develop a system-dependent management besides delivery of diagnostic services and storage of genetic data in the secured places. Some of the GLP practices lacking in India must be followed as below:

1. **Master Schedule:** Each research staff could prepare a weekly plan of genetic analysis work to be completed in a month. Master schedule can then be submitted to quality assurance (QA) before the beginning of the month. QA can then review the progress of the research and technical staff at the end of the month.
2. **Quality Assurance**: Independent study, infrastructure and facility-based QA reviews could be carried out once in a month to record and monitor the deviations in genetic analysis. Study-based QA inspections can monitor the work as per their master schedule. Deviations from the master schedule can be documented and followed up in the next month. Independent checks of experiment are carried out to check the compliance to SOP.
3. **Formulation of Documents:** Standard operating procedures (SOPs), data recording sheet (DRS), and raw books can be maintained by QA and provided to research worker from time to time. Any experimental procedure performed in the laboratory could thoroughly adhere to respective SOPs enabling verifiability and back traceability of data and procedures carried out in lab from time to time. Any deviation can then be reported in DRS as well as raw book which could be the source of information for identification of problems. SOP and DRS should be stored in secured premises. Such systems can automatically impart quality checks at various procedures.

Standard Operating Procedures (SOPs) SOP can be prepared to streamline the experimental protocol and make administrative functioning of the genetic unit transparent and auditable. This may include specifications of experiments, along with time-dependent log sheets of chemicals and equipments used in the procedure. It facilitates the system dependence of research workers and reduces the scope of errors or confidentiality breach in handling genetic data of eye disorders. Any experimental and administrative procedure performed in the laboratory should adhere to respective SOPs approved by the management.

Data Recording Sheet (DRS) To minimize the procedural errors, DRS could be formulated for the real-time monitoring of genetic analysis. DRS can be prepared in consultation with study director and typically consist of procedures for identification of SOP, patient coding, sample locations, reagents used, and document control with assistance of QA. DRS can be issued only at the time of conducting the experiment and resubmitted to the QA after approval from the study director.

Personal Discussion and Lab Meeting A day in a week/month can be allocated to every research worker for quality discussion regarding the genetic testing platform, research problems, progress, and validation of vendors from which purchases are being planned so that there is continuous communication and sharing of information to avoid confusion and mismanagement.

Logbook Logbooks for each instrument used in genetic analysis could be helpful in not only maintaining the record of usage of resources but also ensuring error reporting and back traceability of data.

Log Sheet Log sheets can be helpful in organizing resources and their utilization in a timely manner. This may contain vendor information, expiry date, total amount, purchase information, and stock entry information.

34.14 Formulation of Checklists, Price list/Benchmark/ Instrument Files

Checklist Checklists can be developed to ensure the completeness of the task assigned to research workers, which compensate for the human limitations. Checklists can be formulated for all of the academic or administrative lab procedures including consent forms, human ethical clearance, and storage of research data as well as confidentiality proformas.

34.15 Instrument File

A logbook can be installed along with the instruction sheet and equipment maintenance file applicable to the experimental protocol at hand. Any experimental procedure performed by the use of these instruments in the laboratory can be adhered to, by following the respective instruction sheets. Any deviation can be reported in the logbook as well as instrument maintenance file which could be the source of information for identification of problems in the instrument. Instrument file can include calibration chart; service and maintenance chart; installation, operational, and performance qualifications; instrument manual; instrument password; and information of person to be contacted in case of emergency.

4. **Auditing:** Internal and external auditing of genetic data enhances the accountability and acceptance of the study. The quality assurance (QA) could conduct periodical audit of the progress and compliance and reproducibility of experimental protocol. The data generated can be filed in a defined format using raw book, calibrated instruments (with IQ, OQ, PQ), master code, log sheets, and regulated room environment providing backup for each facility (including power outrage). Validation of data from an independent lab is desirable in order to enhance transparency.
5. **Archive:** The archiving facility coupled with quality assurance program can allow maintainability of important records and samples, thus reducing the time of both the research personnel and patients.
6. **Master Coding:** Coding chart can be developed by laboratories to mask the direct sample information in the format, which can be easily decoded. Once a human sample enters in the laboratory, it must be made mandatory to code the samples in order to protect the confidentiality of valuable genetic information.
7. **Periodic Meetings:** Research workers who deal with genetic information can conduct periodic meetings to discuss the problems of genetic analysis in the experiments, storage, ethical issues, and compliance to quality control-related issues which can then be recorded and documented in the defined formats to further link the information in the common folders.

