South American Journal of Clinical Research

Jan 2014

Volume 1, Issue 1

ELITE TEAM OF EDITORIAL MEMBERS

The following are our esteem Editorial Team Members for the South American Journal of Clinical Research

1) **Dr. Kannan Sridharan** - DM (Clinical Pharmacology)

2) **Dr. Dharani Gokul.** - MBBS (Medicine)

3) **Dr. Shivashankara A.R –** PHD Biochemistry

4) **Dr. Deven Parmar** - MD in Clinical Pharmacology & Therapeutics FCP & FACP (American College of Clinical Pharmacology)

EDITORIAL POLICY

Papers must be submitted with the understanding that they have not been published elsewhere (except in the form of an abstract or as part of a published lecture, review, or thesis) and are not currently under consideration by another journal published or any other publisher. The submitting (Corresponding) author is responsible for ensuring that the article's publication has been approved by all the other coauthors. It is also the authors' responsibility to ensure that the articles coming from a particular institution are submitted with the approval of the necessary institution. Only an acknowledgment from the editorial office officially establishes the date of receipt. It is a condition for submission of a paper that the authors permit editing of the paper for readability. All enquiries concerning the publication of accepted papers should be addressed to **ejournal.assist@tau.edu.gy**

ABOUT PLAGIARISM

Plagiarism is the use or close imitation of the language and ideas of another author and representation of them as one's own original work. Duplicate publication, sometimes called self plagiarism, occurs when an author reuses substantial parts of his or her own published work without providing the appropriate references. This can range from getting an identical paper published in multiple journals, where authors add small amounts of new data to a previous paper.

Plagiarism can be said to have clearly occurred when large chunks of text have been cut and pasted. Such manuscripts would not be considered for publication in EIJASR Journals. But minor plagiarism without dishonest intent is relatively frequent, for example when an author reuses parts of an introduction from an earlier paper. The editors will judge any case of which they become aware (either by their own knowledge of and reading about the literature, or when alerted by referees) on its own merits.

The paper containing the plagiarism will be obviously returned back to the author/s for review, but we earnestly request the authors to avoid submitting plagiarized

DISCLAIMER

E-International Journals of Academic & Scientific Research (EIJASR) make every effort to ensure the accuracy of all the information (the "Content") contained in its publications. However, the EIJASR and its agents make no representations or warranties whatsoever as to the accuracy, completeness or suitability for any purpose of the Content and disclaim all such representations and warranties whether express or implied to the maximum extent permitted by law. Any views expressed in this publication are the views of the authors and are not necessarily the views of the Editor/s or E-International Journals of Academic & Scientific Research

TABLE OF CONTENTS

TRANSLATIONAL RESEARCH

A Case Study by Manali Khawle, India
(*PG Diploma in Hospital Administration, PhD in Clinical Research Student of Texila American University*)
Email: mkhawle@gmail.com

SOURCE

Francesco M Marincola * J Transl Med. 2003; 1: 1. Translational Medicine: A two-way road Published online 2003 July 24. doi: 10.1186/1479-5876-1-1
http://pubmedcentralcanada.ca/pmcc/articles/PMC202357/

INTRODUCTION

This review critically reviews the article 'Translational Medicine: A two-way road "in the Journal of Translational Medicine of Biomed central. The review will first summarise the article. Secondly, it will briefly analyse the effectiveness of the article's structure, investigating how the information is set out and whether the reader can access it efficiently. Thirdly, the review will critique the article, evaluating its authority, currency, accuracy, objectivity and coverage. The review will finally judge the article's accessibility and credibility. Overall the article was well written, clear and relevant.

KEYWORDS:- Translational medicine, Traditional medicine, Diagnosis

REVIEW OF LITERATURE

Translational research is generally described as the application of basic science discoveries to the treatment or prevention of disease or injury. Its value is usually determined based on the likelihood that exploratory or developmental research can yield effective therapies. Translational research encompasses the effective movement of new knowledge and discoveries into new approaches for prevention, diagnosis, and treatment of disease. There are many important in successful bench to bedside research, but regrettably Bed side to Bench side has kept aside. This article is discussing the two way roads of the translational research

ARTICLE SUMMARY

The purpose of the article is to explore the need and advantages of traditional medicine based research with public health. The article is concentrated on translational research methods authoritative knowledge that use in bench to bed side and bed side to bench side efforts in scientific aspect that can provide successful strategies to improve the health of human. The article discuses about translational research that has two way roads, viz Bench to Bed side and Bed to Bench side. According to article Bed side to Bench side is bit of neglected because scientific aspects are poorly understood by full time clinicians and the difficulty of dealing with humans poorly appreciated by basic scientists.

ARTICLE STRUCTURE

The article was introduced with an abstract, which provided the brief overview of main point's of translational research. The introduction for the article it describes article main points. The article was very short and therefore the information in each paragraph was easy to access, however there were only 3 body headings, these paragraph has mentioned the reason of relegated translational research in quite detailed information contained under each heading and also future collaboration for the research study. The article talked about Specific hurdles translational research challenges' in ethical and practical considerations, as the article described translational research it has also mentioned phases involve in translational research. The next paragraph of article mentioned reasons of failure. With the good example article showed methodology of translational research and mistakes and learning from the mistakes. In article's more effective collaboration mentioned responsibilities' of Governmental regulatory agencies, ethical committee in development of translational research. In end of the article the article mentioned a new journal of peer review and rapid research result in benefit if human and scientific community.

ARTICLE CRITIQUE

AUTHORITY

BioMed Central is an STM (Science, Technology and Medicine) publisher of 257 peer-reviewed open access journals. The portfolio of journals spans all areas of biology, biomedicine and medicine and includes broad interest titles, such as *BMC Biology* and *BMC Medicine* alongside specialist journals, such as *Retrovirology* and *BMC Genomics*. All original research articles published by BioMed Central are made freely accessible online immediately upon publication. BioMed Central levies an article-processing charge to cover the cost of the publication process. Authors publishing with BioMed Central retain the copyright to their work, licensing it under the Creative Commons Attribution License which allows articles to be re-used and re-distributed without restriction, as long as the original work is correctly cited. BioMed Central is owned by Springer Science+ Business Media, and also hosts the SpringerOpen platform

ACCURACY

The source of the information in the article was from 2003 and before 2003. It was also backed up and supported by a comprehensive, recent reference list with these sources cited in-text to support both the literature review and the research itself. The strict editorial and refereeing processes also contributed to the article's accuracy as did the links to other expert sources (the journal for example).

CURRENCY

 The article was published in 24 July 2003 Received in 17 June 2003 and while the article was accepted for publication in 24 July 2003. Article discussed about translational research and current scenario but after 2003 translational research is progressing the article was, but the focused topic is still important part in human health and translational medicine.

RELEVANCE

This article was from Journal of Translational Medicine are provided here courtesy of Biomed Central, which has high credibility in an academic context. It was written to inform researchers and students rather than to entertain. It would be relevant to both these groups but particularly any academic interested in all clinicians, Governmental regulatory agencies and ethical committee that involve in public health related programs.

OBJECTIVITY

The information was objectively developed, well supported with a current research base and with all evidence acknowledged and referenced. There was no evidence of bias, a fact that was reinforced by the recognition that the article documents research, be to encourage opportunities to pursue Bedside to Bench.

STABILITY

The article, with its source an academic journal on an academic data base is stable as a resource.

CONCLUSION

This review summarized and critically reviewed "Translational Medicine: A two-way road". The content, structure, strengths and limitations of the article were analyzed and critiqued. The article has contributed to the literature in terms of its valuable critique of current research of translational research and current views and limitation of the research and health issues and the implications provided for both health interventions and future research collaborative possibilities. The article explained importants of translational research and evidence based medicine that helps in public health. Also article suggested future aspect to the translational research. Article mentioned about limitation, reasons of failure, scope of translational research and possible methodology for translational research. Article was based on all evidenced based report and researches. Article successfully explained the slightly neglected part of translational research that is Bed side to Bench side research technique. Article did not contain evidence and more research example in past years that's why it was not more informative. Article met expectations of appear more fascinated with the modern mythology of transgenic and knock-out preclinical than the clinical research or human disease. Thus, new ideas and related therapies based on genetically engineered results.

REFERENCE

1. Cameron, D., Norman, Tim, Huerta, (2006). September Knowledge transfer & exchange through social networks: building foundations for a community of practice within tobacco control 25. *Doi: 10.1186/1748-5908-1-20 PMCID: PMC1599751*.

2. Christian, Brander, Soldano, Ferrone, Francesco, M., Marincola, J. (2006). Rewarding patient-directed research: Excellence in Translational Medicine Award. *Doi: 10.1186/1479-5876-4-19 PMCID: PMC1468429.*

3. Ena, Wang, András, Falus, J. (2004). Changing paradigm through a genome-based approach to clinical and basic immunology 17. *Doi: 10.1186/1479-5876-2-2 PMCID: PMC331423.*

4. Francesco, M., Marincola, (2003). Translational Medicine: A two-way road. *Doi: 10.1186/1479-5876-1-1*.

5. Global informetric perspective studies on translational medical research [BMC Medical Informatics and De...].

6. Heidi, Hörig, William, Pullman, J. (2004). From bench to clinic and back: Perspective on the 1st IQPC Translational Research conference Heidi Hörig, William Pullman J Transl Med. 2004; 2: 44. Published online 2004 December 20. *Doi: 10.1186/1479-5876-2-44 PMCID: PMC544857*.

7. John, P., A., Ioannidis, J., (2004). Materializing research promises: opportunities, priorities and conflicts in translational medicine *Doi: 10.1186/1479-5876-2-5 PMCID: PMC343300*.

8. Kai-Christian, Sonntag, J., (2005). Implementations of translational medicine. *Doi: 10.1186/1479-5876-3-33 PMCID: PMC1236966*.

9. Maurizio, Chiriva-Internati, Fabio, Grizzi, Robert, K., Bright, W., Martin, Kast, J., (2004). Cancer immunotherapy: avoiding the road to perdition. *Doi: 10.1186/1479-5876-2-26 PMCID: PMC509287*.

10. M., U., R., Naidu(2011). Promise of translational medicine: An evidence-based therapeutics Indian. *J Pharmacol, 43(2), 103–104.*

11. P., A., Ioannidis (2006). Evolution and Translation of Research Findings: From Bench to Where?. *PLoS Clin Trials Jo1(7): e36. 10.1371/journal.pctr.0010036*.

12. Stacey, P., Mankoff, Christian, Brander, Soldano, Ferrone, Francesco, M., Marincola, J., (2004). Lost in Translation: Obstacles to Translational Medicine. Transl Med, 2, 14 *Doi: 10.1186/1479-5876-2-14 PMCID: PMC420261*.
13. Translational medicine *Nature Reviews Drug Discovery* ISSN: 1474-1776 EISSN: 1474-1784.

14. To Be or Not To Be Translational [Translational Medicine @ UniSa].

15. W., Martin, Kast, Hyam, Levitsky, Francesco, M., Marincola, J.(2004) . Synopsis of the 6th Walker's Cay Colloquium on Cancer Vaccines and Immunotherapy, Transl Med, 2: 20. *Doi: 10.1186/1479-5876-2-20 PMCID: PMC441417*.

FORMULATION, EVALUATION AND PHARMACOKINETICS OF FLURBIPROFEN FAST DISSOLVING TABLETS

A Case Study by Opeyemi Orhekafore BEDU, Nigeria
(B.LMS in Histopathology, M.Sc Clinical Research Student of Texila American University)
Email: orhekabedu@yahoo.com

INTRODUCTION

Fast dissolving tablets disintegrate and dissolve rapidly in the saliva without the need for water. This tablet format is designed to allow administration of an oral solid dose form in the absence of water or fluid intake. Flurbiprofen is an anti-inflammatory and analgesic drug used in the treatment of chronic rheumatoid diseases which is a painful condition and therefore requires drugs that has rapid onset of action. Hence the intent of the authors to formulate fast dissolving tablets of Flurbiprofen using different superdisintegrants to improve the dissolution rate and bioavailability of the drug. Flurbiprofen fast dissolving tablets were prepared using various superdisintegrants and the resultant formulations were characterized for different physical parameters. The results of the statistical analysis carried out by the authors on the various data obtained showed that the use of superdisintegrants to formulate fast dissolving tablets of Flurbiprofen was a good way to enhance bioavailability, dissolution rate and absorption rate of the drug.

KEYWORDS:- Fast dissolving tablets, Flurbiprofen, Tablets, NDDS, Crospovidone

Due to the recent advances in novel drug delivery system (NDDS) to enhance safety and efficacy of already existing drugs, the authors decided to formulate fast dissolving Flurbiprofen tablets and study the effect of superdisintegrants on bioavailability of the Flurbiprofen tablets in the research work titled “formulation, evaluation and pharmacokinetics of Flurbiprofen fast dissolving tablets” in the early part of the year 2013. This was to also serve as an addition to the currently available database on studies of fast dissolving tablets which probably began at the middle of the 20th century. Since then various studies have been carried out by several researchers in attempt to formulate various orodispersible tablets of some of the already existing drugs. But only few have been able to attribute the orodispersability and enhanced bioavailability of Flurbiprofen fast dissolving tablets to the incorporation of Crospovidone in their formulations. That is what the authors were able to discover from the evaluations in their own study with similar results having been obtained by Vemura et al (2009) which the authors also cited in their work.

In the introductory part of the research report the authors defined Flurbiprofen as a phenylalkanoic acid derivative which belonged to a group of poorly water soluble drugs and classified as a non-steroidal anti-inflammatory drug whose major indication is in the long-term treatment of chronic rheumatoid diseases. Flurbiprofen being a class II drug is therefore limited in its therapeutic activity due to its slow rate of absorption from the oral route of administration which is currently considered as the gold standard in the pharmaceutical industry.

Based on the above stated limitation, the authors attempted to study the improvement of dissolution rate of Flurbiprofen using the basic approach in the development of fast dissolving tablets which required the use of superdisintegrants. This might also be based on the fact that most of the chronic rheumatoid disease patients belong to the geriatric population and may suffer from mild hand tremors and dysphasia which makes it difficult to swallow tablets hence the urgent need for fast dissolving tablets of Flurbiprofen in order to enhance the ease of administration and also increase patient compliance.

Several attempts had been made in the past to prepare fast dissolving tablets through various means out of which the authors combined the wet granulation method with subsequent direct compression of the tablets. The composition of the fast dissolving tablets included superdisintegrants e.g. Crospovidone, lubricants e.g. aerosil, taste mask (aspartame), binding agent i.e. starch alongside other excipients. Twelve formulations were prepared with the conventional tablets serving as control. All were evaluated for physical properties, in vitro disintegration time and dispersion time, wetting time, d5rug-excipient interaction, water absorption rate and stability studies. The authors went a step further by carrying out an in vivo crossover study involving six healthy volunteers who received the drug and had their blood sample obtained for HPLC analysis. Statistical analysis was carried out on determined parameters of both conventional and optimized fast dissolving tablets of Flurbiprofen at significance level 0.05 using a paired t-test.

Evaluation of the physical parameters showed that all the tablet formulations passed the requirements of the India Pharmacopoeia, 1996. From the results of the statistical analysis of data obtained from both in vitro and in vivo studies, formulation F6 showed both rapid disintegration time and in vitro dispersion time. This was due to the Crospovidone content of the formulation. The drug release studies also corroborated the finings by showing that increase in super disintegrant (Crospovidone) quantity from 2-8% was a factor. This was similar to the results obtained by Vemura et al as cited by the authors although their result was obtained using 10% Crospovidone in their formulation.

Furthermore, the thermograph of the Differential Scanning Calorimetry studies suggested no significant drug-polymer interaction. It is important to note that the authors did not carry out a drug-drug interaction studies to examine its suitability for concomitant administration with other drugs as many of the patients with chronic rheumatoid disease conditions might be on medications for other ailments. Pharmacokinetic analysis of the plasma obtained suggested increased bioavailability of Flurbiprofen when superdisintegrants are added.

At this juncture, it would be worthy to commend the authors for the good attempt at developing fast dissolving tablets of Flurbiprofen using a minimal concentration of superdisintegrants. The authors' use of tables and graph to explain some of the details did not go unnoticed. However mention must be made of the omission of pharmacodynamics of the fast dissolving tablets of Flurbiprofen which the authors should consider investigating in future. Also, further research to establish the efficacy of these fast dissolving tablets using appropriate clinical studies is recommended. Overall, the authors have done well in updating the use of fast dissolving tablets as a Novel drug delivery system for an important existing anti-inflammatory drug such as Flurbiprofen.

