ETHICAL ASPECTS OF BIOMEDICAL AND HEALTH RESEARCH

After the overwhelming response of three workshops on research methodology conducted over the past 6 months, RUHS conducted workshop on ethical aspects of biomedical and health research on 8th and 9th April which was third in row.

The workshop was declared open by the Hon'ble Vice Chancellor, Dr Rajababu Panwar. The objectives of the workshop were briefed by Dean, faculty of Medicine, Dr Bharti Malhotra. Dr Reshu Gupta, Assistant professor, Physiology moderated the 2 day workshop. The workshop conducted by Rajasthan University of Health Sciences, Jaipur was supported with grant in aid by Indian Council Of Medical Research, New Delhi and Rajasthan Medical Council accredited the workshop with credit hours to participants.

The workshop was graced by dignified speakers like Dr VM Katoch, former Director General of ICMR; Dr Nandini Kumar, former Addl Director General of ICMR; Dr Nalin Mehta, Professor, Physiology, AIIMS, New Delhi; Dr Lalita Savardekar, Scientist E at National Institute for Research and reproductive health, Mumbai; Dr Visala Annam, Deputy Drugs Controller, Govt. Of India, New Delhi; Dr Urmila Thatte, Professor and Head, Pharmacology, Seth GS Medical College, Mumbai; Dr Bharti Malhotra, Sr. Professor, Microbiology, SMS Medical college, Jaipur; Dr Hemant Malhotra, Professor and Head, Medicine, SMS Medical College, Jaipur; Dr Kiran Katoch, former Director at National JALMA Institute for leprosy and other mycobacterial diseases, Agra; Dr Manoj Das, Director Projects at INCLEN, Trust International, New Delhi.

The workshop commenced with the session on *'History of evolution of research ethical guidelines'* by **Dr. Nandini Kumar**. She talked about how ancient civilizations over 4000 years ago acknowledged the influence of cosmos and the external environment over people's bodies. All traditional medicine, be it Ayurveda, Unani or Siddha requires a doctor do his very best to obtain information that will benefit his patient. The basic codes of ethic that existed in ancient India (30th century BC) can be divided in two fundamental sects; Sadharana and Visesa Dharma. The former relates to the moral values that are instilled in every human since birth (doing good, honesty, diligence) while the latter concerns the professional and societal obligations (based on caste, sex, age) a person has. Meanwhile, the earliest bioethical code found in the West is the Hippocratic Oath in 4th century BC. A set of codes which bore semblance to bioethics in the modern history was born in 1740. The first National AMA code was established in 1846 and internationally in 1897 while the term 'bioethics' was coined in 1960.

A set of moral beliefs most individuals agree with is shape the societal code of ethics which are translated into legal terms to be properly executed and regulated by the law. There are 2 schools of ethical thought; Utilitarianism and Kantianism. The former believes that the actions are right if they cause the greatest good for the vast majority even if it needs incurring

some minor losses along the way (Means to an end) while the former dictates that every deed done should strictly adhere to moral principles no matter what the outcome be (the ends are means themselves).

The 4 main principles of modern ethics are Autonomy, Non-malevolence, Beneficence and Justice.

The need for ethics in the 20th century arose due to atrocious human experiments like Guatemala trials and the ones carried out by the Nazis during World War 2 in the name of science. This led to the establishment of Nuremberg Code and Declaration of Helsinki in 1947 which stated need of an ethical committee to add or subtract and review ethical codes, independent of people associated with the research. MCI followed up with a set of guidelines in 1956.

Instances of code violation after 2000 include Bhopal gas tragedy, implanting a pig heart into a human, HPV vaccine trials in Andhra Pradesh, etc. These further reinforce the need to apply and execute bioethical guidelines.

Next in line was the session on *'Roles and Responsibilities of Ethics Committees: Ethical Review - Objective manner, Scientific Review Ensure scientific soundness'* by **Dr. Lalita Savaredkar**.

It is essential that all proposals on biomedical research involving human participants should be cleared by an appropriately constituted - Institutional Ethics Committee (IEC), Institutional Review Board (IRB), Ethics Review Board (ERB), Research Ethics Board (REB), Ensure Technical appropriateness. Roles & Responsibilities of Ethics Committee Ensure protection of the rights, safety and well being of the research participants, initial and continuing review of all scientific, ethical, medical and social aspects of research proposals objectively, timely and independently. The committee should ensure that universal ethical values and international scientific standards are followed in terms of local community values and customs. It should assist in the development and education of the research community responsive to local health care requirements. Responsibilities of Members should be defined to ensure the scientific soundness of the proposed research (scientific review committee prior ratification).