34.16 Conclusion

Quality control covers periodic training, knowledge of bioethics, confidentiality, and ownership of inventions, which is essential for supervising data quality. With the advancement of high-throughput genotyping and sequencing techniques together with improved analytical methods, the contributions of genetic and

environmental factors in the development of eye diseases needs to be clarified. Yet much remains to be explored and more quality control with appropriate applications is needed in genomics so that the data generated is helpful in practicing precision medicine. The ultimate goal is the development of a panel of quality standards for genetic testing in eye disorders in order to improve patient care and research.

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excellence in medical research – can we make it in india?

Introduction

The health-care system across the world has witnessed a phenomenal improvement so that the life expectancy in almost every country has increased significantly. Besides improvements in public hygiene, the newer non-invasive methods of diagnosis, newer drugs and unprecedented technological advances in treatment and patient-care have all contributed to the longer life span. This puts further demands on applied research for developing new drugs, tests, imaging techniques, surgical modalities etc, especially because the increasing population burden and longer lifespan have generated novel health issues that were not so critical even a few decades ago.

The recent unprecedented progresses in our understanding of Nature, biological systems and the amazing technologies now available to common man give an impression that we have solved most mysteries of the Nature's laws and principles that govern us. Armed with this belief, most of the economically advanced countries have placed priorities on "applied research", especially in the biomedical field, in order to ameliorate the increasing load of old age and life-style diseases. With detectable improvements in the overall performance of scientific research in India, it is often asked if India should also not place greater priorities on applied research in Medical Institutions.

Basic research as tool for transforming medical practice

Basic research in bio-medical field is usually understood as a tool to help unravel the disease mechanisms and identify drug targets through genetic and/or biochemical analyses. Such studies are generally carried out by MSc-PhDs. Ability to reading the human genome fuelled ideas that we understand most human disorders and therefore, can develop and apply personalized medicine. However, a deeper probing compels us to ask if we have really learnt enough about Nature's laws and life processes? A serious reflective thinking makes us realize that a very long path still lies ahead before we reach even near that goal. Consequently, concerns are already being expressed in the US and other developed nations about the wisdom on relegating basic research to non-essential, and therefore, avoidable entity. India has so far followed a balanced view and not succumbed to oft repeated question as to why we should spend limited resources on basic research. While technological advances appear stupendous and attractive, one must not forget that their roots are deeply embedded in knowledge gained through basic research carried out by passionate people whose only objectives were to unravel mysteries of nature. Only when the "mystery" becomes "knowledge", we can apply and exploit it. Mysteries of Nature continue to exist and baffle us and, therefore, stimulate basic research. Newer basic findings in conjunction with appropriately developed technology leads to affordable and integrative healthcare.

Where are the roadblocks?

While basic research efforts have generally been supported in India, we have not had many breakthroughs, either in biological or in physical sciences. Unfortunately, as a nation we do not also have many technological advances to our credit. Obviously, there is something wrong in the system, notwithstanding the large human and other resources being used in the process. Paradoxically, Indian scientists outside India have been doing very well and make us proud but when it comes to 'make in India', we are not able to feel the same sense of pride as most of the drugs, diagnostic kits or equipments used in healthcare are made outside India, including in China. Obviously, besides the limited resources, we have more serious systemic issues that underlie the country's generally poor performance.

Overburdened with patient load or human resources or both?

Our medical institutions, medical colleges as well as the mandated research institutions, are expected to be actively involved in research since all MD, MS, MCh, DM aspirants are required to carry on some "original" research and submit a thesis for earning the degree. In addition, the various regulations for appointments and promotions require research publications as essential components. Several institutions have also introduced MD-PhD dual degree programmes beside the PhD programmes. Thus, there is, in principle, a sizeable work force in place for carrying out research in the medical colleges and institutions. Unfortunately, only a small proportion of this large work force has the opportunity to work at places with fairly well-equipped infrastructure. Most others work under rather difficult conditions including very long continuous "duty" hours. They are also constrained by inflexible time-limit for completing the "research" component of the degree. A continuity of research is also not maintained so that each new student works on different topics rather than extending the theme where the previous one had left. As a result, the research output remains rather disappointing and the enormous advantages offered by the human resource on one hand and the diversity of Indian population on the other is almost completely lost, and we continue to rely, for diagnosis as well as prognosis, on data generated in other countries with very different genetic and physiological backgrounds.