REFERENCES

1) Grri, M., Rangoni, C., Maestraelli, F., Corti, G., Mura, P. (2005). Development of fast developing tablets of flurbiprofen-cyclodextrin complexes. *Drug dev Ind Pharm, Aug, 31(7), 697-707.*

2) http://www.drugs.com/flurbiprofen. Accessed July 7, 2013.

3) Kuchekar, B., S., Badhan, A., C., Mahajan, A., S. (2003). Mouth dissolving tablets; A novel drug delivery systems. *Pharma. Times, 35,7-9.*

4) Shid, S., L., Hiremath, S., P., Borkar, S., N., Sawant, V., A., Shende, V., S., Tote, M., V., Birari, R., B., and Changrani, S., R. Effect of superdisintegrants in rapidly disintegrating flurbiprofen sodium orodispersible tablets via direct compression and camphor sublimation.

5) Watanabe, Y., Koizumi, K., Zama, Y., and Matsumoto, Y. (1995). New compressed tablet rapidly disintegrating in saliva in the mouth using crystalline cellulose and a disintegrant. *Bio. Pharm. Bull, 18(9), 1308-13*

6) Wenat, A., K., Patel, S., M., Patel, S., R., Patel, N., M. (2012). Fast dissolving tablets: A novel approach to drug delivery. *Asian journal of pharmaceutical sciences and research, 2(8).*

PRECLINICAL STUDIES IN THE DRUG DEVELOPMENT PROCESS: PROSPECTS AND CHALLENGES

A Case Study by Livinus Chibuzo Abonyi, Nigeria
(Masters in Medical Ultrasonography, PhD in Clinical Research Student of Texila American University)
Email: chibuzoabonyi@yahoo.com

ABSTRACT

The process of drug discovery is lengthy and tortuous, spanning several years. These years are characterized by different stages of differing development processes. A major stage in this development process is the preclinical stage, which is characterized by testing the drug candidate in animal models as a predictor of its efficacy and tolerability in humans. Preclinical drug trial is froth with challenges, which range from choice of the appropriate animal species to generation of the relevant data for filling application for IND.

A successful pre-clinical trial is still not a guarantee of the drug product scaling through the clinical stage. These have been attributed to heterogeneity differences in the animal and human species. Effort in genomic research to circumvent this challenge is presently on-going.

KEYWORDS:- Tortuous, Pre-clinical trial, Drug product, Drug discovery

INTRODUCTION

Drug discovery according to Steven, et al. (2010), is still a lengthy, expensive and inefficient process with low rate of new therapeutic discovery. Discovering and bringing one drug to the public, typically costs a pharmaceutical or biotechnology company a budget range of $800 million to more than $1 billion and takes about an average of 10 – 15yrs, according to Pharmaceutical Product Development Inc (2012), a pharmaceutical research laboratory. This is supported by a similar study by Hughes et al,(2011) in which they maintained that a range of 12-15ys is required for a new drug product to successfully reach the market for clinical application.

Only preclinical studies can last for 1 – 5yrs. In addition to the cost implication and rigors of the development process, the efficiency or success rate is a great challenge. Only five in five thousand or 10% of the drugs that begin pre-clinical testing ever make it to human testing. Only one of these five is ever approved for human usage (Hughes et al, 2011).

The journey of finding a new drug for an identified disease process involves high thorough-put screening (HTS) where large number of chemicals is tested for ability to influence the target and achieve desired effect (Fox et al. 2006) This screening also helps to determine the selectivity of the chosen compound to the target. The more selective a molecule is to the target the better. This implies that it interacts with only the target and less with other related targets. A successful identification of an active compound or intended new drug sets the stage for pre-clinical trials.

This paper on the types of pre-clinical studies conducted during drug trial will be discussed by reviewing generally pre-clinical drug development, the types of preclinical drug trials conducted and the choice of animal species. The rising controversy over the use of animals for pre-clinical drug trials and the possible way forward will also be discussed.

PRE-CLINICAL DRUG DEVELOPMENT

Pre-clinical drug development (trials) as pointed out by Steinmetz & Edward, (2009), involves all the activities that link drug discovery in the laboratory to initiation of human clinical trial .They also postulated that preclinical studies can be designed to indentify a lead candidate from several target hits, develop the best procedure for new drug scale-up, select the best formulation, determine the route, frequency and duration of exposure, and support the subsequent clinical trial design. Pre-clinical testing therefore analyzes the bioactivity, safety and efficiency of the formulated drug product, according to Pacific biolabs, (2012); a pharmaceutical development research laboratory.

During the pre-clinical stage of drug development process, plans for clinical trials and an investigative drug (IND) application are prepared. The Wikipedia; free encyclopedia, (20120, puts it as the stage of research that begins before clinical trial; (the testing of drugs in humans), can begin. It is during this period that important feasibility iterative testing and drug safety data is collected. Many project development teams find it helpful to develop a target product profile (TPP) to guide preclinical development. The TPP, according to Steinnmetz & Edward, (2009), is a useful tool for delineating the required and/or desired treaties of the new drug product, critical milestone and metrics to success.

The TPP is also affirmed by Curry & Brown, (2003) as a framework that ensures that the preclinical development programme supports the intended clinical trial design and therapeutic use. The content of a TPP depends on the drug product or research team. However, the general profile includes therapeutic indication, expected clinical use, drug target and mechanism of action, market size, competition and differentiators, drug target route, form and frequency of administration, patient's age, bioavailability and duration of action, safety precaution and contraindications, chemistry, manufacturing and controls profile, including solubility, manufacturing process, formulation, storage conditions and stability, patent status and modifiers of exclusivity of usage, such as in organ drug status.

The main aim of pre-clinical drug trial or studies is to determine a product's safety profile. Products may be new or iterated or like-kind medical devices, diagnostic devices, drugs; gene

therapy solutions etc. All products, as noted by Wikipedia; free encyclopedia,(2012), don't necessarily undergo the same process of preclinical studies. Drugs may undergo pharmacokinetics, pharmaco-dynamics, absorption; distribution, metabolism and excretion (ADME), and toxicity testing using animals. This enables researchers to estimate the safe starting dose of the drug for clinical trial in humans.

Medical devices will not pass through these processes if they do not have any drug component. They are subjected to Good Laboratory Practice (GLP) testing for safety of the device and its components. Some devices may undergo compatibility testing which will demonstrate if the device and all its components are compatible and sustainable in a living model. Some of such devices are sophisticated and are of high technology like in medical imaging sciences. Here, such devices may be computed Tomography Scan, Magnetic Resonance Imaging (MRI), Ultrasonography, Positron Emission Tomography, Photoacoustic Tomography (PAT) etc. Preclinical imaging versions of these devices abound for research involving animals. Imaging modalities as pointed out by a Wikipedia Imaging Website, (2012), have long been crucial to the researcher in observing changes, either at the organ, tissue, cell or molecular levels, in animals responding to physiological and environmental changes. These imaging systems were broadly categorized by William et al. (2008), into two major groups. These are those used primarily for morphological/anatomical studies and those for molecular imaging techniques.

These devices such as high frequency micro-ultrasound, magnetic resonance imaging (MRI) and computed tomography are usually used for anatomical imaging while positron emission tomography (PET) and single photon emission computed tomography etc are usually used for molecular visualization. Micro-ultrasound device using high frequency (15MHz – 80MHz) harmless sound waves from transducers can insonate living tissues from which the reflected waves are converted by the transducer to produce 2D and 3D images of the living structures. In a study by Foster et al, (2009), imaging of up to 30μm is possible; which makes visualization of tiny vasculature in cancer angiogenesis a reality. In clinical application in humans, frequency ranges of 2.50 MHz – 15MHz are used.

Most pre-clinical studies must adhere to the Good Laboratory Practice (GLP) standard, as stipulated in the International Conference on Harmonization (ICH) guidelines, in order to satisfy acceptability for submission to the regulatory agencies. Information collected from pre-clinical studies is vital in determining the safety of clinical trials in human beings. It is equally a prerequisite for a new drug application.

CHALLENGES

Despite careful planning, most drugs that enter clinical trial stage fail. According to Kareen & Edward, (2009), the reasons for failure include poor solubility, life threatening or undesirable side effects, poor bio-distribution by the proposed clinical route of administration, prohibitive scale-up and manufacturing costs, market competition, and poor efficacy in early clinical trial. In the modern drug discovery pipeline, as noted by Radloff et al,(2008), the assessment of the

efficacy and toxicity of the therapeutic agents are based on relatively homogeneous cell or animal model.

The heterogeneity issue is encountered once the most expensive clinical trials are underway in human subjects. The poor success rate, especially in some daunting disease conditions such as in cancer, to drug development informs Janghui's,(2010) suggestion that the standard preclinical models are failing to predict how the drug candidate works in clinical trials. This failure rate is attributed to inherent heterogeneity between the animal models and human beings involved in clinical trial. Furthermore, recent results from comprehensive genomic efforts such as The Cancer Genome Atlas (TCGA), (2008) have highlighted the marked heterogeneity of genetic alterations in patient population. It suggests that the intrinsic heterogeneity in genetic and /or epigenetic alterations which are driving the tumorigenesis might be one of the main causes for the observed discrepancies between clinical and standard preclinical models.

Thus, efforts according to Radloff et al,(2008) and Kamb, (2005), are presently geared towards establishing new animal models which will mimic heterogeneous patient population. This is considered a challenging task, in view of the multi-stage scientific intricacies required.

CHOICE OF ANIMAL SPECIES

In animal testing of drugs during pre-clinical drug trials, two animal species are involved. The most commonly used models are the rodent and non-rodent species; the murine and canine. However, pocrine and primate species, according to Wikipedia; free encyclopedia can also be used. The choice of a specie is guided by which specie will give the best correlation to the human trial. The pre-clinical trial environment should be close to the actual clinical trial environment as much as possible. The choice of the specie is also guided by the characteristics of the drug candidate, the organ or system involved, formulation, route of administration, site of activity, metabolites to be produced, among other factors.

In oral dosage form of a preclinical research, canines may not be good models because the characteristic carnivore intestine is underdeveloped and cannot be compared with that of the omnivores. In carnivores, gastric emptying is faster. In antibiotic drugs, rodents are disqualified due to the state of their intestinal flora, which may cause significant adverse drug reactions.

Medical equipments or devices testing are best performed using larger animal models. Such animals may be dogs, pigs etc. To illustrate further the consideration of organ or body system type in choice of specie model, swine are more suitable for coronary stent and dermatological studies while goats or cow are good for mammary implant testing. Gastric studies are appropriate in dogs.

However, there is growing challenge against the use of animals in research by animal rights activists. Animal studies are currently in decline in spite of the implementation of the three 'Rs' (Replacement, Reduction and Refinement) principle in the use of animals in researches. The ethics of animal testing is currently becoming a world-wide controversy. Many non-

governmental organizations and rights activist exist in different countries, fighting against ill-treatment of animals whether for research purposes or as delicacies on family dining tables. In the United States of America, according to Foster et al,(2009), People for the Ethical Treatment of Animals (PETA) and the Humane Society, believe that animal testing amounts to cruelty and injustice to the animal kingdom . They see no justification in the use of animals in research despite its contribution to quality of life of the human race.

Counter organizations like the Americans for Medical Progress (AMP) feels that the benefits of use of animals in researches has lead to the betterment and longevity of the human race. The pro-animal groups claim that millions of animals are experimented on and killed annually; for food, clothing and entertainment. In reality most of the animals used for experiments are reared or bred in the laboratory for that purpose. They spare no thought on the impact the absolute restriction of the use of animals for research would have on the scientific progress of the human race.

In view of these controversies, alternative to animal testing in preclinical research is being explored. One of such is the exploration of the possibility of predicting the effect of biochemical preparations in humans from its chemical/pathophysiological characteristics in in-vitro studies. This is presently a tall order in preclinical research trials. However, a compromise reached so far among 'agonists and antagonists' of animal testing is that animal testing should cause as little suffering to animals as possible, and as suggested by William et al,(2008), tests should only be performed where 'necessary'

The principle of Three Rs' has been adopted as a guide in the use of animals in research. Many countries; especially where animal right issues are prominent have adopted this principle. The 'Three Rs' stand for: -

1. *Replacement:*- This advocates use of alternative methods instead of animals testing procedures, provided same scientific aim is achievable. This principle is otherwise requesting for total replacement of animals in the preclinical trials of drug discovery process. The current introduction of automation and computational biotechnology in the drug discovery process may hopefully offer a window of opportunity in this direction.
2. *Reduction:*- this principle advocates the application of methods that employ less number of animals in an experiment while achieving the same or more level of information if more number of animals were used. It therefore encourages less number of animals for comparable level of information or use of same number of animals for more level of information.
3. *Refinement:* - This preaches the principle that methods adopted should be such that pain, suffering and distress is minimized for the animals that are still in use in the preclinical research process. It encourages animal welfare and care.

These principles are still being contested by the extreme animal rights protectionists. This has led many governments of some countries to legislate on the Regulatory Requirements/Guidelines for the use of animals in laboratories. The guidelines differ from one country to the other but the underlying principles are the same. Though the choice of a specie for trial is made to be as close

to the human as possible, there exists, differences which has to be taken into consideration when evaluating the findings from the study.

To account for differences in species and individual, an uncertainty factor or safety margin of $^{1}/_{100}$ is given. Inter-specie safety margin is 1/10 while inter-individual differences is also $^{1}/_{10}$.

The documentation of the result of the pre-clinical study, according to the Pharmaceutical product development Inc, (2012), should provide information about the pharmaceutical composition of the drug, its safety, formulation and manufacture process. Further required information is the route of administration to the human subjects, packaging and handling guidelines; including storage, among other factors.

PRE-CLINICAL STUDIES

Pre-clinical studies involve in-vitro and in-vivo experiments involving the identified drug compound.

In "Vitro" (glass) tests are experiments carried out in the laboratories using test tubes, beakers etc., while in "Vivo" (life) are experiments conducted in living cell cultures or animal models Pre-clinical drug studies are appropriately called toxicity studies. These studies are carried out in animal species in which the following among others are evaluated: -

1. Acute Toxicity Effect in a single large dose.
2. Sub-acute toxicity; involving multiple doses.
3. Chronic toxicity in case of prolonged usage.
4. Reproductive Toxicity of possible effect on Reproduction function.
5. Genetic toxicity for possibility of mutagenicity and;
6. Carcinogenicity

Acute Toxicity Effect in a single large dose

This study involves the use of two animal species, of which one should be a non-rodent specie. Acute toxicity study may involve the administration of a single dose or more over a period of up to twenty four hours. The goal is to determine the toxic dose levels and observe indications of toxicity on the study animals. Animals should be observed for fourteen days. Post-administration mortality (if any) and morbidity (clinical signs and Symptoms) are recorded. Other factors documented are time of onset of any reaction, duration and reversibility. The histopathological changes are also recorded.

Sub-acute toxicity involving multiple doses

This study involves a minimum of fourteen days daily drug administration of three or more doses in at least two animal species. The effects of this prolonged multiple doses are evaluated

and recorded for use as a pre-requisite for the human clinical trial. Similar findings as in the acute single dose study are documented.

Chronic toxicity in case of long term application

Certain medications for some disease conditions last for up to one week or more. Such drugs may also be used in the treatment of chronic diseases. Such drugs require animal studies of three to six months and up to one year or more for any chronic diseases to demonstrate its safety. The specific duration should determine the length of the trial of the new drug. Here also, at least two animal species are required. Allotted effects are noted and documented.

Reproductive Toxicity

Reproductive toxicity study is a requirement for any new drug compound before administration to any female of child bearing age. The studies are used to determine any effect of active ingredients on the reproductive system. This study may be divided into three segments:

Segment I reproductive toxicity study documents effects of the drug on fertility. Segment II and III documents such effects as on the embryo, pre and post natal developments. Multigenerational effects and teratology are also studied.

Genetic Toxicity

These tests are aimed at ruling out mutagenic effects of a new drug compound. Any effects on the chromosomes or the DNA strands may be a precursor for gene mutation.

Salmonella typhimurium is usually used in assays to detect mutation.

Carcinogenicity Studies

Testing for carcinogenicity usually applies to drugs for treatment of chronic disease conditions. The duration of this test is about 18 – 24 months. The surviving animals are killed and studied at specified weeks during the period of the study. Data collected are animal deaths, tumour incidence, type and site of tumour appearance (if any) and pre-neoplastic tissue changes etc.

CONCLUSION

Pre-clinical studies constitute an important segment in the drug development process. A successful pre-clinical trial provides extensive information for perfection of the drug development and subsequent trial in human beings. It is a pre-requisite for investigational new drug application. However, preclinical drug trial has mainly relied on animal species for testing prior to application on humans. This is greatly being challenged and hampered by the animal right activists who are advocating for total ban on the use of animals for research and experimentation. Though efforts are ongoing to find alternatives to animal testing of drugs prior to clinical trial, the use of animals may still go on for some time to come.