Role of Ethics committee members was discussed in details – To declare any Conflict of interest to the Chairperson, recording in the Minutes, Review protocols, attend EC Meetings and participation in Discussions and deliberations, Review the progress reports and final reports, Review Serious Adverse Event reports and recommend appropriate action(s), Carry out Monitoring visits at study sites as and when needed, Maintain Confidentiality of the documents and deliberations of EC meetings .Role of each member of committee was communicated in detail.Large institutions/ Universities with large number of proposals can have more than one suitably constituted ECs for different research areas. Benefit-risk assessment should also be seen by Ethics Committee.

Participation in Continuing Education Activities in research ethics with updates on relevant guidelines and regulations.

Overview on the steps taken by IEC (Ethics Committee) for protection of volunteers' interests in genetic research (stored samples, clinical trials and gene therapy). IEC plays a central role by assessing risks and benefits and tries to anticipate unknown harms, makes sure the researchers respect the cultural values of the place, reviews conflict of interest, ensures the privacy and anonymity of patient is protected.

The elements of consent form, along with asking the patient if s/he is really willing to participate, include informing the patient about nature of research, probable consequences (aftermath), direct/ indirect benefits. At times, the researchers may take broad consent which means they collect the patients' samples for research on unspecified topics at a later time. The IEC also looks into the how the samples are stored, return of results and publication aspects.

Dr Urmila Thatte delivered her talk on *'Ethical Issues in Genetics and Stem cells research'* She started her talk by a question on Who should consider the ethical implications

- Sponsor/PI (Design)
- Conduct (PI)
- Participation (Patient)
- Regulation and Ethical review (IEC)

Types of Genetics Research which is being submitted is Genetics testing, Using stored samples and Gene therapy – clinical trials. Broad issues which should govern such issues are:

- Sensitive to and respectful of local values and cultures
- Benefit of local people (also generalisation)
- Community participation: fairness, equity and reciprocity

Role of IEC in such issues are: Privacy and confidentiality, Conflict of Interest (IEC and Investigator),as a matter of fact Prospective participants in research should be informed of the sources of funding of research, so that they become aware of the potential conflicts of interest and commercial aspects of the research. IEC should consider Qualifications of PI/Team, experience and Communication skills. Written informed consent mandatory for research with Full information [known harms, unanticipated harms as in Jesse.]If participant is a child consent from – LAR and If illiterate – literate witness. If Genetic research is on a "community" or "population groups" consent must be taken from the community head and/ or the culturally appropriate authority. This does NOT replace individual consent. Role of IEC is to take four tiered consent. IEC should also consider inclusion and exclusion criterion, Benefits V/S Harms. In publishing results care should be taken in publication of pictures, pedigrees or other identifying information about individual or family members or secondary participant(s) should be done with fresh or reconsent. Features on the face masked to prevent identification. If these features have to be revealed for scientific reasons, this fact should be stated clearly in the consent form and fresh consent must be obtained if not taken earlier. All gene therapies are considered as Research and all precautions should be taken.

An excellent example which accentuates the need of an Independent Ethics Committee to regulate research activities is the case of Jesse Gelsinger, a 17 year old boy who died within 4 days of taking part in a clinical trial due to negligence and lack of transparency from the researchers' side. On proper investigation it was discovered that the complications and deaths of animals who took this drug were kept hidden from the volunteers as the head of ethics associated with this project had money invested in it, leading to obvious conflict of interest.

An emerging branch of genetic research is stem cell research/ In India it falls under 3 categories; permitted (In vitro studies for understanding their basic biology, Research on SSCs , restricted (with the specific aim of deriving ES cell line for any purpose and prohibited in Human germ line gene therapy, etc. In Stem Cell Research it is mandatory to maintain registry of its investigators who are conducting stem cell research and maintain confidentiality and privacy, provision made for traceability in a contingency situation (and donor told this) and Donors should not be exploited and commoditized

The presentation by **Dr. Visala Annam** on '*Drugs and Cosmetics Act and good clinical practice guidelines*' focussed on the legal enactment for clinical trials for new drugs, function of CDSCO, Schedule Y and conducting the clinical trial. A new drug includes something not used before in the conditions prescribed, all vaccines and rDNA products or a modified version of an old drug. A drug is considered 'new' for 4 years. The testing, approval, banning, licensing and registration as well as amendments to existing acts are dealt with by CDSCO. Schedule Y consists of rule 122A, 122B, 122D, 122DA, 122DAA and 122E in the Drugs and Cosmetics Rules. It deals with the responsibilities of the sponsor (monitoring, record keeping, compensation for participation, supply and storage of pharmaceutical drugs, safety information), investigators (compliance to protocol, reports, data handling, communicating with ethic committee) and ethics committee (composition, terms of reference, review procedure, record keeping, special considerations).