The formal teaching load of a typical medical college faculty is usually not as high as those teaching in basic science departments in a university or college, although in most of the clinical disciplines, teaching continues in OPDs, wards and on the operation table as well, somewhat parallel to "teaching" that goes on in basic research labs. A common explanation for the rather limited novel research output from medical institutions is that the medical college faculty members have patient load amidst meager infrastructure which leaves them with little time and energy to think about any serious research. This may possibly be true to some extent for faculty in clinical disciplines at a medical college attached to big hospital. However, the medical faculty in better endowed medical institutions may not be engaged with OPDs/surgeries or wards on every working day and, therefore, the average per week workload may not be exceptionally or unduly high.

This may be due to large number of physicians in such Institutes. Compared to

the many private/corporate hospitals, faculty positions at publicly funded medical colleges generally fare poorly in terms of service conditions, salary/promotions and facilities. Existence of significant disparity amongst different state and central institutions, poor infrastructure for research in medical colleges, inevitable bureaucracy associated with administrative issues of running hospitals, all add to the medical teaching institutions becoming less favoured places of work. This adversely affects the academic output of the institution.

Medical colleges generally seem to have a strong hierarchical and authoritative set-up. This thwarts the enthusiasm of young and capable faculty who wish to go beyond the routine health-care. A healthy academic and productive environment demands equal participation, incentives and opportunities for research.

Collaborative involvement of basic scientists in research, administration and policies relating to medical research

Medical institutions also have "non-clinical" or "para-clinical" departments/units whose faculties are not directly involved in clinical practices or patient care. Unfortunately, even their research output is also generally not impressive. At the same time, the administrative dichotomy created by differential privileges and responsibilities of the "clinical" and "non-clinical" faculty members remains a major cause, often unnecessary and avoidable, for heart-burn and conflict that affects basic as well as applied bio-medical research in medical institutions

Notwithstanding our *ad libidum* appreciation of practices followed in western countries, we have kept the medical education and research separate from basic sciences as well as technology. On the other hand, almost all the leading biology departments in US universities are parts of Medical schools. Although models for integrative learning and teaching have been frequently discussed in the country and many detailed reports prepared, the fact is that we continue to ensure compartmentalization and fragmentation that percolate down to the smallest unit possible. Absence of integrative research with collaborative basic science leadership remains a major impediment to 'Make in India' based innovation in Medical Institutions.

In the context of "conflicts" between "clinical" and "non-clinical" or "basic" scientists in our medical institutions, an idea has sometimes been mooted that the country should have "Basic Science Council" along the lines of the existing "Medical Council", "Dental Council", "Pharmacology Council" etc. However, whether establishment of such councils and formulation of rules will solve the conflict or promote any better research environment remains to be seen. An example of well-meaning but poorly formulated and implemented rules that result in more serious ill-effects is the introduction of the "Academic Performance Index" by the University Grants Commission to ostensibly promote academic activities. Paradoxically, these measures have generated more graft than promoting any better academic environment or performance. Thus even well-intentioned rules can become counter-productive when driven in the wrong direction.

It is indeed a sad commentary on the state of affairs that while we have not been able to make significant inroads in modern medicine, we have also failed to capitalize on our age-old health-care system of Ayruveda, in spite of our sense of pride at the great wisdom of our far-removed ancestors. As discussed elsewhere, including in these pages (Lakhotia, 2013, Ann Neuro), Ayurveda continues to suffer because of want of serious unbiased inter-disciplinary research, which alone will help us understand its principles and to resolve between myths and reality. It is notable that Chinese have smartly integrated Chinese Medicine as part of formal Medical curriculum. Such integration in Indian context can be promoted by inclusion of multi-disciplinary basic science experts together with practicing clinicians in various committees, governing bodies and other advisory bodies of Ministry of Health and Family welfare.

Basic scientists and clinicians as complementary stakeholders in medical education and research

How do we initiate and establish a more stable and interactive dialogue between the clinical and basic scientists and also involve technological experts in translating basic bio-medical research into real applications? One of the steps initiated in recent times to bring in some integration is the introduction of M.D.-Ph.D. dual degree programmes. However, it is not clear as to how these would be qualitatively different from the regular MD or PhD dissertations, since such programmes do not ensure interactive participation of basic and medical scientists, especially when PhD-MD candidates are rather rare (Anand and Rao, Ann Neuro 2014). In any case, what we need are long-term research collaborations on specific themes which, on one hand generate new basic knowledge/databases and on the other promote better health-care or usable indigenous technology.