REFERENCES

1) Curry, A.., Brown, R. (2003). The target product profile as a planning tool in drug discovery research. *Pharmatech, 67 – 71.*

2) Foster, F.S., Mehi, J., Lukacs, M., Hirson, D., White, C., Chargares, C, et al.(2009) A new 15 – 50mHz array-based micro-ultrasound scanner for preclinical imaging. *Ultrasound Medical Biology, 5(10): 1700-8.*

3) Fox, S., Farr-Jones, S., Sopchak , L., Bogg, A., Nicely A.W., Houry, R.(2006) . High throughput screening; update on practices and successes. *J Biol Sreen, 11,864-869.*

4) Hughes, P.P., Rees, S., Kalindjian, S.B. & Philpott, K.L.(2011), Principles of early drug discovery. *Br. J Pharmacology, 162(6) , 1239-1249.*

5) Janghui, X., Jaun, L., Simon ,R., Ze ,T., Yinghui, L., Shanguang, C. (2010) Preclinical Drug Prioritization via Prognosis. Guided Genetic interaction Networks. PLoS One; 5(11): e13937. *Doi:10.1371/journal.pone.0013937.*

6) Kamb ,A.(2005). What's wrong with our cancer models? Nat Rev Drug Discov.; 4: 161-165. doi: 10.1038/nrd 1635

7) Kareen L,S & Edward, G.S. (2009) .BMC Neurology Volume 9, Supplement 1, 2009: Proceeding of the 2009 Drug Discovery for Neurodegeneration conference. http://www.biomedcentral.com/147- 2377/9:?issue=S1 Accessed June 20.2012.

8) Kareen, L.S, & Edward, G. S. (2009). The basics of pre-clinical drug development for neurodegenerative disease indications. *BMC Neurology; 9 (suppl I): 52 http://www.biomedcentre.com/1471 - 2377/9/51/52 (Website).*

9) Network CGAR. (2008).Comprehensive genomic characterization, defines human glioblastoma genes and core pathways. Nature; 455:1061-1068. *Doi.10.1038/nature 11903.CrossRef. PubMed/NCBI. Google Scholar. Accessed June 15,2012.*

10) Pacific biolabs (2012). Drug Development process; stages of drug development; http://www.pacificbiolabs.com/drug-stages-asp (website). 94;547 –San franscisco Bay Area. Retrieved June 15,2012..

11) Pharmaceutical product development Inc. (2012), About Drug discovery & Development. PPD Homepage; http://www.ppdi.com/about-ppd/drug-development.htm Retrieved June 20th 2012.

12) Radloff, D.R., Renella, E.S., & Treadgill, D.W., (2008). Modelling cancer patient populations in mice: Complex genetic and environmental factors. Drug Discov Today Dis Models 2008; 4:83-88 doi:10.1016/j.ddmod.2007.06.004. CrossRef. PubMed/NCBI. Google Scholar.

13) Steven ,M. P., Mytelka, D.S, Widdie, D. U., Persinger, C.C., Munos, B.H., Lindborg S.R, et al.(2010). How to Improve R&D Productivity; The Pharmaceutical Industry grand Challenge: Nature Review; Drug Discovery., 9(3) 203 – 214.

14) Wikipedia; free Encyclopedia. (2012).Drug discovery. http://.en.wikipedia.org/wikidrug_discovery: Retrieved June 15, 2012.

15) Wikipedia; free encyclopedia. (2012), Preclinical drug development. http://www.wikipedia.org/wiki/pre-clinical-development (website) Retrieved 30 May, 2012.

16) Wikipedia; free encyclopedia (2012). Pre-clinical Imaging. http://en.wikepedia.org/wiki/preclinical imaging.[website] Retrieved June 12, 2012

17) William, J.K., Van Bruggen, N., Dinkelbors, L.M., Gambher, S.S. (2008). Molecular imaging in drug development, Nat. Rev. *Drug Discovery July 7; 591 – 607.*

A BRIEF OVERVIEW OF PEDIATRICS TRANSLATIONAL RESEARCH

A Case Study by Rahul Tulshiram Ingale, UK
(Masters in Pharmaceutical Science, PhD in Clinical Research Student of Texila American University)
Email: ingalerahul@hotmail.com

ABSTRACT

Translational research is scientific research that helps to make findings from basic science useful for practical applications that enhance human health and well-being. It is practiced in the medical, behavioral, and social sciences. For example, in medicine it is used to "translate" findings in basic research quickly into medical practice and meaningful health outcomes. Applying knowledge from basic science is a major stumbling block in science, partially due to the compartmentalization within science.[1]Translational research is heralded by some as a savior of the biomedical research enterprise by hastening the translation of biomedical discoveries to improved patient care.[2] Although pediatric translational research is a small part of the overall translational research enterprise, it is important for improving child health and provides new opportunities for researchers from all pediatric disciplines.

This article provides an overview of pediatric translational research. It summarizes its evolution, barriers and challenges. The last section provides recommendations for enhancing pediatric translational research.

KEYWORDS:- Pediatric research, Hemophilus influenza, Pediatric, Translational research

INTRODUCTION

Translational research is a paradigm for research alternative to the dichotomy of basic research and applied research. It is often applied in the domain of medicine but has more general applicability as a distinct research approach. It is also allied in practice with the approaches of participative science and participatory action research. As the field of translational research has become increasingly popular in recent years, it has undergone numerous reiterations, such that the specific meaning of the term ‘‘translational research’’ has itself been redefined several times.[3, 4]Translational research helps turn early-stage innovations into new health products, advancing the innovation to the point where it becomes attractive for further development by the medical industry or healthcare agencies. The technical advances have provided the impetus for some radical changes in the way research itself is conceived and performed.

As a result, enhanced interactions and broader collaborations among researchers with different expertise will be required just to keep up with the rapidly changing state of science. In order for a multidisciplinary approach to be effective, better ways to collect and share data (e.g. biorepositories) must be identified. In addition, a more rapid translation of information from basic science into useful clinical applications will require the removal of communication barriers and financial roadblocks that currently prevent basic science teams from working with each other and with clinical researchers. This article summarizes its evolution, barriers and challenges and pediatric translational research.

THE NEED FOR TRANSLATIONAL RESEARCH:

Despite enormous health care expenditures, the quality of health care received by our population is suboptimal and variable. [5,6]More than $2 trillion annually is spent on health care in the United States,[7] amounting to $6000 per individual and16% of the gross domestic product. This is more than triple that of many nations.[8]Yet multiple studies have highlighted the relatively poor health of the population and the inconsistent effectiveness of the health care system in the United States [5,9,10] as well as in other nations.[11–16]

The pediatric literature is also teeming with examples of suboptimal health care delivery, [17–19] the relatively poor health of many children,[20–23] disparities in child health,[24,25] and variations in the quality of health care.[26,27]

The future of pediatric research will be enhanced by strengthening traditional biomedical approaches and embracing emerging opportunities. Biomedical discovery and translation of new knowledge, concepts, and devices into better diagnostic and therapeutic options will require more pediatric physician-scientists, rapid adoption of enabling technologies, increased funding for research and research training (including the creation of federally funded pediatric translational research centers), and a broader distribution of research activities across the academic pediatric community.

Rapid improvement of child health outcomes also will be realized through robust health services research in pediatrics, including the application of rigorous quality improvement science that documents and disseminates successful interventions, leading to better access and effectiveness of care. Improving the value of pediatric care is a realistic goal.

TRANSLATION OF SCIENTIFIC DISCOVERIES TO IMPROVE HEALTH

Research and innovation are essential for improving people's health and savinglives. But too many health conditions in the developing world still lack effective, appropriate, and affordable solutions. Pediatrics abounds with examples of the slow translation of research to improved health care. Despite research highlighting preventable causes of childhood asthma,[28] successive national[29-31] and international guidelines for asthma management,[32,33] and effective therapies,

studies continue to document the rising prevalence of asthma,[34] variability in the level of health care received by children with asthma,[35,36] and significant asthma morbidity.[37,38]

Investigations have uncovered genetic, biologic, and behavioral causes of childhood obesity[39] or autism,[40] yet effective human studies are needed to prevent and successfully manage these diseases. Studies of genetic polymorphisms relating to response to medications[41,42]and investigations of levels of risk with environmental exposures[43]are promising but have not yet realized maximum benefit to children's health.

Considering the second level of translational block (from clinical studies to actual practice), a multitude of studies of asthma care, adolescent preventive services, developmental and mental health screening, and a variety of other content areas demonstrate gaps between evidence-based strategies and actual care.[35,44-47] On the other hand, some pediatric examples of rapid and effective translation also exist. Studies of immunization delivery have demonstrated relatively rapid progress from discovery of a new vaccine, such as hemophilus influenzae[48] or conjugate pneumococcal vaccine,[49-51] and widespread implementation leading to improved health of the child population.[52-54]

BARRIERS TO EFFECTIVE TRANSLATIONAL RESEARCH

General Barriers are as below;

Infrastructure and organization of research programs

Research environment

Public participation in research

Training of investigators

Inadequate funding

Prioritization of resources and types of research

Inadequate collaboration

Pediatric-specific barriers;

Few investigators

Small size of programs

Few subjects

Insufficient leadership positions (including CTSA* institutions)

Challenges in studying the new morbidities

FUNDING OF PEDIATRIC RESEARCH

It is challenging to distinguish pediatric research from other research because many projects have both a pediatric and nonpediatric component and because few funders maintain data on the proportion of funding allocated to pediatrics. NIH maintains data on types of studies funded.[55] Although total NIH spending on pediatric research has increased since 1993, the proportion of NIH funds for research that is devoted to pediatric research has actually decreased, from 13.1% in 1993 to 10.8% in 2008.[56] The proportion of AHRQ funding allocated to child health– related research is similar to that of NIH.[57] The proportion of all biomedical research that is devoted to pediatric translational research from other federal funders, foundations, or from industry is unknown.

CONCLUSION

Although a number of barriers exist to translation, opportunities also abound, including the potential for enhancements in pediatric translational research. The field of translational research has emerged out of the need to more rapidly and effectively translate scientific discovery into better clinical care and improved health of people. NIH is now promoting translational research through CTSAs and other mechanisms, and both federal and private sources are critical to funding all types of translational research. Enhancements at the local and national levels in pediatric translational research will bridge the promise of scientific discovery with the reality of improved child health, which will ultimately result in improved health care and health outcomes for all.

ACKNOWLEDGEMENTS

I am thankful to Miss Ashvini Shitole for conducting literature search.

REFERENCES

1) Acton, J. D., Kotagal, U. (2005). Improvements in healthcare: how can wechange the outcome? *J Pediatr,147, 279–281*.

2) Akinbami, L. J., Schoendorf , K.C (2002). Trends in childhood asthma: prevalence, health care utilization, and mortality. *Pediatrics, 110, 315–322*.

3) Asher, M. I., Montefort, S., Bjorksten, B. (2006). Worldwide time trends in the prevalence of symptoms of asthma, allergic rhino conjunctivitis and eczema in childhood: ISAAC Phases One and Three repeat multicountrycross-sectional surveys. *Lancet, 368, 733–743.*

4) Bethell, C., Reuland, C.H., Halfon, N., Schor, E.L. (2004). Measuring the quality of preventive and developmental services for young children: national estimates and patterns of clinicians' performance. *Pediatrics, 113, 1973–1983.*

5) Broder, K.R., Cohn, A.C., Schwartz, B., et al (2008). Adolescent immunizations and other clinical preventive services: a needle and a hook? *Pediatrics, 121, S25–S34.*

6) Cercenado, E., Cuevas, O., Fenoll, A., et al(2007). Effect of the introduction of the pneumococcal conjugate vaccine on invasive disease produced by Streptococcus pneumoniae. *Int J Antimicrob Agents, 29, S294.*

7) Christakis, D.A., Feudtner, C., Pihoker, C., Connell, F.A. (2001). Continuity and quality of care for children with diabetes who are covered by Medicaid. *Ambul Pediatr, 1, 99–103.*

8) Direct and indirect effects of routine vaccination of children with7-valent pneumococcal conjugate vaccine on incidence of invasive pneumococcal disease—United States, 1998–2003. *MMWR Morb Mortal Wkly Rep,54, 893–897.*

9) Ebbeling, C. B., Pawlak, D. B., Ludwig, D. S. (2002). Childhood obesity: public health crisis, common sense cure. *Lancet, 360, 473–482.*

10) Estimates of funding for various diseases, conditions, research areas. National Institutes of Health[online] . Retrieved from //www.nih.gov/news/fundingresearchareas.htm.

11) Etheredge, L., M. (2007). A rapid-learning health system. *Health Aff (Millwood), 26, w107–w118.*

12) Evans, W.E., Relling, M.V (2004). Moving towards individualized medicine with pharmacogenomics. *Nature, 429, 464–468.*

13) Finkelstein, J.A., Lozano, P., Farber, H.J., et al (2002). Underuse of controller medications among Medicaid-insured children with asthma. *Arch Pediatr Adolesc Med, 156, 562–567*

14) Genel, M., McCaffree, M. A., Hendricks, K., et al (2008). A National Agenda for America's Children and Adolescents in 2008: recommendations from the 15th Annual Public Policy Plenary Symposium, Annual Meeting of the Pediatric Academic Societies, May 3, 2008.

15) Grijalva, C.G., Poehling, K.A., Nuorti, J.P., et al (2006). National impact of universal childhood immunization with pneumococcal conjugate vaccine on outpatient medical care visits in the United States. *Pediatrics, 118, 865–873.*

16) Halterman, J. S., Aligne, C.A., Auinger, P., et al (2000). Inadequate therapy for asthma among children in the United States. *Pediatrics, 105, 272–276.*

17) Horn, I.B., Beal, A.C. (2004). Child health disparities: framing a research agenda. *Ambul Pediatr, 4, 269–275.*

18) Homer, C.J., Szilagyi, P., Rodewald, L., et al (1996). Does quality of care affect rates of hospitalization for childhood asthma? *Pediatrics, 98, 18–23.*

19) Institute of Medicine TNA. Crossing the Quality Chasm: A New Health System for the 21st Century. National Academy Press; 2001.

20) Jencks, S., F., Cuerdon, T., Burwen, D. R., et al (2000). Quality of medical care delivered to Medicare beneficiaries: a profile at state and national levels. *JAMA, 284, 1670–1676.*

21) Juniper, E. F., Guyatt, G, H., Feeny, D.H., et al (1996). Measuring quality of life in the parents of children with asthma. *Quality Life Res, 5, 27–34.*

22) Katon, W., Russo, J., Richardson, L., et al (2008). Anxiety and-depression screening for youth in a primary care population. *AmbulPediatr, 8, 182–188.*

23) Kaplan, S.H., Greenfi http://bcs.bedfordstmartins.com/resdoc5e/res5e_ch09_s1-0009.htmleld, S., Connoly, G.A., et al (2001). Methodologic issues in the conduct and interpretation of pediatric effectiveness research. *Ambulpediatr, 1, 63-70.*

24) Landrigan, P. J., Kimmel, C.A., Correa, A., Eskenazi, B.(2004). Children's health stand the environment: public health issues and challenges for risk assessment. *Environ Health Perspect, 112, 257–265.*

25) Lara, M., Rosenbaum, S., Rachelefsky, G., et al (2002). Improving childhood asthma outcomes in the United States: a blueprint for policy action. *Pediatrics, 109, 919–930.*

26) Levine, O.S., Cutts, F.T. (2007). Pneumococcal vaccination and public health. *Lancet, 369,1144–1145.*

27) Lord, G. M., Trembath, R. C. (2007). A strategy for translation. *Lancet, 369, 1771–1773.*

28) Lost in clinical translation. Nat Med,(2004), 10, 879 [PubMed].

29) Mathers, C. D., Vos, E.T., Stevenson, C. E., Begg, S.J. (2001). The burden of disease and injury in Australia. *Bull World Health Organ, 79, 1076–1084.*

30) Mangione-Smith, R., DeCristofaro, A.H., Setodji, C.M., et al (2007). The quality of ambulatory care delivered to children in the United States. *N Engl J Med, 357, 1515–1523*.

31) McGlynn, E., A., Asch, S., M., Adams, J, et al (2003). The quality of health care delivered to adults in the United States. *N Engl J Med, 348, 2635–2645*.

32) Measuring the health of nations: updating an earlier analysis. The Commonwealth Fund[online]. Retrieved from http://www.commonwealthfund.org/publications_show.htm?doc_id=640980.