There are 4 phases of clinical trial; Human pharmacology, Therapeutic exploratory, Therapeutic confirmatory, and Post marketing.

The conduct of trial is as follows- screening of subjects by the investigator with various diagnostic tests to ascertain if they fit the inclusion/ exclusion criteria, A-V recording of informed consent process. The tests are then properly documented and it's made sure the drugs are given according to protocol. Storage, dispersal, quality and quantity regulation must also be diligently recorded. The patient's medical records should be updated to indicate s/he is taking part in the trial and any adverse effects must be noted as well as treated accordingly. In case the study is abruptly terminated, the respective committees and people involved must be informed along with the reason.

Dr. Nalin Mehta delivered his talk on 'Research with Vulnerable Populations.'

Talk started with definition of Vulnerable populations i.e. those whose ability to exercise autonomous decision is restricted. CIOMS defines vulnerable people as those "who are relatively or absolutely incapable of protecting their own interests because they may have insufficient power, intelligence, education, resources, strength, or other needed attributes. Individuals, communities, groups or countries may be vulnerable. Special protection - measures taken to remove the obstacles restricting the subjects ability to exercise autonomous decision maker. DeBruin states "Vulnerability ought not to be conceived as a characteristic of groups. Rather, certain traits may render certain persons vulnerable in certain situations"

Vulnerability may vary from situation to situation Criteria for permissible research, Levels of risk justified , Capacity assessment, Surrogate decision-making and consent, details about vulnerable population, its definition(Cognitive. Juridic, Differential, Medical, Allocational, Infrastructural) , taxonomy of vulnerability, examples of vulnerable subjects, impaired decision making capacity, Protections invoked for vulnerable populations, capacity to consent, competence and capacity, Formal procedures for capacity assessment, use of stored samples: Sample, Use – application, Fallout , Ethical issues, Consent. Risk can be reduced by appropriate Inclusion/exclusion criteria and "Aggressive monitoring"

Informed Consent - Content & Process

Fully informing the patient or volunteer about the research or treatment is known as consent. Points to be taken under consideration are: Free power of choice, Sufficient knowledge and comprehension. Legal capacity Need for consent arises due to Moral obligation (Respect for person's rights) and Legal obligations. "Competence" to give consent -- legal and moral status of individuals that entitles them to make their own decisions "Capacity" to give consent – cognitive, affective, and volitional abilities that underlie competence Provide a plan for determining the incapacity . Formal procedures for capacity assessment should be done by Structured questionnaire or Clinical care model: leave the decision to a disinterested 3rd party. Surrogate consent is when prospective patient is incompetent or has impaired decision-making capacity. Legally authorized person can also give consent. Details of Informed vs understood, Compensation vs coercion, Essentials of Informed consent, The process, Children - special mention. Helsinki Declaration (2000 revision) Informed Consent, Event vs. Process, Informed vs. Understood, Children Deserve Special Protection, what is assent and when it is not required, benefits of assent to child. Translations while taking consent sometimes fail miserably. For Example when the doctor speaks in English and it has to be explained in Hindi.In USA and Canada the doctors are supposed to explain at Grade six level which means very basic and simple two way communication is required.

Dr. Mehta also focused the factors to which they are vulnerable that is physical control, coercion, undue influence, manipulation and degree of risk; capacity to consent, competence vs capacity. He concluded his presentation explaining the use of stored samples.

In the next session **Ms Visala Annam** emphasized on *'Payment of Compensation for injury'* She mentioned difference between Compensation versus inducement. Compensation is the amount of money you should give to compensate for whatever cost or time loss they incur

while taking part in these researches. Unfortunately, sometimes the patient or volunteer is offered so much money that he or she cannot refuse due to poverty ,desperation for treatment in any form or willingness to participate without understanding the consequences.This is inducement. In conclusion, the patient/ volunteer should be fully informed about the nature, reason and duration of research as well as the benefits (monetary or otherwise), possible adverse effects of taking part. The participants must have absolute freedom to choose and no penalty for not taking part or withdrawing in the middle of the trials.