Creating positions of basic scientists within the medical colleges/institutions, who lead well furnished and independent laboratories, can provide opportunities for MD/MS/DM/MCh as well as PhD students to work under joint supervision of Scientists and medical faculty. Physical placement of such labs within the medical college/hospital is expected to facilitate better interaction since the clinician can walk in any time for interaction with scientists, who can similarly walk to OPDs or surgery tables. Such basic research scientists can guide and monitor "directed basic research" in identified core areas that impinge on basic health-care in the country. A model of "directed basic research" was initiated some years ago, with success, to revive understanding of the basic science underlying Ayurveda.

Recent years have witnessed an increasing number of better equipped corporate health-care systems with lucrative pay-packages. These are good destinations for utilization of basic science research skills but have remained untapped. With increasing involvement of the better equipped corporate sector in health care, it would be prudent to engage them into a public-private partnership so that they function as technology incubators utilizing research outputs from both public and private medical institutions.

Initiating teaching programmes which involve co-participation of basic scientists and clinicians is another avenue that fosters sustainable partnerships. An example is the discipline of Human Genetics. An increasing proportion of contemporary health issues centres around genetic factors. Unfortunately, the medical curriculum does not adequately prepare the medical doctors to understand the complexities of genetic disorders, their diagnosis and possible treatment. Formal co-training of science students by basic scientists and medical professionals, through didactic lectures, would not only prepare appropriately skilled human resource, whose demand is continuously increasing world-wide, but would also

foster a better dialogue between the basic scientists and medicos. The Molecular and Human Genetics MSc programme started at the Banaras Hindu University about 15 years ago is an example of such success story. Next step in this direction should be to prepare courses for Genetic Counselors. Equally rewarding would be development of training and research programmes in metabolomics and microbiomes, which have also become hot areas in contemporary health-care.

Appropriate changes in the archaic rules that govern medical education and profession together with active participation of all concerned would make a value addition and generate the much needed manpower to collect and understand data for genetic and physiological makeup of Indian populations. Such data are essential to provide "Make in India" health care in the country.

Conclusion

Medical research is not singularly poor in our country. We have less than impressive performance in other spheres of research, innovation and technological development. The poor performance of medical research, however, has more serious repercussions since it directly affects health of people and therefore, of the nation. Obviously, we need to ensure quality medical research on a much larger scale. More than rules and regulations, what we really need to achieve these goals include: i) commitment and passion, rather than compulsion, for research and innovation combined with necessary mentoring, ii) bi-directional interactive and integrative environment that promotes and sustains collaboration between clinical and basic scientists on one hand and the technologists on the other, who can convert innovative findings into usable technology for affordable healthcare, iii) good training of medical students in clinical research especially for those who are inquisitive and research-oriented and iv) adequate independence of doing research to take their discovery to masses.

There is an element of "conflict of interest" when it comes to considering the medical profession as a profession that is directed solely to treat patients and earn the livelihood in return. It is argued that to be able to get into active clinical profession, which usually implies obtaining super-specialization degree, the young person has to spend many more years of life, often under rather unpleasant conditions, than is the case in other professional courses. Therefore, they feel that they are entitled to greater monetary rewards than the NPA available in most academic institutions as a compensation for losing on private practice. Such disgruntled persons cannot obviously give their best just like those basic scientists who seek introduction of non consultancy allowance (NCA). New salary structures of medical faculty. normalized to per hour risk free engagement, is often argued to provide remunerations equivalent to private centres. A substantial increase in the NPA or introduction of NCA for basic scientists may, therefore, not be the best or lasting solution. As long as we do not develop a system of identifying the right kind of human resource for a given job, such conflicts of interests and poor outputs would continue. Just as every MSc or PhD degree holder does not by default become a scientist, a basic medical or even a super-specialty degree would not generate a medical researcher. While we need a large number of researchers in the bio-medical fields, we need equally large numbers or more of medicos to attend to basic health issues in rural and semi-urban areas. Therefore, what is required is to identify and promote the young aspirants into paths that better suit their temperament and capabilities than stereotypes. There is no point in trying to fit square pegs in round holes or vice-versa. Facilitation of suitable matches and optimally promoting their activities is essential for us to really make excellence in India.

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National model for replicating benchmarking of basic research investigations in govt institutes: a case for ministries of science and technology and health and family welfare

"Good Laboratory Practices (GLP)" enshrined under the OECD guidelines provide an excellent framework in raising the bar in research productivity in our country. Ironically, none of the publicaly funded labs in the country have adopted these norms for basic research investigations. If these norms are adopted it may result in enhancing the quality standards, increase credibility, efficiency and transparency of research and diagnostic facilities. This is the first time that the Neuroscience Research Lab at PGI chandigarh was awarded National Award by Quality Council of India for implementing quality principles voluntarily. This innovation has led to a system dependent technical and managerial procedures facilitating research audit and document control, improving purchase and accounting procedures as well as human resources besides delivery of patient care diagnostic services.