33) Medical research: Saving lives through new cures and treatments. Association of American Medical Colleges Web site.[online], Retrieved from http://www.aamc.org/research/ftp/ftpsavinglives.pdf. Accessed August 28, 2008.

34) Miller, M.R., Gergen, P., Honour, M., Zhan, C.L. (2005). Burden of illness for children and where we stand in measuring the quality of this healthcare. *Ambul Pediatr, 5, 268–278*.

35) Mirror, mirror on the wall: an international update on the comparative performance of American healthcare. The Commonwealth Fund[online]. Retrieved from http://www.commonwealthfund.org/usr_doc/1027_Davis_mirror_mirror_international_update_final.pdf?section¼4039.

36) Murray, C., Frenk, J. (2001). World Health Report 2000: a step towards evidence-based health policy. *Lancet, 357, 1698–1700*.

37) National Institutes of Health (NIH). What is Translational Research. Retrieved from http://ccts.uth.tmc.edu/what is-translational-research.com.

38) National Healthcare Disparities Report, Agency for Healthcare Research and Quality [online] (2006). Retrieved from http://www. ahrq.gov/qual/nhdr06/nhdr06.htm.

39) National Heart Lung and Blood Institute and National Asthma Education and Prevention Program. Expert Panel Report: Guidelines for the Diagnosis and Management of Asthma. Bethesda, Md: National Institutes of Health; (1991). *NIH Publication No. 91, 3042*.

40) National Heart Lung and Blood Institute and National Asthma Education and Prevention Program. Expert Panel Report II: Guidelines for the Diagnosis and Management of Asthma. Bethesda, Md: National Institutes of Health; (1997). *NIH Publication No. 97, 4051*.

41) National Heart Lung and Blood Institute and National Asthma Education and Prevention Program. NAEPP Expert Panel Report: Guidelines for the Diagnosis and Management of Asthma-Update on Selected Topics. Bethesda, Md: National Institutes of Health, (2002). NIH Publication No. 02-5075.

42) National Institutes of Health. Workshop Report, Global Strategy for Asthma Management and Prevention. Bethesda, Md: National Institutes of Health, (1995*). NIH Publication No 95, 3659*.

43) National Institutes of Health. Global Initiative for Asthma, Global Strategy for Asthma Management and Prevention. Bethesda, Md: National Institutes of Health, (2002). *NIH Publication No. 02, 3659.*

44) Newacheck, P. W., Halfon, N. (2000). Prevalence, impact, and trends in childhood disability due to asthma. *Arch Pediatr Adolesc Med,154, 287–293*.

45) Perrin, J.M., Hicks, P.J. (2008). The future of disability in America: review of the Institute of Medicine report. *Ambul Pediatr, 8, 71–72.*

46) Poehling, K.A., Szilagyi, P.G., Grijalva, C.G.(2007). Reduction of frequent otitismedia and pressure-equalizing tube insertions in children after introduction of pneumococcal conjugate vaccine [published correction appears in *Pediatrics, 119, 1270*.

47) Ramani, R.R., Hall, W.N., Boulton, M., et al (2004). Impact of PCV7 on invasive pneumococcal disease among children younger than 5 years: a population-based study. *Am J Public Health. 94, 958–959*.

48) Rodwin, V. G. (2003). The health care system under French National Health Insurance: lessons for health reform in the United States. *Am J Public Health, 93, 31–37.*

49) Seid, M., Schultz, D., McClure, J., Stoto, M.A (2007). Evaluation of AHRQ's Children's Health Activities. *AHRQ Publication No. 08-M013-EF; 2007.*

50) Schroeder, S., A., Shattuck, Lecture (2007).We can do better—Improving the health of the American people. *N Engl J Med, 357, 1221–1228.*

51) Szatmari, P. (2003). The causes of autism spectrum disorders—multiple factors have been identified, but a unifying cascade of events is still elusive. *Br Med J, 326, 173–174.*

52) Szilagyi, P.G., Schor, E.L. (1998). The health of children. *Health Serv Res, 33, 1001–1039.*

53) The Long-Term outlook for health care spending. Congressional Budget Office [online] November (2007). Retrieved from http//www.cbo.gov/doc.cfm?index¼8758.

54) Wolf, C.R., Smith, G., Smith, R.L. Science, medicine, and the future—pharmacogenetics. *Br Med J, 320, 987–990*.

55) Woolf, S., H. (2008). The meaning of translational research and why it matters. *Jama, 299, 211–3 [PubMed]*.

56) Zhou, F., Bisgard, K.M., Yusuf, H.R., et al (2002). Impact of universal Haemophilus influenzae type b vaccination starting at 2 months of age in the United States: an economic analysis. *Pediatrics, 110, 653–661*.

57) Zuckerbrot, R. A., Jensen, P. S. (2006). Improving recognition of adolescent depression in primary care. *Arch Pediatr Adolesc Med, 160, 694–704*.

PAIN MEASUREMENT TOOLS AND METHODS, AMBULATORY BLOOD PRESSURE MONITORING AND QUESTIONNAIRES IN CLINICAL RESEARCH- OVERVIEW

A Case Study by Praneeth Kumar Kamarapu, India
(M.Sc in Formulation Science, PhD in Clinical Research Student of Texila American University)
Email: praneethuk4@googlemail.com

ABSTRACT

An Expert Working to review the status of the use of pain measurement tools (PMTs), Ambulatory blood pressure monitoring (ABPM) and Questionnaires in Clinical Research. The present work recommends that standardized methods should be applied for the use of PMTs in research. Unidimensional pain measurement tools (PMTs) and multidimensional pain measurement tools (PMTs) designed to assess pain, the McGill Pain Questionnaire and Brief Pain Inventory are valid in many multilingual versions.

The diagnosis and management of hypertension is based on blood pressure (BP) measurements taken by doctors or nurses with conventional sphygmomanometers. Asking the patient to take their own BP at home has been sporadically reported for many years, but the potential value of patient home measurement has been overshadowed by the development of continuous ambulatory BP monitoring.

Ambulatory blood pressure monitoring have been shown to improve the management of hypertension. Twenty practices were asked to monitor hypertensive patients, in particular those about to start drug treatment and those who were poorly controlled.

A good questionnaire design for a clinical trial will minimize bias and maximize precision in the estimates of treatment effect within budget. The mode of administration can also impact on the cost, quality and completeness of data collected. There is good evidence for design features that improve data completeness but further research is required to evaluate strategies in clinical trials. Theory-based guidelines for style, appearance, and layout of self-administered questionnaires have been proposed.

KEYWORDS: pain measurement tools (PMTs), Ambulatory blood pressure monitoring (ABPM), Questionnaire design, Mode of administration, Guidelines.

1. PAIN MEASUREMENT TOOLS AND METHODS

1.1 INTRODUCTION

Pain is a complex and subjective experience that poses a number of measurement challenges. However, in the current culture of evidence-based medicine, it is important that clinicians and researchers utilize sensitive and accurate pain outcome measures. Currently, there exists no valid and reliable method of objectively quantifying an individual's experience of pain. Therefore, we rely mainly on self-report measures to determine the impact of pain. Despite the challenges that pain measurement presents, a number of tools and approaches can be employed to collect useful pain estimates.[1]

Interpretation of research data requires that the data be valid and recorded in an interpretable format. In clinical studies on pain, valid and reliable outcomes should be used. Furthermore, in order to compare data between studies, a standardization of outcomes, namely, pain measures, will increase the validity of the comparisons.[2]

Success in meeting this challenge requires delineation of the scope of the problem, characterization of the pain syndromes, determination of optimal therapeutic strategies, identification of barriers to implementation of effective strategies, determination of strategies to overcome these obstructions, and the monitoring of outcomes for purposes of continual quality improvement.

Many approaches to the measurement of pain attributes have evolved over the past four decades. Some of them have been applied to cancer pain and palliative care, but the selection and application of these approaches in palliative care has often been capricious and idiosyncratic.[3]

No valid instrument is applicable at the moment for the assessment of pain in the cognitively impaired. A behavioral scale has been recently designed for pain assessment in the cognitively impaired patient and its validation is ongoing.[4-6]

1.2 DESCRIPTION OF PAIN MEASUREMENT TOOLS (PMTS)

Because resources and time are always limited, we are forced to make decisions on which outcomes to include in our measurements. In some cases, a simple measure of pain intensity may be the most logical primary outcome variable. In other cases, a general indicator of work or social functioning may be more clinically relevant. Pain clinicians will recognize cases in which an individual is profoundly disabled by seemingly low pain intensity, and cases in which an individual maintains a productive and fulfilling lifestyle despite reporting a high degree of pain. Some interventions may have little impact on pain intensity scores, but may benefit mood, motivation, and functioning.

Therefore, one of the most important decisions to make in testing a new treatment is determining what outcomes are most clinically relevant. We now review a few of the available pain outcome measures, which range from simple and narrowly defined, to large and multidimensional. Each has its proper place in measuring pain outcomes. We also refer readers to the IMMPACT recommendation on a core set of outcome measures.[7-10]

1.2.1 UNIDIMENSIONAL PAIN MEASUREMENT TOOLS

Three types of unidimensional pain measurement tools are considered,

- Visual analogue scales (VAS),
- Categorical verbal rating scales (VRS), and
- Categorical numerical rating scales (NRS).

All of these approaches are commonly used to measure pain intensity and are well validated in the cancer population.[11]

VAS, VRS, and NRS are also commonly used to measure pain relief. The VAS has been studied and is often considered an ideal scale, because it is continuous, approximates a ratio scale, and is more independent from language than verbal scales (although the choice of the extreme anchor words or end-phrases can be relevant).On the other hand, its validity more strongly depends on the appropriateness of administration method and of the instructions given to the study subjects.[12-15]It is, therefore, more difficult to use than other scales.

Evidence suggests that numeric rating scales are easier to apply and are associated with better compliance than the VAS. Based on the available evidence, the use of a standard 0-10 numeric rating scale and 100-mm horizontal visual analogue scale can be recommended.[16] although these are typically administered with pen and paper; other valid approaches include the use of touch screens for VAS and NRS, sliding scales, and verbally administered numeric rating scales.

For purposes of intervention studies, both pain intensity and pain relief can be measured. Pain relief can be measured by asking the patients to compare pain now with previous pain experiences.

Pain relief measurement validity is limited to short-term intervention studies (24 hours or less); in chronic studies, its validity has been seriously questioned and the construct underlying its meaning in descriptive studies is uncertain.[17]

1.2.2 MULTIDIMENSIONAL PAIN MEASURING TOOLS

Three multidimensional scales are considered,

- the McGill Pain Questionnaire,
- the Brief Pain Inventory, and the
- Memorial Pain Assessment Card.

Although recognizing that other instruments exist or are under study, the Expert Working Group recommends the use of the Short form of the Brief Pain Inventory or the McGill Pain Questionnaire.

The Brief Pain Inventory (BPI) is a simple and easy to administer tool that provides information about the history, intensity, location, and quality of pain. Numeric scales (range 0 to 10) indicate the intensity of pain in general, at its worst, at its least, and right now. A percentage scale quantifies relief from current therapies. A figure representing the body is provided for the patient to shade the area corresponding to his or her pain.[18-20]

The McGill Pain Questionnaire (MPQ) is a self-administered questionnaire that provides global scores and subscales scores that reflect the sensory, affective, and evaluative dimensions of pain. It has been validated in cancer pain.

A short form of the MPQ (SF-MPQ) was developed for use in research settings. The SF-MPQ consists of 15 representative words from the sensory (n _11) and affective (*n*_4) categories of MPQ. The Present Pain Index, verbal rating scale, and visual analogue scale (VAS) measuring pain intensity is included.

The 15 words are scored using a 4-point verbal rating scale, ranging from none, mild, moderate, to severe pain. The SF-MPQ correlates highly with the MPQ. Whereas the MPQ is available in many languages, the SF-MPQ is not.[22-25]

1.3 PHYSICAL METHODS USED IN PAIN MEASUREMENTS

A large number of techniques for pain threshold determination have been described. The painful stimuli used in these methods fall into several categories:

CHEMICAL STIMULI: Several alkaline and acid solutions, amines and peptides have been used. They are generally ineffective when use, don't intact skin and therefore methods of applying these substances intraepidermally, intradermally, intramuscularly and at the exposed base of a blister have been used. Problems include the inability to repeat the test frequently due to accumulation of the chemical, measurement of the concentration of the substance within the tissue, and determination of the precise site of action.[26]

THERMAL STIMULI: Thermal stimulation is favored by most investigators as the most adequate for pain threshold determination studies. Radiant heat has been widely used since the popularization of the method by Hardy et al.(1940). However, potential tissue damage is associated with repetitive stimulation of the same point of the skin and there is not a strict linear

relationship between the intensity of the stimulus and the heat delivered to the skin. This is probably related to regional blood flow and can introduce errors in the measurement. A recent improvement in this field has been the introduction of infrared laser beam stimulation. This method shortens the exposure time required for thermal noxious stimulation to a few milliseconds, avoiding co-activation of non-noxious thermoreceptors.[27]

Conducted heat for noxious thermal stimulation does not have the specificity of radiant. Heat methods due to simultaneous activation of mechanoreceptors. Recently, a method for Routine clinical practice using a mode has been developed by Fruhstorfer et al. (1976). It is a rapid and repeatable method that can be used on any part of the body surface.

ELECTRICAL STIMULI: Electrical stimuli are widely used in experimental pain research. Usually a Square wave pulse or train of pulses is delivered to the skin. The current applied may vary considerably as a result of changes in the electrical resistance of the skin unless a device to Maintain a constant current is incorporated.[28]

MECHANICAL STIMULI: Compression of skin, tendons and underlying bone structures by means of a calibrated device is the commonly used method. The rate of application of the pressure is an important factor and should be taken into account in the experimental design. Differences in tissue compliance affect the distribution of the applied force and can be another source of variation.[29]

1.4 PRINCIPLES IN THE APPLICATION OF PAIN

Several principles are relevant when incorporating a PMT into the methodology of a descriptive or interventional study.

APPROPRIATENESS: The selected tool must be appropriate to the study design and the intended study population.[30]

FREQUENCY OF APPLICATION: The frequency of pain measurement must be relevant to the research question to be addressed and the study population. It must be practical and not excessive burdensome.

DATA COLLECTION: Data should be collected in a standardized format, which is applied identically to all participating patients.[32]

The procedure should be documented as part of the study protocol. Where the patient population is heterogeneous and comprises sub populations that require different measurement approaches, contingencies for the application of differing methods of group specific data collections should be documented. However, in general, it is not recommended that different measurement approaches be applied sub populations in the same study.[33-34]

2. AMBULATORY BLOOD PRESSURE MONITORING (ABPM)

2.1 INTRODUCTION

The diagnosis and management of hypertension is based on blood pressure (BP) measurements taken by doctors or nurses with conventional sphygmomanometers. Asking the patient to take their own BP at home has been sporadically reported for many years,[35-39] but the potential value of patient home measurement has been overshadowed by the development of continuous ambulatory BP monitoring.[40]

Home BP monitoring is recommended in some national[41] and local guidelines (Burns-Cox, personal communication, 1998) as an adjunct to the diagnosis and management of hypertension because it has been shown to diagnose sustained 'white coathypertension' (WCH)[42,43] improve patient compliance with follow- up and medication, help in the management of poor BP control[44] and drug side-effects, and reduce prescribing costs. It has not been widely used in the United Kingdom because it has required patient training in the use of mercury or aneroid sphygmomanometers and because of doubts about the accuracy of
Patient measurements.

Now that accurate, reliable, and inexpensive semi-automatic monitors are available and have been validated, home monitoring has become feasible. We saw the need to establish the feasibility of home BP monitoring in the diagnosis of sustained WCH and assess its acceptability to doctors, nurses, and patients. This study therefore investigated the use and acceptability of home monitoring and estimated the incidence of WCH as diagnosed in a primary care setting.[46]

2.2 METHOD

Local practices were offered participation in the study and the 20 who agreed were offered a monitor in exchange for data on its use. Each practice was provided with an Omron 705CP monitor, which enabled the storage of up to 14 measurements within its mechanism and a print out of these with mean values. They were asked to monitor new hypertensive patients before starting drug treatment (the 'untreated' group), those who were poorly controlled before increasing or changing their medication (the 'uncontrolled' group), and others whom they thought might benefit.