Dr Nandini Kumar took session on '*Responsible conduct of Research*'. Responsible conduct of Research refers to Practice of scientific investigation with integrity It was mentioned that Research in Health Sciences is of two types i.e. From Bench to Bedside (Basic Research) and from Bedside to Bench (Physician Scientist). Honesty and integrity are essential in Research. "For a scientist, integrity embodies above all the individual's commitment to intellectual honesty and personal responsibility." Components are: Research Integrity – Values & Policies, Planning & conducting research, Reviewing & reporting and Responsible authorship & publication. Research Integrity is Active adherence to the ethical principles and professional standards essential for the responsible practice of research. Misconduct is – violation of code of conduct for scientific research more than FFP; may not be intentional. Singapore statement on Research Integrity mentions Four principles- Honesty in all aspects of research, Accountability in the conduct of research, Professional courtesy and fairness in working with others, Good stewardship of research on behalf of others.Responsible Authorship Principles:To abide by ICMJE, COPE & WAME Guidelines, Submission to one journal at a time and with consent/ knowledge of co-author Final version to be read by all authors, Giving authorship to those who made significant intellectual contribution, No duplication of publication, Avoidance of redundant publication, Consent and ethics committee approval a must, Acknowledge the supporting staff/ agency and funding/ sponsoring agency, Do not acknowledge routine work or duty, Publication of even negative results (Helsinki Declaration), Registration of clinical trial mandatory in India before initiation of regulatory clinical trial. Salami Publication: Salami slicing - Salami publication (sometimes called bologna or trivial publication) is the practice of dividing one significant piece of research into a number of small experiments (least publishable units or LPUs). Conflict of Interest: "A set of conditions in which professional judgment concerning a primary interest (such as patients' welfare or the validity of research) tends to be unduly influenced by a secondary interest (such as academic/ financial gain)"

Common Types of Misconduct : Failure to - follow an investigational plan, report adverse drug reactions, get or document IEC approval, notify IEC of changes/progress reports , Inadequate completion or absence of informed consent forms, Lack of data integrity & inadequate records, Lack of responsible authorship and Self peer-review. Common Reasons for Misconduct : Ignorance about ethics of scholarly writing , Publish or perish system for career build up, Ambition causing fierce competition, Peer pressure , Lack of clear knowledge about topic for publication. Research Misconduct: Research misconduct means fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in

reporting research results but Research misconduct does not include honest error or differences of opinion.

"Most people say that it is the intellect which makes a great scientist. They are wrong: it is character." Albert Einstein

Session on *'Conflict of Interest'* was taken by **Dr Nandini Kumar**. Primary interest : Patient Health and well being, Teaching students & health professionals, Clinical Research and secondary interest : Academic – publication, promotion, awards, grants, Financial – shares, speaking fees, family obligations. Problem occurs when secondary interests dominate, unduly influence, distort, corrupt the integrity of a physician's judgment in relation to patients health, clinical research or medical education

Dr Manoj Das, delivered his talk on *'Public Health Research'* (the art and science of preventing disease, prolonging life and promoting health through the organized efforts of society). Research is defined as "A systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalised knowledge" and Public Health Research involves systematic collection of data through surveillance, vital statistics, disease reporting, registries, outbreak investigation, prevention, and program development and evaluation. Principles of Public Health Research involves - Principle of autonomy , Principle of beneficence ,Principle of proportionality , Principle of non-maleficence , Principle of justice and Principle of solidarity. Community advisory board has important role in Public Health Research.

On the second day of workshop 9th April 2017, session started with the talk of **Dr. Nalin Mehta** on the topic *'Research involving vulnerable population and use of stored samples-national & international perspective.'* He first explained the term vulnerable populations those whose ability to exercise autonomous decisions is restricted, by quoting the subjects involved that is children, prisoners, pregnant women, handicapped and mentally disabled persons, students, etc. then he explained taxonomy of vulnerability that includes cognitive, juridical, differential medical, allocation and infrastructural.