The conventional system of running research labs in India is based on no established or uniform method of management relying on individual preferences and experiences. Unfortunately, even the individual medical institutes do not define modules of running research facilities unless mandated by GMP requirements defined by regulatory authorities. This happens in the case of clinical trials where patient's safety and care is involved. These trials have been presumably halted due to questionable data and lack of back traceability of information. The ability to bring clinical level safety at the pre-clinical (basic research investigation) level makes this innovation unique transparent and credible for effective clinical translation. This can stimulate knowledge economy and attract huge investments from around the globe.

The current quality systems in Neuroscience Research Lab encourages goal driven, self proposed monthly master schedule of activities in consultation with the study director, using the combination of Standard Operating Procedures (SOPs), Data Recording Sheets (DRSs) and master schedules. The Quality Assurance (QA) conducts periodical audit of the progress, compliance and reproducibility of experiments giving a new lease to research output. The data generated is filed in a defined format using a mandatory raw book, master code, calibrated instruments (with IQ, OQ, PQ), log sheets with continuously regulated infrastructure and room environment providing back up for each facility (including power outrage). This data and samples (if any) are archived in defined shelves or freezers as the case may be so that research productivity and quality is enhanced. The electronic repository of entire data is maintained in dedicated servers secured by physical installation of firewalls.

The entire system in the research facility operates under a moral obligation for biannual external audit by senior quality assurance experts which includes proficiency testing. This innovation encompasses periodic training of research personnel and staff to not only engage in academic activities but also bio waste management, sanitation, fire extinguisher safety, firsy aid, animal handling, and development of IQ (Intelligence quotient), SQ (Spiritual quotient), EQ (Emotional quotient) through periodic orientation programs which are essential for mentoring of independent neuroscience research leaders for tomorrow.

This innovation aims to enhance the reproducibility and error reporting of research data and sustain quality system in research practices, thereby facilitating a higher sincerity of purpose for research in medical institutes in India. This system also seeks to bridge the credibility chasm that exists between data generated from India and that from the West, because of which the best research from India is rarely taken seriously. The frequency and quality of research papers from this research facility provide for an innovation which has improved the credibility of research generated from this research facility. This is expected to boost discovery and innovation thereby accelerating translational research.

Implementation of this concept has led to benchmarking of research projects which are usually considered a soft activity in medical institutes of India, thereby enabling reliable translation of bench to clinic. This innovation has led to a system dependent technical and managerial procedures facilitating research data reproducibility, audit control and document control.

It is a perfect time for new Ministers of Science and Technology and Health and Family welfare to take note of this and consider instructing the funding agencies like DST, DBT, ICMR, DAE, DRDO under them to demand quality systems to be implemented in labs before releasing tax payer's money to them for research and development. Neuroscience Research lab can be converted into a national reference laboratory to mentor this activity.

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Akshay Anand
Editor in Chief

need for innovation in medical institutions

Practice of Medicine is rapidly changing the health seeking behavior around the world, however, an important aspect of this field hasn't changed in India. For instance, we have not witnessed credible translation of medical training or knowledge into indigenous solutions for surgical modalities or diagnostics. Can we do something about bringing transformation in order to make larger impact on Indian society? Let us discuss the various models of how to fill that big gap: the distance between competence and excellence, and how by doing so, one could attempt to amplify the efforts through multi disciplinary patient centric approach.

Overcoming stereotypes

There are a number of things that one is taught which are believed to be correct at the time of medical training. However, much of it has the possibility of being incorrect as one begins to test waters in real life. Avoiding the trap of thinking that one knows everything as well as projecting this to patients as such generally helps one excel and maintain an honest relationship with patients. Therefore, carrying the amber of doubt in the practice of medicine is the key to advancement in the field. For the very reason that doctors are often perceived as having certain stereotypes: all knowing, upright, trustworthy, clever, conservative, authoritarian etc, as medical students, one may have pressures to conform to one of these stereotypes. One shouldn't. A lifetime spent trying to become something you are not may destroy you. Being oneself and trying to learn steps that help bridge the gap that separates one from simply being competent to being excellent and innovative is the basis of originality in research and translation. One of the recipes to instill innovation is also to become investigative, carrying the amber of doubt while accosting every patient in a clinic or ward. There are many thinkers that argue that doctors should even share their ignorance with patients and together help patients overcome their misery. Evidence shows that genuine partnerships with patients generates better outcomes and greater satisfaction for both patients and doctors.