Details of prior BP measurements, medication, and cardiovascular risk were requested, and nurses were asked to brief patients to take the patients' BP 14 times over five days, recording the figures automatically in the device and on a written chart. Patients completed a simple questionnaire on acceptability. Doctors and nurses detailed their experiences and opinions during the study. Focus groups with patients and with doctors and nurses were held.[47]

Guidelines on monitoring and using the results were provided for practices. We used the British Hypertension Society Guidelines on the criteria for the diagnosis (≥160/100) and control

(<160/90) of hypertension12 using clinic readings. Home BP levels are known to be similar to those of daytime ambulatory monitoring, 13 and we defined the normal as a mean home BP of <150/95 for untreated cases and <150/85 for those poorly controlled. Mean home levels could be compared with clinic readings by adding the correction factors of 10 mmHg to the mean home systolic and five to the mean home diastolic as discussed below.

Sustained WCH was diagnosed if clinic levels were hypertensive but corrected mean home levels were normal.14 We advised that patients with WCH, mild to moderate clinic levels, and no evidence of cardiovascular damage or major risk factors could be treated by non-drug strategies and observation with further home monitoring.[48]

2.3 RESULTS

The practices' age–sex distributions, their setting, their teaching status, and their socioeconomic profiles varied considerably, but these were not associated with any differences in monitor use.

There were 81 full-time equivalent doctors, a total list size of 142 000, a mean of 7200 patients per practice, and 1760 per doctor. Most practices quickly developed a waiting list for monitoring And five were lent second monitors by the project. Others purchased one so that, within a few months of the beginning of the investigation, 12 practices had more than one monitor.

THE PATIENTS

A total of 672 patients were offered monitoring. One refused and a further 11 were excluded from the analyses; three because they provided no monitor readings, two where the practices did not provide records of clinic BP measurements and a further six because of unacceptable readings. Of the 660 remaining, 236 (36%) were new patients, 258 (39%) were poorly controlled, and 166 (25%) were monitored for other reasons (Table 1).

This latter group was mainly borderline cases not fulfilling the study criteria for hypertension or poor control, while three were pregnant and several others were monitored for undocumented reasons. Twenty-nine (4.4%) of the total had diabetes and 45 (7%) had a history of cardiovascular disease.

Table 1. Numbers of patients monitored by age and sex.

	Age group (years)						
	<40	40–49	50–59	60–69	70–79	>80	Total
Male	27	65	80	70	28	5	275
Female	39	67	110	106	60	6	385
Total	66	132	190	176	88	8	660
Percentage of those monitored	10%	20%	29%	27%	13%	1	100%
Per 1000 of total population	3	6	10	12	8	1	5

MONITOR USE

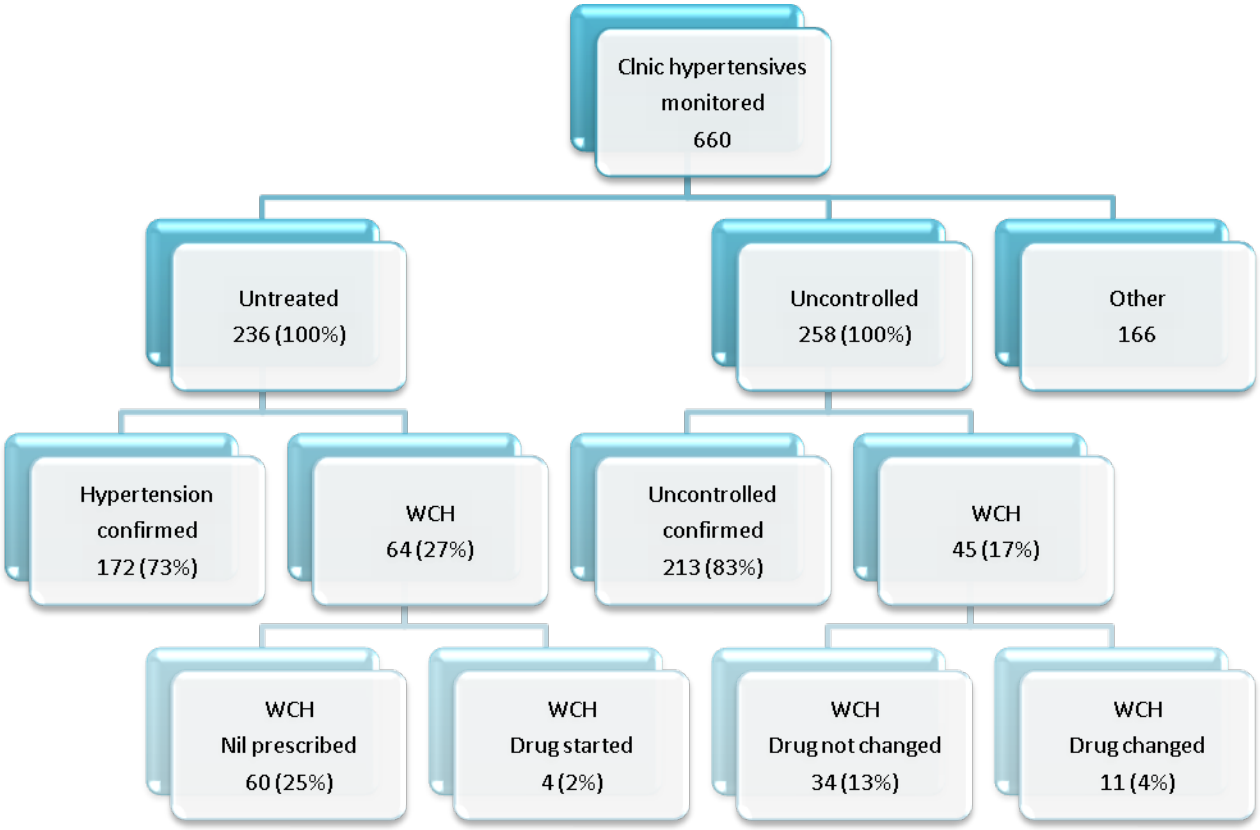
The 37 monitors in use for a period between six and 12 months had only minor technical problems. Two reported faulty printers; one of which was resolved by correcting the paper feed and the other was replaced by the supplier. The standard cuff containing a bladder measuring 23.5 cm by 12 cm was supplied, and this was found to be too short for a few patients with very fat arms.

A feature of modern semi-automatic sphygmomanometers is that mechanical problems, rather than causing inaccurate readings, produce an 'error' reading, and patients were asked to record these on their chart. The commonest, 'cuff over-inflation', is often a result of the cuff being too loosely applied. The total of58 error readings recorded represented less than 1% of the 9240BP measurements taken, and no patients had more than two. Occasional unexpectedly high readings occurred for no obvious reason, but a second attempt usually gave a reading in the expected range. However, six patients produced records with consistently exceptionally high values, which we were unable to explain and which were excluded from our analysis. In these cases, practices used office values for management decisions.

OUTCOME OF MONITORING

Where WCH was diagnosed, no change in drug status was made for 60 (94%) out of 64 untreated patients and 34 (76%) out of 45of the uncontrolled patients (Figure 1).

(Figure 1): ***Outcome of monitoring***



PATIENT ACCEPTABILITY

Practices asked patients to record BP measurements using the 'memory' button on the machine and on a chart. Twenty-three patients (3.5%) had problems with the memory button and a further Two (0.3%) had difficulty in reading the figures on the monitor. Nine (1.4%) had difficulty in entering figures on the chart. A total of 14 entries (the maximum number that the memory will Store) were requested, and we found that chart records were more complete than those in the memory. Of chart entries, 533 (81%) patients made all 14 entries and only 11 (1.7%) made less

than10, whereas, of memory entries, 501 (76%) made 14 and 75(11%) made less than 10. Using both machine and chart entries, 98% of patients produced 10 or more recordings.

A focus group highlighted the interest and enthusiasm that patients had for monitor use, their views on anxiety and BP variability, difficulties making recordings at work, and the importance of help from the practice nurses. Two hundred and one (30%) patients said that cuff inflation was comfortable, 349(53%) said it was uncomfortable, and 90 (14%) said that it was very uncomfortable or painful. Forty-one (6%) patients said that monitoring interfered with normal living; most of these having found that it was inconvenient to take a BP reading while at work.

DOCTOR AND NURSE QUESTIONNAIRES

Seventy-one questionnaires were returned from 15 practices: 49from doctors and 22 from nurses. Seventy responders said that monitoring had improved patient management, and other replies expressed satisfaction and interest. The median reported number of monitors needed per practice was 2.6.

MONITOR VALIDATION

Periodic checks are advised in recent American guidelines,[6] and the European Union is expected to introduce regulations concerning annual checks on medical instruments. Checks by practice enurses were made in this study using 'Y-tubes' to connect a mercury sphygmomanometer in parallel with their monitor and take 10 random readings. Of the 40 mean systolic and diastolic figures received, 32 were within less than 2 mmHg, four within 3mmHg and four between 3 and 5 mmHg.

3. QUESTIONNAIRES IN CLINICLA RESEARCH

Much of the data in clinical research is gathered using questionnaires or interviews.
The validity of the results depends on the quality of these instruments. Poorly designed questions can result in poor data quality. Critical to improve our understanding of the inherent flaws of Survey questions.

To assess the empirical evidence for how questionnaire length and other design features might influence data completeness in a clinical trial; a systematic review of randomized controlled trials (RCTs) was conducted, and has recently been updated. The strategies found to be effective in increasing response to postal and electronic questionnaires are summarized in the section on increasing data completeness below.

Clinical trial investigators have also relied on principles of questionnaire design that do not have an established empirical basis, but which are nonetheless considered to present 'good practice', based on expert opinion. The section on questionnaire development below includes

some of that advice and presents general guidelines for questionnaire development which may help investigators who are about to design a questionnaire for a clinical trial.

3.1 REGULATORY GUIDELINES

The International Conference on Harmonization (ICH) of technical requirements for registration of pharmaceuticals for human use states:

'The collection of data and transfer of data from the investigator to the sponsor can take place through a variety of media, including paper case record forms, remote site monitoring systems, medical computer systems and electronic transfer. Whatever data capture instrument is used, the form and content of the information collected should be in full accordance with the protocol and should be established in advance of the conduct of the clinical trial. It should focus on the data necessary to implement the planned analysis, including the context information (such as timing assessments relative to dosing) necessary to confirm protocol compliance or identify important protocol deviations. 'Missing values' should be distinguishable from the 'value zero' or 'characteristic absent'.

This suggests that the choice of variables that are to be measured by the questionnaire (or case report form) is constrained by the trial protocol, but that the mode of data collection is not. The trial protocol is unlikely, however, to list all of the variables that may be required to evaluate the safety of the experimental treatment. The choice of variables to assess safety will depend on the possible consequences of treatment, on current knowledge of possible adverse effects of related treatments, and on the duration of the trial. In drug trials there may be many possible reactions due to the pharmacodynamics properties of the drug.

The Council for International Organizations of Medical Sciences (CIOMS) advises that: 'Safety data that cannot be categorized and succinctly collected in predefined data fields should be recorded in the comment section of the case report form when deemed important in the clinical judgment of the investigator'.

3.2 DESIGNING A QUESTIONNAIRE

- Requires development of a set of questions used to obtain clinically and statistically useful information from an individual.

- Difficult for several reasons

    - Each question must provide a valid and reliable measure.
    - The questions must clearly communicate the research intention to the respondent.

- The questions must be assembled into a logical, clear instrument that flows naturally and will keep the respondent sufficiently interested to continue cooperation.

Good questionnaires are difficult to construct. Bad questionnaires are difficult to analyze

.

- Start early and plan for plenty of time.
  - More challenging and time-consuming than you think.
  - Time spent =Quality of questionnaire.
  - Wrong approach:
  - A questionnaire is finished when time runs out, not necessarily when it is the best it can be.

3.3 THREE DISTINCT PHASES

- Initial questionnaire planning.
- Development of specific questions.
- Final construction of the data collection instrument as a whole.

3.3.1 INITIAL QUESTIONNAIRE PLANNING

Prior to writing any questions:

- Define the problem and specific aim(s) of the study, including the population of interest.
- Make a detailed list of the information to be collected and concepts to be measured.
  - Don't forget about demographics and possible inclusion/exclusion criteria to define the target population.
  - Formulate a statistical analysis plan that outlines how every item will be analyzed.
  - Helpful to list the role of each item (predictor, outcome, or confounder) in addressing each specific aim.
  - Useful to think ahead to the reporting of results (i.e., sketch out the final results tables).
  - Review the literature and collect any existing measures, related surveys, and/or data collection instruments that might have measured similar concepts.
  - Saves development time and allows comparison with other studies if used appropriately.
  - Ideal to use existing instruments without modification.
  - Existing instruments may not be entirely appropriate for the question or the population, or may be too long; may be necessary to delete, change, or add a few items.
  - Direct comparison with other studies may no longer be possible if original instrument has been modified.

3.3.2 DEVELOPMENT OF SPECIFIC QUESTIONS

- First goal: Shorten the set of questions.

- Questions not essential to addressing the specific aim(s) increase the amount of effort involved in entering, cleaning, and analyzing the data.
- Decrease the overall quality and productivity of the study.
- Every item in the questionnaire must be a meaningful contribution to the intended analyses.
- Compare the draft questions to the survey objectives to ensure that the right types of questions (e.g., knowledge) are being asked for a given topic.
- Resist the temptation to include additional questions or measures or just in case" they might produce interesting data.

➢ Second goal: Refine the remaining questions.
- Every word in a question can influence the validity and Reproducibility of the responses.
- Iterative cycles of review and revision.
    - Refine and clarify the research objectives.
    - Focus the concepts included in the survey.
- Target:
    - Terms and concepts should be familiar and easy to understand.
    - Cues and ordering of questions should serve to stimulate recall.
    - Ordering and format of questions should be unbiased and balanced.

➢ Terms and concepts should be familiar and easy to understand.
- Questions should be simple, be free of ambiguity, and encourage accurate and honest responses without embarrassing or offending the respondent.
    - Clarity: specific and concrete wording.
    - “How much exercise do you usually get?" vs. \During a typical week, how many hours do you spend exercising (e.g., vigorous walking or sports)?”
    - Simplicity: short non-technical words and simple grammar.
        - “Over-the-counter medications" vs. \Drugs you can buy without a doctor's prescription".
    - Neutrality: avoid “loaded" words and stereotypes.
        - “During the last month, how often did you drink too much Alcohol?" vs. during the last month, how often did you drink? More than five drinks in one day?”

➢ Cues and ordering of questions should serve to stimulate recall.
- Respondents often asked to recall and access information from memory.
    - Problems: asked to recall too much information or asked to recall information from too far in memory.
    - Regarding behavior, interested in the average or the extremes?
- Steps that can help the respondent's memory search:
    - Ask a short series of related questions.
    - Provide an anchor for the reference period of time frame.

- Goal: To ask about the shortest recent segment of time that accurately represents the characteristic over the whole period of interest for the research question.
- Example: “During the last 7 days, how many beers did you have?"

- Keep recall to a minimum and focus on the recent past.

3.3.3 ASSEMBLING THE FINAL QUESTIONNAIRE

- Objective: Fit the items together in a meaningful way so that the entire questionnaire is unified.
  - Order of sections of questions and order of questions within sections.
  - Question and response formats.
  - Skip patterns/Branching questions.
- Also need to consider mode of administration.
  - Self-administered questionnaire, face-to-face interview, telephone interview, or computer-assisted approaches?
  - For self-administered questionnaires, give to respondents in person or administer through the mail, by email, or via a Website?

3.4 MODE OF ADMINISTRATION

- Self-administered questionnaires:
  - More economical, more readily standardized, and the added privacy can enhance the validity of responses.
  - No middle-man bias (no verbal or visual clues from an interviewer to inuence the respondent); more uniform.

- Interviews:
  - Can ensure more complete responses and enhance validity through improved understanding.
  - May be necessary when participants will have variable ability to read and understand questions.
  - Requires substantial training and practice of interviewers.

- Self-administered questionnaires vs. interviews
  - Both susceptible to errors caused by imperfect memory.
  - Both affected by the respondent's tendency to give socially acceptable answers, although not necessarily to the same degree.

- Another decision to make: software.
  - Software to aid creation/formatting, administration (e.g., create Web site), and/or data collection/entry.
  - An option: REDCap Survey.

- Go to www.mc.vanderbilt.edu.
- Click on “StarBRITE" link under “For Employees" area.
- Login with your VUnetID and password.
- Click on the “Data Management" tab.

4. CONCLUSIONS

Despite the difficulty inherent to measuring pain, there are a number of accepted tools for tracking pain-related treatment outcomes. The proper use of these tools can allow clinicians and researchers to demonstrate both statistically and clinically significant treatment effects. These instruments range from quick, one-item assessments of pain intensity, to long surveys that tap into multiple dimensions of the pain experience and overall functioning.

As with the use of continuous ambulatory monitoring, it is necessary to establish arbitrary levels of the normal BP, and this we did on the best available evidence. Having done so, we then adopted the use of correction factors as a practical guide to diagnosis.