The second talk was taken by Dr. Nandini Kumar on *'Conflict of Interest.'* She gave a brief introduction on two types of interest i.e. primary interest (patient health & well being, clinical research) and secondary interests (academic-publication, promotion, awards, financial-shares) Problems occur when Secondary interests dominate Primary interests. Conflicts can be - Administrative conflicts – institute , with ethics committee members,Key issue to worry is that some interest might threaten - valid research design, data integrity, patient safety, dissemination of results may enter into a contractual relationship with a company that presents a conflict. Information regarding reviews and Metanalysis regarding Conflict of Interest were communicated. Management of COI in US- Researcher to declare involvement of spouse and dependent children in design, conduct and reporting of research or when submitting proposal for funding. Some Journals require that Authors of research articles should disclose any financial arrangement they may have with the company whose product figures prominently in the submitted manuscript or with the company making a competing

product. She also focused on influences of COI, management strategies. Dr. Nandini explained the conflict of interest to researchers with quoting some examples of Italian scientist Giuseppe Sanarelli's desire for fame - he discovered bacillus of yellow fever and produced yellow fever in 5 patients in 1897.

The fourth session began with lecture by **Dr. Hemant Malhotra,** Sr. professor and Head, Department of Medicine, SMS Medical College, Jaipur on *'Regulatory & Non regulatory Clinical Trial Issues.'* He gave an overview on what are clinical trials, why do we do clinical trials and phases of clinical trials. He explained that there is a global need for more, quick and good quality trials and new drug discovery is possible only with more and more number of trials. Dr. Malhotra discussed the process involved in drug development, safety, efficacy & effectiveness of new medicines, why are clinical trials important, different phases of clinical trials, types of clinical trials. He said that protecting participants before a trial and protecting participants during a clinical trial is a sign of good clinical practice. He quoted that while doing a research, looking at the whole picture is necessary. Dr. Malhotra also focused on benefits as well as risks of participating in clinical trials, role and relevance of clinical trials. He also discussed non regulatory issues: patients, principal investigator and research site briefly.

Last pre-lunch session was taken by **Dr. N.C. Jain** on *'Ethical issues in Science and Technology Publications.'* He began his talk by explaining research misconduct: fabrication, falsification & plagiarism. He also discussed staircase of research misconduct, publish and perish syndrome, predatory journals, and method to avoid research misconduct, authorship and contributor ship, importance of peer review, duties of editor. He quoted that a global movement has started which is 'THINK, CHECK, SUBMIT' movement. He also highlighted few online sites which offer free courses like WIPO, Health Research Fundamentals.

Post lunch session began with the talk of **Dr. Kiran Katoch** on the topic '*Academic Research in Medical Colleges, Responsibilities of Ethical Committees.'* She explained the main responsibilities of ethics committees that include health services, teaching and research and also the mandates of research ethics that include autonomy, beneficence, non munificence, justice. She then discussed the elements the ethics committee review, some of them are Scientific design and conduct of the study, Approval of appropriate scientific review committees, Examination of predictable risks/harms, Examination of potential benefits, Procedure for selection of subjects including inclusion/ exclusion.

Dr. Kiran Katoch outlined the constitution of IEC which constitutes 8-12 members, minimum of five persons are required to form the quorum- Chairperson, One - two persons from basic medical sciences, One - two clinicians from various Institute, One legal expert or retired judge, One social scientist/ representative of non-governmental voluntary agency, One philosopher/ ethicist/ theologian, One person from the community, Member Secretary. She then explained the principles of ethics committee-Principles of essentiality,Voluntariness, informed consent and community agreement, Non-exploitation, Principle of accountability and transparency,Principles of institutional arrangements, Totality of responsibility etc. She then gave some guidelines for sample collection and explained the process of submission of

research proposal to IEC. She concluded her talk by discussing some important issues for promoting ethics in research.

The last talk of the workshop was by **Dr. Bharti Malhotra** on the topic '*Evaluation of diagnostics on routine samples in hospital settings*'. She started her talk by giving an overview on classification of IVD in India. She then discussed the notified and non notified products, also the regulatory requirements for notified products and indigenous vs imported products. Dr. Bharti discussed the sample size calculation, prevalence of diseases. She emphasized on ethics committee approval, application for funding and points of evaluation- sensitivity, specificity and turn around time. She ended her talk by discussing some ethical and design issues- validation, evaluation, unlinked anonymous.

This marked the end of the learning experience which left the participants much more informed and insightful. Vice Dean Research, RUHS delivered vote of thanks to the speakers and participants followed by distribution of certificates of participation.