Innovation

Medicine is not only clinical work, it is much more: working out relationships, teamwork, communication skills, research, innovation, publishing and critical appraisal. With the amber of doubt one is more likely to discover new clinical associations, syndromes, and solve problems that medicine had never previously resolved. However, such efforts require multidisciplinary approach that should include individuals from basic sciences, engineers, MBAs and even patients. Some of us wonder why is this important when rush of patients need to be immediately addressed. This editorial is an attempt to argue that a link exists between such innovative endeavours and value addition in practice of medicine. As mere glance at the make of hospital instruments or prescription of drugs reveals that most of these are imported, invented by individuals outside India. India pays a huge cost for buying these drugs and instruments in the form of inventorship costs i.e patents acquired by scientists who are not resident Indians. These individuals have even gone out to win Nobel prizes in Medicine. Eventually, the cost of import combined with commercial cost of patents held by these individuals (read countries) is recovered from the end user i.e the patients. If the these individuals could be one among us, being passionate about converting the zeal into undertaking that journey between competence and innovation, such inventions could transform the Indian medical world. This is possible in collaboration with other stakeholders in healthcare systems such as Pharmacologists, basic scientists, venture capital and engineers. Such models have capacity to drastically reduce the healthcare costs directly affecting the costs of healthcare delivery. This is exactly why many of us argue research and innovation as the potent tool to advance our knowledge economy (or health economics), in whatever way one puts it.

There are limited number of innovators in India such as Dr. Sathya Jeganathan who invented low cost incubators, Dr. V Mohan who spearheaded mobile telemedicine clinic, Dr. Prakash Khanzode who invented affordable patient beds and so on. There are even student role models who have published over two dozen articles in international Journals while in final year of MBBS. However, such examples need to increase in numbers. Kalam-Raju stent is another example of home grown stent which could not have been possible without residents not taking such an initiative outside immediate call of duty. The ability to say 'Yes' to opportunities outside immediate world of clinics and surgeries and venturing into medical innovation may add even great value to the healthcare landscape in India. It is time that our residents and trainees step out of the routine medical world and play 'larger' role in patient care through innovation driven entrepreneurship.

Research learning cycle

Learning is the basic ingredient for innovation. Orthodox learning may have stopped for us today, with acquisition of degrees, however, neither us nor our senior teachers can claim to know everything. They are still students as much as we are and are still learning. There are many methods of learning that are available in the field of medical education and depending on the one you adopt, you can make bigger impact in your field. Conversational or blended learning involves combined interaction and discussion at multi disciplinary level which has often been advocated to result in innovative spirit and should therefore be encouraged. Every patient, for that matter, can be regarded as a learning material as well as a research project that requires one to pause, listen and investigate, treating a patient not as organism replete with similarity of symptoms that characterize a certain disease, instead, one with a unique phenotype. Documenting and building patient data and compiling various investigations from various patients examined, may result in generation of new knowledge that can be useful drug trials and systematic reviews of tomorrow. These ideas can also become the grant applications seeking research funding from funding agencies. The colleagues in research learning approach could become our collaborators and the data we generate can become original research papers and patents.

Applying such knowledge for innovative solutions to existing clinical situations may then lead to discovery of new drugs, surgical techniques or diagnostics which is what India needs today at an affordable price in order to transform its healthcare infrastructure.

Nobel Prizes

At this point it would be pertinent to be introduced to the world of high achievers most of whose research and innovation has transformed healthcare. Analysis shows that majority of Nobel prizes, constituted by Alfred Nobel's foundation, to reward the outstanding contributions towards mankind, have been won by individuals from West. Closer analysis also shows that average age of research productivity of these Nobel Prize winners peaks at 35-45, which is the age we reach in a couple of years after getting the regular tenure track. With an award coming from Alfred Nobel's will, each prize continues to approximatea staggering USD 1 million. Many surgeons and physicians have distinguished themselves by winning Nobel Prize in last few decades. These include Prof Banting (for Insulin), Prof Yamanaka (for induced pluritotent stem cells), Prof Mansfield (for MRI) etc. With growing number of MD Nobel laureates the national focus has shifted towards capitalising the potential of the physicians and surgeons so that they could convert clinical knowledge into innovations. Such innovations from India can have immense ripple effect on patients whom we have not even seen. This was also the reason cited by Prof Yamanaka when he described his shift in focus on medical research (than just clinic) while choosing to work with induced pluripotent stem cells and providing a technology to convert skin cells into embryonic like stem cells, a feat that won him the Nobel Prize in 2012.