A good questionnaire design for a clinical trial will minimize bias and maximize precision in the estimates of treatment effect within budget. Attempts to collect more data than will be analyzed may risk reducing recruitment and increasing losses to follow-up. Questionnaire design still does remain as much an art as a science, but the evidence base for improving the quality and completeness of data collection in clinical trials is growing.

5. REFERENCES:

1) Brown, G.E. (1930). Daily and monthly rhythm in the blood pressure of a man with hypertension: a three year study. *Ann Intern Med, 9, 1177-1189.*

2) Bullinger, M., Alonso, J., Apolone, G., et al. (1998). Translating health status questionnaires and evaluating their quality: the IQOLA Project approach. International quality of life assessment. *J Clin Epiderm, 51, 913–923.*

3) Burns–Cox, C. J., Russell, Rees, J., Wilson, R.S.E. (1975). Pilot study of home measurement of blood pressure by hypertensive patients.

4) Clark, C.W., Ferrer-Brechner, T., Janal, M.N., et al (1989). The dimensions of pain: a multidimensional scaling comparison of cancer patients and healthy volunteers. *Pain 37, 23–32*.

5) Cleeland, C. S. (1984). The impact of pain on the patient with cancer. *Cancer, 54, 2635–2641*

6) Cleeland, C. S. (1989). Measurement of pain by subjective report In: Chapman CR, Loeser JD, eds. Advances in pain research and management, vol 12. Issues in pain management. *New York: Raven Press, pp 391–403.*

7) Daut, R. L., Cleeland, C.S. (1982) the prevalence and severity of pain in cancer. 50, 1913–1918.

8) De, Wit, R., Huijer, Abu-Saad, H., Loonstra, S., et al. (1999). Empirical comparison of commonly used measures to evaluate pain treatment in cancer patients with chronic pain. *J Clin Oncol, 17, 1280–1287*.

9) Deschamps, M., Band, P.R., Coldman, A. J. (1988). Assessment of adult cancer pain shortcoming of current methods. *Pain, 32, 133–139*.

10) Design and use of questionnaires: a review of best practice applicable to surveys of health service sta_ and patients", *Health Technology Assessmen,.(2001), Vol 5, No 31*.

11) Feine, J.S, Lavigne, G.J, Thuan, Dao, T. T, et al. (1998). Memories of chronic pain and perception of relief. *Pain, 77, 137–141*.

12) Fishman, B., Pasternak, S., Wallenstein, S. L, et al. (1987) The Memorial Pain Assessment Card: a valid instrument for the evaluation of cancer pain. *Cancer, 60, 1151–1158.*

13) Galer, B. S., Jensen, M., P. (1997). Development and preliminary validation of a pain measure specific to neuropathic pain. *Neurology, 48, 332–338.*

14) Gracely, R. H., McGrath, P. A, Dubner, R. (1978). A ratio scales of sensory and affective verbal pain descriptors. *Pain, 5, 5–18.*

15) Gracely, R. H., McGrath, P. A., Dubner, R. (1978). Validity and sensitivity of ratio scale of sensory and affective verbal pain descriptors: manipulation of affect by diazepam. *Pain, 5, 19–29.*

16) Haynes, Sackett, D. L., Gibson, E. S., et al.(1976).Improvement in medication compliance in uncontrolled hypertension. *Lancet, 119, 1034-1039.*

17) Houde, R. W., Wallenstein, S. L., Beaver, W. T. (1965). Clinical measurement of pain. In: de Stevens G, ed. Analgesics. *New York: Academic Press, 75–122*.

18) Houde, R. W., Wallenstein, S. L., Beaver, W. T. (1966). Evaluation of analgesics in patients with cancer pain. In: Lasagna L, ed. International encyclopedia of pharmacology and therapeutics, vol 1. *New York: Pergamon Press, 59–67*.

19) Jensen, M. P., Karoly, P., Braver, S. (1986). The measurement of clinical pain intensity: a comparison of six methods. *Pain, 27, 117–126*.

20) Jensen, M. P., Karoly, K. (1993) Measurement of cancer pain by self report. In: Chapman CR, Foley KM, eds. Current and emerging issues in cancer pain: research and practice. *New York: Raven Press, 193–218*.

21) Jensen, M. P., McFarland, C. A. (1993). Increasing the reliability and validity of pain intensity measurement in chronic pain patients. *Pain, 55, 195–203*.

22) Jensen, M. P., Turner, J. A., Romano, J. M. (1994). What is the maximum number of level needed in pain intensity measurement? *Pain, 58, 387–392*.

23) Julius, S. (1991). Home blood pressure monitoring: advantages and limitations. *J Hypertens, 9(3), S41-46*.

24) Kerns, R.D., Turk, D.C., Rudy, T.E. (1985). The West Haven Yale multidimensional pain inventory (WHYMPI). *Pain, 23, 345–356*.

25) Kleinert, H. D., Harsh, G. A., Pickering, T. G., *et al (*1984). What is the value of home blood pressure measurement in patients with mild hypertension? *Hypertension, 6,574-578*.

26) Kremer, E. F., Atkinson, J. H., Ignelzi, R. J. (1981). Measurement of pain: A patient preference does not confound pain measurement. *Pain, 12, 153–163*.

27) Littman, G. S., Walker, B. R., Schneider, B. E. (1985). Reassessment of verbal and visual analog ratings in analgesic studies. *Clin Pharmacol Ther, 38, 16–23*.

28) Mancia, G., Sega, R., Bravi, C., *et al* (1995). Ambulatory blood pressure normality: results from the PAMELA study. *J Hypertens, 13, 1377-1390*.

29) McQuay, H., Moore, A. (1998). An evidence-based resource for pain relief. *Oxford: Oxford University Press, 9(6), 41-49*.

30) O'Brien, E., O'Malley, K. (1988). Over diagnosing hypertension, 297, 1211.

31) O'Brien, E. T., Beevers, D. G., Marshall, H. J. (1995). ABC of Hypertension [Third edition.] *London: BMJ Publishing Group*.

32) O'Brien, E., Mee, F., Atkins, N., Thomas, M. (1996). Evaluation of three devices for self measurement of blood pressure according to the revised British Hypertension Society Protocol: The Omron HEM-705 CP,Philips HP5332 and Nissei DS-175. *Blood Pressure Monitoring, 55-61*.

33) Pickering, T. G. (1987). Ambulatory blood pressure monitoring as a predictor of cardiovascular risk. *Am Heart J, 114, 925-928*.

34) Pickering, T. G. (1993). Blood pressure variability and ambulatory monitoring. *Curr Opin Nephron Hypertens, 2, 380-385*.

35) Price, D. D, McGrath, P. A., Rafi, A., Buckingham, B. (1983). The validation of visual analogue scales as ratio scale measures for chronic and experimental pain. *Pain, 17, 45–56*.

36) Price, D. D., Bush, F. M., Long, S., Harkins, S. W. (1994) A comparison of pain measurement characteristics of mechanical visual analogue and simple numerical rating scales. *Pain, 56, 217–226*.

37) Questionnaire Design by Cathy Jenkins and Mario Davidson

38) Rinck, G. C., van den, Bos, A.M., Kleijnen, J., et al. (1997). Methodologic issues in effectiveness research on palliative cancer care: a systematic review. *J Clin Oncol, 15, 1697–1707*.

39) Sauders, C., Doyle, D., Hanks, G. W. C., and eds. (1998). Oxford textbook of palliative medicine, 2nd ed. *Oxford: Oxford University Press. V–IX*.

40) Scott, J., Huskinsson, E. C. (1976). Graphic representation of pain. *Pain, 2, 175–184*.

41) Sever, P., Beevers, G., Bulpitt, C., *et al. (*1993). Management guidelines in essential hypertension. *Report of the second working party of the British Hypertension Society, 306, 983-987*.

42) Seymour, R. A., Simpson, J. M., Charlton, J. E., Philips, M. E. (1985). An evaluation of the length and end-phrase of visual analogue scales in dental pain. *Pain, 21, 177–185*.

43) Soghikian, K., Casper, S. M., Fireman, B. H., *et al. (*1992). Home blood pressure monitoring. Effect on use of medical services and medical care costs. *Med Care, 30, 855-865*.

44) The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. (JNCVI.) *Arch Intern Med 1997. 157, 2413-2446*.

45) Wallenstein, S. L. (1975). Analgesic studies of aspirin in cancer patients. *Proceedings of the Aspirin Symposium. London: Aspirin Foundation, 5–10.*

46) Wallenstein, S. L., Houde, R. W. (1975). The clinical evaluation of analgesic effectiveness. In: Ehrenpreis S, Heidle A, eds. Methods of narcotic research. *New York: Marcel Dekker, 127–145*.

47) Wallenstein, S. L., Heidrich, G. I., Kaiko, R., Houde, R. W. (1980). Clinical evaluation of mild analgesics: the measurement of clinical pain. *Br J Clin Pharmacol, 10, 319S–327S*.

48) Wallenstein, S. L. (1991). Commentary: the VAS relief scale and other analgesic measures: carryover effect in parallel and crossover studies. In: Max MB, Portenoy RK, and Laska EM, Eds. The design of analgesic clinical trials, vol 18. *New York: Raven Press, 97–104*.

49) Winer, R. T., Clark, W. C., Keohan, M. L., et al. (1999). Validation of the multidimensional affect and pain questionnaire (MAPS) in cancer patients. 9th World Congress on pain. *Vienna: IASP Press, 214*.

A REVIEW: USE OF DEUTERATED INTERNAL STANDARDS IN MASS SPECTOMETRY TECHNIQUES

A Case Study by Opeyemi Orhekafore BEDU, Nigeria
(B.LMS in Histopathology, M.Sc Clinical Research Student of Texila American University)
Email: orhekabedu@yahoo.com

ABSTRACT

Immunosuppressive drugs are used to prevent transplant rejections in organ-transplanted patients but there has to be effective therapeutic drug monitoring because an inadequate or incorrect dosage could lead to intoxication or transplant rejection. There have been many designed protocols for the quantification of these drugs and most of them involve the use of high performance liquid chromatography but Armin et al in their research work chose to design a protocol following the mass spectrometry method which is an upcoming method due to its specificity and sensitivity which was observed to be notably higher. Five immunosuppressive drugs which included Cyclosporine A, Tacrolimus, Sirolimus, Everolimus and Mycophenolic acid were evaluated in whole blood and plasma using deuterated internal standards.

KEYWORDS:- Immunosuppressive, Therapeutic drug, Tacrolimus, Everolimus

INTRODUCTION

After observing that previous methods using high performance liquid chromatography lacked appropriate internal standards / mycophenolic acid to complete the analytic spectrum, the authors decided to use mass spectrometry method incorporating deuterated standards. Cyclosporine A, Tacrolimus, Sirolimus, Everolimus were measured in whole blood while mycophenolic acid was measured in plasma. In order to minimize imprecision, elaborate sample preparation was required to separate the molecules of interest from patients' blood matrix molecules.

Generally, the sample preparation consists of precipitation with a mixture of zinc sulphate and organic solvents. The authors made sure that the protocols used were according to internationally accepted guidelines. They also discovered that adding water before sample precipitation prevented sample clotting and improved extraction efficiency but this was observed to also

increase the dilution which makes the need for a highly mass spectrometer almost inevitable. An intra-assay precision test was carried out in which each concentration was extracted five times and measured in series.

During the erythrocyte lysis stage of the protocol, the authors discovered that the use of water alone for lysis left some erythrocytes undamaged when examined microscopically, they then introduced treatment which yielded complete erythrocyte lysis which is a mandatory criteria for good reproducibility. The data obtained from the mass spectrometry analysis showed that all drugs revealed linear behavior up to the highest concentration of calibrator Assay sensitivity as well as data forprecision and accuracy exceeded clinical requirements. Retention of analytes and deuterated standards were concordant in time, whereas the common standards showed a slight difference in retention time.

The authors were able to overcome the challenge of accuracy and precision which is usually the case when internal standards are used by using deuterated standards and this served as a plus especially in the quantification of cyclosporine A. Furthermore, it was noted that the use of this deuterated standards compensated for most of the measurement errors that could have resulted from either ion suppression or enhancement since deuterated standards co-elutes with the analytes.

Surprisingly, the authors did not fail to state some of the challenges encountered in the course of their research such as identification of most appropriate sample dilution, matrix composition of material used and asserting the purity of the reagents used. It is worthy to note that the results of their findings were also compared with those of other laboratories and from this they suggested that it is not only the immunoassays that need to be standardized but also the physical methods.

From the above results and discoveries, the mass spectrometry was seen to have better specificity, higher sensitivity and was considered to be “economic”. Although the use of the term economic by the authors was not very clear because in stating the likely demerits of the mass spectrometry method they included high acquisition costs alongside the need for academic expertise, complete validation process and back-up system.

Commendation goes to the authors for maintenance and cost reduction wits as they stated that rinsing with methanol for one minute during separation in the analytical column lifetime to at least three months or 4500 analyses. Overall, the mass spectrometry should be subjected to thorough validation process as the authors already suggested in their work, and also mass

spectrometry standards should be established and made available so that results from different laboratories can be reliably compared. More people should also be trained on the mass spectrometry techniques in order to include the available technique since it will help overcome one of the challenges associated with setting up the mass spectrometry method.

The authors have done a good job by writing the paper with an enticing flow and choice of words that carries along the reader to the very end.

REFERENCES

1. Athol J., David W.H. (1999). Therapeutic drug monitoring of immunosuppressant drugs. *Br J ClinPharmacol April, 47(4): 339-350.*

2. Siuzdak G. (1994). The emergence of mass spectrometry in biochemical research. *ProcNatlAcadSci U.S.A. 22, 91(24): 11290-7.*

3. Skoog D.A. (1998). Principles of instrumental analysis: introduction, pp.18. *Harcourt Brace.*

4. Weiling J. (2002). LC-MS-MS experiences with internal standards. *Chromatographia volume 55 issue 1 supplement, pp S107-S113.*

.

THE PREVENTION AND TREATMENT OF MISSING DATA IN CLINICAL TRIALS

A Case Study by Prajna Kumar, USA
(Masters in Health Service Administration, PhD in Clinical Research Student of Texila American University)
Email: prajna.2.kumar@gsk.com

SOURCE

Little RJ. et.al. 2012, "The Prevention and Treatment of Missing Data in Clinical Trials, New England Journal o f Medicine 2012; 367:1355-1360October 4, 2012DOI: viewed 10 October 2013, http://www.nejm.org/doi/full/10.1056/NEJMsr1203730.

KEYWORDS:- Clinical Trials, Critically analyzes, Medicine

INTRODUCTION

This review critically analyzes the article 'The Prevention and Treatment of Missing Data in Clinical Trials in the New England Journal of Medicine (NEJM). The review will summarize the article by providing the purpose for the article, how research was conducted, the results and other pertinent information from the article. The review will also critique the article analyze the article's accessibility and credibility based on its relevance to the subject matter. It will highlight some relevant progress in the topic under study that might have occurred since the article was published.

The article was well written, clear and relevant to the challenges facing the clinical research industry. Missing data points threaten the validity of many clinical trials. At the request of the Food and Drug Administration (FDA) and with its funding, the panel on the handling of missing data in clinical trials was created by the National Research Council's (NRC) Committee on National Statistics. This panel published a report with recommendations that was intended to be used by the FDA for guidance on handling missing data for the entire clinical trial community so that the latter can take measures to improve the conduct and analysis of clinical trials. The current article provides an overview of the findings and recommendations of the resultant report from the perspective of one member of the NRC panel.

Overall the paper succinctly summarizes issues related to missing data and the current state of challenges pertaining to the topic. It creates an understanding of the topic for the reader by discussing some of the main recommendations from the NRC panel's report on this topic

ARTICLE SUMMARY

Consumers and stakeholders need reliable and evidence-based information for making health care choices. As stated earlier, Author RJ Little was part of the panel handling the issues with missing data in clinical trials. This article was part of the clinical problem solving series and has been well cited by others given that it is a very recent article.The purpose of the article was to provide a synopsis of the problem and the recommendations regarding the design, conduct, and analysis of studies to minimize that threat. The authors define missing data as "values that are not available and that would be meaningful for analysis if they were observed." They find that there is no analytic approach that can assuredly produce unbiased estimates of treatment effects when relevant data are missing and therefore recommendationconcludes that a more principled approach to design and analysis in the presence of missing data is both needed and desirable.Authors explored issues with missing data in clinical trial and aimed to document recommendations regarding 1) careful design and conduct to limit the amount and impact of missing data,(2) analysis that makes full use of information on all randomized participants based on careful attention to the assumptions about the nature of the missing data underlying estimates of treatment effects and 3) identified challenges and research gaps. Authors developed their methods based on the key steps suggested in the NRC Committee recommendations.

ARTICLE STRUCTURE

The article was divided into 6 keys sections. It was introduced with a background on how missing data compromises the inference drawn from clinical trials and went on to describe the key findings on how missing data in clinical trials can compromise scientific credibility and the need for sensitivity analysis. The paper then focused on proposing solutions and recommendations on limiting missing data in clinical trial from focus on trial design, planning, conduct follow through and analysis. The article was not based on conventional research study and therefore does not have the traditional sections expected in an article.

The article provides a synopsis on the recommendations from NRC on handling of missing data in clinical trials. The different sections in the paper are well defined, concise and yet narrative enough to draw deductions. The paper is not free from challenge, however, it does succinctly provides the readers an understanding on how the level of missing data can be reduced by creative approaches in the formulation of protocols design, study conduct, subject follow through, as well as in the selection and education of both investigators and patients. Authors did develop future research directions but did not wrap it up with a very well defined conclusion and therefore seemed to lack the closure in the main points. References were clearly cited in the literature section.

There were links to author and journals in the citations and references which allowed the reader to evaluate the articles more effectively. It also referenced the peer review letters which directed towards the critical analysis and feedback by the scientific community. The article also addresses all the members of the review panel and lists them under the source reference.

ARTICLE CRITIQUE

AUTHORITY

The article was published in the NEJM which is a peer-reviewed medical journal published by the Massachusetts Medical Society and is considered among the most prestigious in the world. The author's credibility was established by his PhD; the fact that the article was a peer reviewed article; the fact that the author is a distinguished professor of Biostatistics at the University of Michigan in the United States and has published well over 50 articles just in the area of missing data; the fact that the research described in the article was supported by FDA, (NRC) Committee on National Statistic, prominent universities across the globe and that the content of the article was part of the published report that was supposed to be used by the FDA for guidance on handling missing data for the entire clinical trial community. We are yet to see a clear guidance from the regulatory agency on this topic.

ACCURACY

At the time of the article there was little to no regulatory guidance on the design, conduct, and analysis of clinical trials and minimum specific advice on how to address the problem of missing data. In 2008 the FDA requested that the Committee on National Statistics convene a panel of experts in statistical approaches to handling missing data in clinical trials and analyzing results. The panel had multiple stakeholders, including clinical researchers, statistical researchers, appropriate experts from the National Institutes of Health and the pharmaceutical industry, regulators from FDA, and participants in the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

From information obtained at the workshop and its deliberations, the panel prepared a summary of the workshop and a report with recommendations that was to become the basis of FDA's development of guidance for clinical trials on appropriate study designs and follow-up methods to reduce missing data and appropriate statistical methods to address missing data for analysis of results. The source of the information in the article was based on some of the main findings and recommendations cited in the report by the NRC to address this gap. These scholarly and well informed sources and the endorsement from the clinical trial community lend accuracy to the information presented. Moreover, the strict editorial, references and sourcing processes also contributed to the article's accuracy as did the expert panel contributors from various disciplines around the globe.

CURRENCY

The journal was published in October 2012. The panel of experts started their deliberation end of 2008 and the program continued for about 15 months with a report produced by NRC in 2010. This article was written post NRC report on "The Prevention and Treatment of Missing Data in

Clinical Trials. This article is fairly current and highlights a very relevant issue in the clinical trial arena that is constantly debated and deliberated on.

RELEVANCE

This article was published in a peer reviewed prestigious journal, which has high credibility in an academic context. It was written to inform researchers, regulators and industryand not meant for amusement, endorsement or publicity. It is relevant to all these groups and to the clinical trial industry as a whole. The article content is driven from the NRC's report and is highly relevant to the issues concerning missing data in clinical trials. It strives to identify ways in which FDA guidance should be augmented to facilitate the use of appropriate methods for controlling missing data by the designers and implementers of clinical trials.

OBJECTIVITY

The information was objectively developed, well supported with a current research base and with all evidence acknowledged and referenced. There was no evidence of bias, a fact that was reinforced by the recognition that the article documents decision from a panel of experts chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the report review committee of the NRC.

The fact that the article was based on was an independent review that provided candid and critical comments to assist the institution in making its published report. This independent review also ensured that the report met institutional standards for objectivity, evidence, and responsiveness to the study charge. Although the reviewers listed in the panel provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations nor did they see the final draft of the report before its release. The review of the report was overseen by members that were appointed by the NRC's Report Review Committee.

These members were responsible for making certain that an independent examination of the NRC report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rested entirely with the authoring panel and the institution. Finally, the panel was supported by many federal agencies and through a grant from the National Science Foundation. The sheer meticulously cautious and independent review process lends credibility to the source of the article.

STABILITY

The article, with its source as apeer reviewed medical journal on an academic data base is stable as a resource. Also, the origin of the contents, endorsement by the medical, scientific and regulatory bodies qualifies the stability of the material discussed and the proposal recommended.

ANALYSIS OF TABLES

The article has no graphs, listings or figures. It has two tables, one highlighting ideas for limiting missing data in the design of clinical trials and other on conduct of clinical trials. By way of these tables and suggestions, Little et al. state that there is no easy fix for missing data at the analysis stage. Too many current analyses of clinical trials apply naive methods for missing-data adjustment that make unjustified assumptions, such as the last-observation-carried-forward approach. The handling of missing data requires a scientifically defensible analysis coupled with a sensitivity analysis to assess robustness. The key is to design and carry out the trial in a way that limits the problem of missing data.

Little et al. mention that limiting "the burden and inconvenience of data collection on the participants" as one of several ideas for limiting missing data in the conduct of clinical trials. Actually, critiques say that this idea should have been listed as one of the design feature. This would have not only helped limit missing data but also would have been important in limiting the burden on the investigators which is a critical factor in successful data retrieval as well as patient accrual.

Another feedback was that excessive data collection creates more opportunities for missing data. The best way to avoid missing data would be to collect minimal critical datathat relates to the overall research quality, patient safety and intervention efficacy.This concept is sometimes difficult to sell to investigators/industry who may envision ancillary studies and additional publications ensuing from more data. However, scientific community acknowledges that quality trumps quantity, and perhaps this should be made clearer in criteria for academic, scientific promotion.

Little and colleagues haveclearly stated that missing data are often the result of study designs that mandate study discontinuation when treatment is terminate. Intention-to-treat inference based on randomization requires that patient data be collected regardless of treatment status. However, according to peer reviewed feedback an issue that requires further clarification on is following patients who are off treatment, and methods used to address data that are missing at random. The authors proposed the idea to impute the results for those who have discontinued treatment based on the subjects who are following treatment seems to bechallenging. The goal should be to recreate a result that would have been obtained if patients who discontinued treatment had been followed. In addition, if the common practice of no longer considering data on patients after treatment discontinuation is not altered, methods to address missing data that are based on statistical models will have no similar patients from whom to model the missing data.

Overall the tables clearly outline the strategies for the design and conduct of clinical trials that will prevent missing data.

RECENT ADVANCES RELATED TO THE TOPIC

Missing data in research studies are the rule rather than the exception. Many reasons contribute to data missing from research projects. Whatever the reason(s) for missing data,their impact on quantitative research has been a great concern to methodologists.This topic has been the perennial topic in almost all facets of clinical trial design, conduct and analysis.An examination of articles published for the past year reveals that studies have incorporated design elements and suggestions proposed by the NRC report into consideration however, there has been no official guideline from FDA regarding the missing data handling.

The two reports on handling of missing data endorsed by regulatory agencies are:

The prevention and treatment of missing data in clinical trials

• FDA-sponsored report by the National Research Council, published by the National Academy of Sciences (hereafter "FDA report")

Guideline on missing data in confirmatory trials

• European Medicines Agency (EMA), 2 July 2010

Other guidance that covers elements of handling missing data

Guidance for Industry and FDA Staff –"Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data"

• Sponsored by the U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER) , May 2013 Drug Safety.

CONCLUSION

The content, structure, strengths and limitations of the article were analyzed and evaluated. The article has provided a synopsis on the NRC's comprehensive report and serves as the basis for the recommendations provided to FDA for development of guidance for clinical trials on appropriate study designs and follow-up methods to reduce missing data and appropriate statistical methods to address missing data for analysis of results. The article gave great insight into the future of prevention and treatment of missing data in the clinical trials and has scientific merits.

As stated earlier, there has been no official guideline from FDA regarding the missing data handling. It would be helpful for the scientific and clinical community if there was a guidance directed firstly to prevent missing data through changes in study design and subject follow-up

methods, and second, to use appropriate statistical methods to deal with missing data in clinical trials.

REFERENCE

1. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM243537.pdf, viewed 15October, 2013

2. http://www.nejm.org/doi/full/10.1056/NEJMc1213388, viewed 19October, 2013

3. James, D., Dziura, Lori, A., Post, Qing, Zhao, Zhixuan, Fu, and Peter, Peduzzi. Strategies for Dealing with Missing Data in Clinical Trials: From Design to Analysis

4. Little, R. J., D',Agostino, R., Cohen, M. L., Dickersin, K., Emerson, S. S., Farrar, J.T. et al. The prevention and treatment of missing data in clinical trials. *N Engl J Med, 367(14):1355–1360*. [PMC free article][PubMed]

5. Liu, G., Gould, A. L. (2002). Comparison of alternative strategies for analysis of longitudinal trials with dropouts. *J Biopharm Stat, 12(2):207–226. [PubMed]*.

6. NAS. The Prevention and Treatment of Missing Data in Clinical Trials. The National Academies Press; 2010.

7. O'Neill, R. T., Temple, R (2012). The prevention and treatment of missing data in clinical trials: an FDA perspective on the importance of dealing with it. *ClinPharmacolTher, 91(3), 550–554. [PubMed]*.

8. Silvia, P. J., Kwapil, T. R., Eddington, K. M., & Brown, L. H. (2013). Missed beeps and missing data: Dispositional and situational predictors of non-response in experience sampling research. Social Science Computer Review. *Doi:10.1177/0894439313479902*.

9. Scharfstein, D. O., Hogan, J., Herman, A. (2012). On the prevention and analysis of missing data in randomized clinical trials: the state of the art. *J Bone Joint Surg Am, 94(Suppl 1),80–84. [PMC free article][PubMed]*.

10. Scharfstein, S., Neaton, J., Hogan, J., Little, R., Daniels, M., Roy, J. (2012). Minimal Standards in the Prevention and Handling of Missing Data in Observational and Experimental Patient Centered Outcomes Research [Internet]. Retrieved from: http://www.pcori.org/assets/Minimal-Standards-in-the-Prevention-and-Handling-of-Missing-Data-in-Observational-and-Experimental-Patient-Centered-Outcomes-Research.pdf .

11. Trials PoHMDiC. The Prevention and Treatment of Missing Data in Clinical Trials. National Academy Press; 2010.

TRANSLATIONAL RESEARCH IN CANCER RESEARCH

A Case Study by Manali Khawle, India
(PG Diploma in Hospital Administration, PhD in Clinical Research Student of Texila American University)
Email: mkhawle@gmail.com

ABSTRACT

Translational research is basic research that uses in betterment of the patient health. It includes laboratory based research and research in human subjects, populations and communities. In past decades researcher and theirs researches have clearly focused on importance of the basic research in clinical improvement, human health, etc.

Implementation of translational research as a key component of drug development and clinical research is complex and involves patients in various ways. Thereby it imposes some new ethical, legal, logistical and management constrains. Moreover translational research may require highly sophisticated machines, specific imaging techniques, biochemistry laboratories and imposes other infrastructural prerequisites, some of which should be in the direct vicinity of the clinical trial site. The usefulness of data generated during monitoring of such clinical trials with biologic/mechanistic endpoints is highly dependent on the quality of the assays and the availability of sufficient numbers of samples to conduct valid analyses.

KEYWORDS: Translational Research, Clinical trial, Basic research, cancer, Cancer treatment.

BACKGROUND

Basic scientists play a key role in generating the research discoveries that are translated into applications that improve human health. A number of obstacles—scientific c, institutional, cultural, and policy—limit opportunities for basic scientists to conduct translational science and may slow the pace at which discoveries are translated into clinical applications. Researchers trained in basic science may face inadequate funding, resources, or infrastructure for developing translational research programs; insufficient experience with essential methods and techniques; complex regulatory requirements; or suboptimal recognition or reward for pursuing applied research that may stretch beyond the boundaries of their department and discipline. These challenges can limit professional interest in translating research discoveries and hamper the

enterprise at a time when it should be expanding to capitalize on the explosion of basic science knowledge.

WHAT IS TRANSLATIONAL RESEARCH?

Translation refers to the application of the results of basic biomedical research to the practice of medicine. More specifically, it describes the process of converting discoveries made in the laboratory into clinical interventions that provide a direct benefit to human health. Laboratory discoveries are not typically made in a form ready for adoption by the clinician to treat patients; therefore, research doesn't end with the discovery in the laboratory. In fact, this constitutes the start on the development pathway leading to the creation of a treatment suitable for humans. Translational research includes two areas of translation. One is the process of applying discoveries generated during research in the laboratory, and in preclinical studies, to the development of trials and studies in humans. The second area of translation concerns research aimed at enhancing the adoption of best practices in the community.

The ultimate goal of translational biomedical research is to improve human health—an outcome that benefits all of society. But participating in translational science also has more direct and immediate rewards for individual investigators and the institutions that support their work. Three teams of panellists—paired as basic scientists and senior leaders from the same university—discussed these benefits from their respective vantage points.

To solve many of the biggest challenges in health care, it is absolutely essential that we have basic scientists working along with the clinical the last scientists. And it is essential that we have the public and the private sectors working together from the very outset. If you have a good idea that you want to try to translate…engage those industry partners as soon as possible in the process. All too often, investigators, whether they are in government or in academia, will wait until they have a solidified plan, a strategy, and then go seek funding from the industrial partner. Another equally important mistake is that industry is looked upon as only potential funders and not scientific collaborators. The most value industry can offer is unique expertise.

Translational cancer research aims to bring about rapid improvements in cancer outcomes by addressing much defined clinical problems. These include accelerating the development and testing of new drugs and diagnostics and the provision of tools that can assist in day-to-day clinical decision-making. Translational research's aims to improve clinical management in a relatively short time frame (typically under 5 years), it usually involves clinical studies and direct analysis of human tissue samples (eg. tumour biopsies), with less reliance on animal models or extensive in vitro studies.

TRANSLATIONAL RESEARCH PROCESSES AND PROGRESS

From the 1970s until the early 1990s, the mindset of basic cancer researchers was that cancer is so complex a process that a real solution cannot be found in our lifetimes, and that basic cancer research must remain aloof from the clinic," said John Glaspy, MD, Director of the Jonsson Comprehensive Care Center's Clinical Research Unit at UCLA. "Pursue pure, rigorous and non-goal-encumbered science to advance the understanding for some future generation that might find practical application feasible. This became an ingrained mindset.

The development of translational research in recent years in treatment of disease, clinical trials, and public heath in given graph we can see progress in 10 years. Many researches in cancer issues with basic Research provide critical examples of the tools and practice of cancer treatment. They all focus on clinically meaningful studies that combine patient observations with smart experiments. The researchers hope these studies will facilitate conversion of individual and disease-specific insight into a collective understanding of emerging gene transfer platforms and their subsequent translation to the bedside.

There have been more than 1 million fewer cancer deaths since 1990 and 1991 for men and women, respectively. The number of cancer survivors continues to increase: the latest data show that 13.7 million U.S. survivors were alive on Jan. 1, 2012. In the past year, the U.S. Food and Drug Administration (FDA) approved 11 new drugs to treat a variety of cancers, three new uses for previously approved cancer drugs, and three new imaging technologies. More than 100 years of fundamental discoveries in immunology have now led to the development of anticancer immunotherapies that are yielding remarkable, long-lasting patient responses (American Association for Cancer Research's (AACR) Cancer Progress Report 2013).

RECENT CLINICAL SUCCESSES IN TRANSLATIONAL RESEARCH

Spectacular advancements have been made in basic research to characterize and understand the fundamental molecular underpinnings that drive cancer. These laboratory discoveries have the potential to completely transform our approach to cancer, but only when the basic molecular knowledge can be 'translated' into practical treatments. The molecular analysis of tumours has revealed significant variation in the pathways that drive tumour growth and metastasis. The discovery of genes linked directly to cancer and the molecular pathways these genes influence has allowed scientists to draw a more accurate road map of the nuances of cancer and its progression. Today's drug development efforts use this map to focus on targeted therapies that tackle cancer specific events with greater precision. Since the tide began to turn in the 90s, there's been plenty of evidence of the power of translational research. The development of breast cancer wonder drug trastuzumab (sold as Herceptin) is a famous example – the clinicians involved struggled for years to get funding for their research on the HER-2 gene, but today Herceptin, which inhibits the growth of cancerous cells, is one of the greatest success stories in cancer drug history.