These efforts could not have been possible but for a care for quality work: generating data that is authenticated, test samples which could be back traced and records and investigations which could be audited. In other words implementation of quality systems is the heart of innovation. Working in an accredited hospital is a definite advantage for those clinicians who wish to organize their time well. Those hospitals who do not have such systems should implement such guidelines in order to bring more transparency and quality in practice of medicine. Medical students should similarly participate in activities of quality clinical care. Collaborative spirit combined with inter disciplinary pursuits in Medicine is the only way one can bridge the chasm that separates competence and excellence.

Mentorship

Mentoring requires a big heart and passion to derive pleasure at one's trainees surpassing our own professional expertise. The joy of celebrating colleague's success is not experienced by each one of us. Only those who have crossed that vital bridge separating mediocrity from excellence experience such a bliss. We should aspire to reach that stage from where we do not envy anyone, from where we are able to disseminate knowledge, wisdom and share experiences.

Last, but not the least, it is important to emphasise the value of creating female medical leaders in the field. With their increase in the field, very few have reached the top managerial positions. Even reviewing the gender based winners of Nobel laureates, only 85 out of 823 Nobel Prizes have been found to belong to females (with Madam Curie topping the list). This needs introspection. Studies have also shown that female students do exceedingly well in their academics but are reluctant to take up leadership positions in academia and innovation enterprises, leaving enough scope for filling the void. Female medical students should therefore seize the opportunity and lead the field by participating in innovation endeavors so that the mankind can benefit from their intellect, compassion and integrity.

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Akshay Anand

Editor-in-Chief

medical education and training: implications for india

(.....continued from page 133, 20–4)

The Curriculum

Unlike other countries in the World, MCI regulates a centralized curriculum for the undergraduate and post-graduate courses. In the US and UK, deciding the medical curriculum is the prerogative of the Universities. Medicine has a vast and comparatively wider array of subjects to be studied. These subjects have both clinical and non-clinical distinctions.

In undergraduate studies, the students are exposed different subjects, which are divided based on the hours of lectures, case studies and practical hours. The sole dependence of the undergraduate students rest on their respective professors, who remain busy practitioners burdened with administrative duties. This makes it very difficult for the students to get their queries and doubts cleared. The non-clinical departments like Anatomy, Physiology, Biochemistry, Pharmacology and Microbiology, where theory is emphasised, are being slowly phased out in the West; replaced by elements of genetics and molecular biology but nearly 1480 course hours have been dedicated by the MCI for the practicals in such subjects. Is it worth it? This uneven and insufficient cocktail of subject-exposure deprives the students of both clinical and research expertise. The undergraduate students are rarely posted to emergency wards and therefore lack the knowledge of how to deal with critical care. Many argue that there should be a proper interface between the teaching module by balancing patient contact and associated classroom teaching. Learning the diagnostic and interventional techniques can be brought about only by the contact with the patient and in-ward studies. The teaching and interpretation of further diagnostic measures like Case study, Report study, Therapeutic learning, history taking skills and short listing of differential diagnostic measures can be carried out in class rooms. In the situation where there is lack of facilities and resources it has been seen that peer-assisted learning provides a tangible solution to the problem of clinical teaching skills to a very large group of students: Indeed, it is a norm worldwide. This can work quite well in the medical colleges in small cities with comparatively less busy work environment but can prove fatal in the present day case scenario wherein the senior medical students are insufficiently and poorly trained. The undergraduate students should be posed with questions based on the cognitive skills and problem solving exercises from the case studies. Perhaps, age old memory based MCQs should be replaced.

The emphasis on problem based teaching, case based questionnaire, clinical-rounds, distinction in class room and in-ward based teaching and developing a centralized promoting examination could prove to be a vital checkpoint for the eligibility and accuracy of the medical graduates. As quoted by Sircar: When an ill-trained MBBS doctor begins his independent private practice, he poses a greater hazard to the patient than the ailment he purports to alleviate.

Some of the deficits in skilled human resources can be overcome by astute planning and by way of integration of nursing services with the medical curriculum. It is almost a requirement in a resource starved country like India that the semi skilled individuals are trained in primary health care and mobilized for health care, especially for rural health care. The deficiency of medical health workers can be met by upgrading the training and standards of paramedical and nursing care. The nursing community worldwide, is fairly experienced and well equipped with various medical procedures like deliveries, midwifery, vaccinations, first aid, primary infections like cough, cold and fever and can perform small interventional surgeries like removing foreign bodies from the eye and nose etc. They can act as full-fledged doctors and take care of the ground level requirements and ailments of the medical field at the primary level. This is very well elucidated by the example of Norwegian nurses running a hospital successfully.

The gaps in teaching because of the time and staff bound discrepancies can be tackled by the intervention of IT in medicine. Training programs and classroom based courses could be launched through internet portals, as already followed in the west. Such a model has been developed by Prof Rakesh Biswas and widely known as the user driven health care system developed at Bhopal's People Medical College. Diplomas involving Telemedicine, Teleradiology, and other paramedical courses could be encouraged as much as courses on Translational medicine as discussed below.

There needs to be re-organization of fee structure in medical colleges. The imposing of heavy Fee-structure on private colleges and relatively stringent regulations have not been matched by fees in Govt Institutes that are purely funded by national tax collected from various states. Like the West, a medical graduate student could be encouraged to pay up for the undergraduate fees and repay it at a flexible rate of interest once he/she begins to earn. The in-service internship mandating service in the villages and remote areas by Ministry of health and family welfare is an admirable step in this direction. This will not only encourage the optimal utilization of tax payer's spending in healthcare but also retain the health workers in the country who begin to write ECFMG tests soon after being trained from national resources.

Mobility between medical and research fields

As elucidated earlier, both undergraduate and post graduate students lack the complete knowledge about the pathophysiology of ailments and this leads to incompetence and lack of innovation in diagnosis and therapeutics, thus impacting sustained enthusiasm in treatment of patients. Opportunities for both MBBS and MD/MS students should be provided to pursue core biomedical research. Both clinical and non-clinical residents should look forward to research as a new frontier for translating knowledge for better affordable healthcare. Likewise, non-clinical researchers i.e. PhD trained personnel, pursuing core scientific research, should exhibit equal enthusiasm in pursuing MD under a two year hospital training under innovative "to be launched PhD MD programs" and advance knowledge for utilization in health care delivery or translational research. Of course this will require bold changes in policy. Tailor made jobs should be simultaneously implemented in research or medical institutions at the faculty level such that these uniquely trained individuals could be recruited after completion of their courses.

Encouragement of medical Entrepreneurship

Innovation is the key to deliver affordable healthcare products in any developing country, including India. Entrepreneurship has a major role to play in medical education in India. Innovations combined with entrepreneurial strategies can bring about a radical reform in reviving the economics of medical education. New healthcare products could be generated as per the needs of the country which should be cost effective and consumer friendly unlike the international and multinational brands. There is an urgent need to include training in innovations in medical entrepreneurship. This can be achieved by chalking out a vibrant program developed with collaboration of technology incubators from different disciplines with the help of industrial tie ups.

Human resource management

The biomedical engineers and lawyers are exposed to labor-management or resource-management at some stage or the other. The knowledge of medical professionals is limited by the exposure to manage patients on an individual basis without much exposure in professional management. There is generally no lateral advancement of knowledge among medical graduates for the administrative acumen applicable to medical education and training. The Department Heads in general need to manage the paramedical staff, medical staff, healthcare and diagnostic duties based on adhoc experiences rather than a structured module.

In already resource starving situations, the lack of vision of deployment of skilled resources in optimizing OPD productivity requires the statutory bodies to review inadequate allocation for human resources for patient care. The above problems can be sorted out and optimized by involvement of educationists, professional managers, physicians and social activists. An assurance of the quality in management of medical institutions can be achieved by the audits of the performance of health care workers. Recently, Times of India published an interesting analysis of working hours of senior physicians in National Medical Institutes, arguing that majority of faculty at such institutes has considerable time for innovation and research, owing to a few OPD hours as per week, due to rotation duties coupled with innumerable vacations, conferences etc. An annual audit of deployment of healthcare workers should be implemented either centrally or by an institution which should govern the smooth running of the hospital based on patient feedback.

Re-organization of medical education managers

Keeping into view the drawbacks in the current managerial system in the publically managed medical education systems, there is an urgent need for re-organizing the panel. The medical education managers and the board need to be re-organized. The panel should constitute members from different spheres rather than medicine alone. A medical institution is a site with plethora of activities with different elements of society working hand in hand. Hence, a proper reconstitution of the statutory body is urgently required. The people form different spheres who constitute the panel, with qualifications as diverse as MD, PhD, Judiciary, Law and civil society have now been incorporated in the newly reconstituted MCI.

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