Translational Research Example is IL-12 Therapy for Cancer. It Represents a heterodimer cytokine and promotes expansion and survival of preactivated T cells, CD4 and CD8 cells, tumour infiltrating lymphocytes and NK cells it directly stimulates production of interferon gamma and other cytokines known to produce anti-tumour effects. IL12 injection decreases tumour volume and improves survival. Translational work was possible due to strong ties with the pharmaceutical industry which supplied the recombinant IL-12 in pre-clinical studies [(3)].

Angiogenesis it is the process where blood vessels formation is carried out. In normal definition it is a process of development and growth of blood vessels. In this process transition of tumours can to become progressively worse and to potentially result in death. Forty years ago, in 1971 Judah Folkman American medical scientist predicted that tumour growth is dependent on angiogenesis and that inhibiting this process might be a new strategy for cancer therapy (4, 8). This hypothesis formed the foundation of a new field of research that represents an excellent example of how a groundbreaking scientific discovery can be translated to yield benefits for patients. Today, antiangiogenic drugs are used to treat human cancers and retinal vascular diseases.

Herpes gene therapy for cancer with A Phase I/II, Open Label Study (with a sequential dose escalation stage followed by an expansion of a selected dose cohort), to Evaluate the Safety and Anti-Tumor Effects of NV-1020, Administered Repeatedly via Hepatic Artery Infusion Prior to Second-Line Chemotherapy, in Patients with Colorectal Adenocarcinoma Metastatic to Liver [(11)]

Discovery-driven translational research in breast cancer is moving steadily from the study of cell lines to the analysis of clinically relevant samples that, together with the ever increasing number of novel and powerful technologies available within genomics, proteomics and functional genomics, promise to have a major impact on the way breast cancer will be diagnosed, treated and monitored in the future. Here we present a brief report on long-term ongoing strategies at the Danish Centre for Translational Breast Cancer Research to search for markers for early detection and targets for therapeutic intervention, to identify signalling pathways affected in individual tumours, as well as to integrate multiplatform 'omic' data sets collected from tissue samples obtained from individual patients. The ultimate goal of this initiative is to coalesce knowledge-based complementary procedures into a systems biology approach to fight breast cancer.

With hypothesis of wide variety of clinical observations including mammography is less effective for women age 40–49 than it is for women age 50–59, randomized clinical trials and adjuvant chemotherapy is most effective for premenopausal women with positive lymph nodes, and there is a racial disparity in outcome. Research outcome was several possible explanations ranging from mechanical to biological that suggest the relapses avoided in the early years do not show up later. It proved that preventing systemic inflammation post surgery will prevent early relapses. This could be controlled by the surgical anesthesiologist’s choice of analgesic drugs. Also research has identified triple negative breast cancer as the ideal subset with which to test this. This is successful, would be relatively easy to implement in developing as well as developed countries and would be an important translational result.

Another example of Translational control is an important strategy by which eukaryotic cells regulate gene expression. Translation is step in the flow of genetic information, and regulation at this level allows an immediate and rapid response to changes under physiological conditions. Because the processes of mRNA biogenesis, including transcription, splicing, and export to the cytoplasm, are time consuming, the use of pre-existing mRNAs via the control of translation is advantageous in many circumstances. A prime target of translational control is the initiation factor eIF4E, which recognizes the m7GpppN cap structure present at the 5′ end of all nuclear transcribed eukaryotic mRNAs.

Another example of patients with breast cancer patient with BRCA1 and BRAC2 mutations had a benefit of world class research and access to experimental therapies and clinical trial at Stanford which tests best practice with potential treatment standards for the future for breast cancer therapy. The research proved better impact on patient before, during and after diagnosis with breast cancer. Research has showed chance of dogging cancer jumps to 73%, with an 8% chance of getting and surviving breast cancer and only 1 % chance of not surviving.

In North America, prostate cancer has become the most commonly diagnosed cancer in men. It is responsible for 4300 deaths each year in Canada alone (30). The key objective is to equip future researchers with the skills to work on the threshold between discovery and applied research. Whether new discoveries begin at the bedside or the bench, our overall goal is to understand and eventually conquer prostate cancer. The research concentrated on two of the most deadly aspects of prostate cancer. The first is early stage prostate cancer detection using nanotechnology in a non-invasive way. The second is the study of metastasis. Ninety percent of mortalities from prostate cancer are due to the escape of cancer cells from the prostate that spread to distant sites like the bones.

CONCLUSION

Over the last some decades, translational research has become an important aspect of cancer clinical research. This has been fostered by the development of new techniques of investigations of the tumour biology and the emergence of new families of potential anticancer agents. Basic science is the foundation of medical advancement. Investigators with a deep understanding of fundamental biology and the mechanisms of disease are essential for translating laboratory discoveries into new and improved health interventions, diagnostics, and treatments. Additional training, resources, and support would enable basic scientists to move their discoveries forward effectively and efficiently. Although significant strides have been made, more can be done to optimize basic scientists' participation in translational research.

The beauty of this approach is that it often results in getting effective treatments to patients as quickly as possible. It means focusing on the clinic in order to drive what happens in the lab, and vice versa: scientists look at diseases on a molecular level and develop tools for physicians to try in clinical trials, while clinicians make observations about the disease in humans that drive the scientists' efforts.

The research community should expand translational research training opportunities for basic researchers and trainees; facilitate their access to the funding, equipment, infrastructure, and other resources needed for translation; encourage and support collaboration between basic and clinical investigators across research disciplines and sectors; and recognize and reward basic scientists for the contributions that they make to this growing field. Implementing these recommendations will require action by research institutions and funders, scientific publishers, professional societies, and investigators themselves.

REFERENCE

1. Baumann, M., Bentzen, S. M., Doerr, W., Joiner, M. C., Saunders, M., Tannock, (2001). If The Translational Research Chain: Is it delivering the Goods?. *Int J Radiation Oncology Biol Phys, 49 suppl 2, 345-351*.

2. Cheung, K., Ruttenberg, A., Clark, T., Bug, W., Samwald, M., Bodenreider O, et al (2007). Advancing translational research with the Sematic Web. *BMC Bioinformatics , 8 suppl 3, S2*.

3. Darja Pavlin, Maja Cemazar, Gregor Sersa and Natasa Tozon (2012) *IL-12* based gene therapy in veterinary medicine. *Journal of Translational Medicine*, 10,234.

4. Davidoff, F., Batalden, P. (2005). Toward stronger evidence on quality improvement: draft publication guidelines: the beginning of a consensus project. *Qual Saf Health Care, 14(5):319-325*.

5. Domenico Ribatti (2008). Judah Folkman, a pioneer in the study of angiogenesis-Angiogenesis. 2008 March, 11(1), 3–10. Published online 2008 February 5. *Doi: 10.1007/s10456-008-9092-6.*

6. Elina, A., Kiss (2011). Natural Aryl Hydrocarbon Receptor Ligands Control Organogenesis of Intestinal Lymphoid Follicles, American Association for the Advancement of ScienceCenter for Organogenesis*; S*cience. *DOI: 10.1126/science.1214914*.

7. Engaging basic scientists in translational research: identifying opportunities, overcoming obstacle. *Doi:10.1186/1479-5876-10-72.*

8. Family Practice Oncology Network Journal Issue Number 21, fall 2013, BC Cancer Agency, taken from www.fpon.ca.

9. Folkman, J., Hochberg, M. (1983). Self-regulation of growth in three dimensions. *J Exp Med 138, 745–753*.

10. Fontanarosa, P. B, DeAngelis, C. D.- JAMA. (2002). *Basic science and translational research, 287(13),1728.*

11. Gaudette, L. A., Lee, J. (1997). Cancer incidence in Canada, 1969-1993. Ottawa: Health Statistics Division, Statistics Canada. Catalogue 82-566-XPB. Occasional.

12. Geevarghese, S. K., Geller, D. A., de Haan, H. A., Hörer, M., Knoll, A.E., Mescheder A, Nemunaitis, J., Reid, T.R., Sze, D.Y., Tanabe, K.K., Tawfik, H.(2010). Phase I/II study of oncolytic herpes simplex virus NV1020 in patients with extensively pretreated refractory colorectal cancer metastatic to the liver, 21(9),1119-28. Doi: 10.1089/hum.2010.020.

13. Girish Sardana (2008). PROTEOMIC ANALYSIS OF PROSTATE CANCER CELL LINE CONDITIONED MEDIA FOR THE DISCOVERY OF CANDIDATE BIOMARKERS FOR PROSTATE CANCER, University of Toronto.

14. Grasso, C. S., Wu, Y.M., Robinson, D.R., Cao, X., Dhanasekaran, S.M., Khan, A.P., Quist, M.J., Jing X., Lonigro, R.J., Brenner, J.C., Asangani, I.A., Ateeq, B., Chun, S. Y., Siddiqui, J., Sam, L., Anstett M., Mehra, R., Prensner, J.R., Palanisamy, N., Ryslik, G.A., Vandin, F., Raphael, B.J., Kunju, L.P., Rhodes, D.R., Pienta, K.J., Chinnaiyan, A.M., Tomlins, S.A. (2012 Jul 12). University of Michigan North Campus Research - *The mutational landscape of lethal castration-resistant prostate cancer, 487(7406), 239-43. Doi: 10.1038/nature11125*.

15. Jennifer, A., Hobin, Anne, M., Deschamps, Richard, Bockman, (2012). Engaging basic scientists in translational research: identifying opportunities, overcoming obstacles. Journal of Translational Medicine, *0:72. Doi:10.1186/1479-5876-10-72.*

16. Kerner, J.F., Guirguis-Blake, J., Hennessy, K. D., et al. (2005). Translating research into improved outcomes in comprehensive cancer control. *Cancer Causes Control, 16(suppl 1), 27-40*.

17. Kerner, J.F., J., Contin, Educ, (2006). Knowledge translation versus knowledge integration: a "funder's" perspective. 26(1):72-80.

18. Linder, S., Shoshan, M. C. (2006). Is translational research compatible with preclinical publication strategies? *Radiation Oncology; 1:4.*

19. Matthew, Bogyo, Pauline, M., Rudd, (2013). New Technologies and their impact on 'omics' research. *Current Opinion in Chemical Biology 2013, 17:1 – 3.*

20. McGlynn, E.A., Asch, S. M., Adams, J., et al. The quality of health care delivered to adults in the United States.

21. Michael Retsky, Romano Demicheli, William, J.M., Hrushesky, Patrice, Forget, Marc De, Kock, Isaac, Gukas, Rick, A., Rogers, Michael, Baum, Katharine, Pachmann, Jayant, S. Vaidya, (2012).Promising development from translational or perhaps anti-translational research in breast cancer. *Clinical and Translational Medicine* 2012, 1:17.

22. Mitesh, Phale,(2009) . Transalational Research: Looking into the crystal. *Asian Journal of Pharmaceutical and Clinical Research, Vol.2 Issue 4.*

23. Mold, J.W., Peterson, K. A., Ann, Fam, Med, 2005. Primary care practice-based research networks: working at the interface between research and quality improvement, 3(suppl 1):S12-S20.

24. Robert Hardie,(2002). Translational Prostate Cancer Research Group , London Health Sciences Centre (LHSC).

25. National Institutes of Health , Breast Cancer - MedlinePlus Health Information.

26. National Institutes of Health, (2007). Institutional Clinical and Translational Science Award (U54).
27. NIH (2004). NIH Roadmap: Reengineering the Clinical Research Enterprise Regional Translational Research Centers Interim Report.

28. NIH (2009). "NIH Announces New Program to Develop Therapeutics for Rare and Neglected Diseases."

29. Roger Kornberg (*2001*). The eukaryotic gene transcription machinery BIOLOGICAL CHEMISTRY Kornberg. *R. D. 382 (8), 1103-1107.*

30. Science Citation Index Expanded; Journal Citation Reports/Science Edition; Biological Abstracts; BIOSIS Preview, Scopus, Google Scholar.

31. Scott, L., Friedman, Dean, Sheppard, Jeremy, S., Duffield and Shelia Violette, (2013). Therapy for Fibrotic Diseases: Nearing the Starting Line , Sci Transl Med 9 January 2013: 167sr1. [*DOI:10.1126/scitranslmed.3004700*].

32. Stanford Medicine – (2012) Clinical Trials & Translational Research - Online tool helps those with BRCA mutations understand options - http://med.stanford.edu/ism/2012/april/brca-tool-0409.html#sthash.erKXavK6.dpuf).

33. Steven, H., Woolf, M. D., M.P.H. (2008). The Meaning of Translational Research and Why It Matters, National Institutes of Health. *JAMA; January 9/16,—Vol 299, No. 2.*

34. Sung, N. S, Crowley, W.F., Jr, Genel M. (2003). Central challenges facing the national clinical research enterprise. et al. *New English Jouranal Med, JAMA, 348(26),2635-2645.*

35. Translational Prostate Cancer Research Group; Prostate Cancer Clinical Trials, University of Western Ontario Division of Urology.

INFORMED CONSENT PROCESS, THE BANE OF UNETHICAL CLINICAL RESEARCH; A REVIEW

A Case Study by Augustine Onyeaghala, Nigeria
(PG Diploma in Clinical Research, PhD in Clinical Research Student of Texila American University)
Email: vip4162003@yahoo.co.uk

ABSTRACT

Clinical Research is a branch of medical science that experiments new drug, medical device or biological on human subjects prior to approval. For the study to be credible, unbiased and generally applicable, all ICH-GCP regulations, other international and local regulations governing ethical clinical research studies should strictly be adhered to. The current regulations for clinical research are based on a combination of ethical thoughts and history. Ethics is different from law and regulation, both of which mandate a certain way of acting. The United States regulations for the protection of human subjects and other regulatory agencies from different countries have provided minimum baseline with which everyone must comply in operating an institutional review board (IRB), obtaining informed consent from research subjects and conducting research in an ethical manner.

The challenge, especially in a practical environment such as clinical research, is to translate these regulatory documents, provisions and different ethical principles into action. In clinical research, the consent of the research participants should be received before they are enrolled for trial. Many years after the document governing ethical principles of clinical research was developed and addressing three major areas: respect for persons, beneficence and justice, abuse of informed consent process has been a major ethical problem in most clinical research conducted across the globe and especially those conducted in Africa.

Is informed consent process well administered? Do these patients have a good comprehension of the entire research process? Is informed consent a mere signing of a paper to participate in a trial, or a continuous process?. Is there a better way of administering informed consent to achieve a better research outcome that will benefit all? This review shall focus on recalling history of abuses of informed consent process and ways to correct the unethical practice shall be discussed.

Key words: Informed Consent, Ethics, Regulations, Clinical Research

INTRODUCTION

The emergence of new infections and the constant changing nature in the genetic components of organisms that elicit infections and disease processes have lead pharmaceutical companies to develop new molecules /drugs that will treat these diseases. The concept of evidenced based medicine, using statistics and testing has prevailed in the West since the end of 19th century (Rothman ,1991). The first formal statement of ethics was the Nuremberg code adopted after the trials of Nazi doctors in 1947 (Mitscherlich and Mielke, 1992) . Before any new medicine is approved and marketed, it should go through formal and rigorous clinical trial. The testing of these drugs are usually performed using human subjects and regulations have stipulated that informed consent should be sought prior to trial. Many scientific atrocities carried out by Scientists in the past were responsible for the development of ethical regulations in research. In 1955, an antiseptic, Stalinon, killed 102 patients in France. Thalidomide was responsible for killing 12,000 feotal abnormalities between 1957 and 1962. A powder, Morhange poisoned 145 infants and killed 36 in 1972 during trial (Shuster, 1997).

In all of these studies, the human subjects used for the studies were neither informed nor aware of the risks associated with the study. Scandals such as these led to the introduction of stringent regulations in clinical research all with a view to protecting the research subjects.

ETHICAL PRINCIPLES OF CLINICAL RESEARCH

Ethical principles guiding clinical research have emanated from different regulations, reports and codes. These are:

The Nuremberg Code (1947)

The modern history of human subject protection began with the discovery of the atrocities committed by Nazi physicians (Rothman ,1991; Mitscherlich and Mielke, 1992). For example, such atrocities included twin experiments, where one twin was exposed to a pathogen and then autopsied to determine the natural progression of the disease. The other uninfected “control” twin was then “sacrificed” to see what the differences were. It may constitute a very interesting comparison from a scientific perspective, but such an experiment was wholly unethical and inhumane. When these atrocities were brought to the public court, the judges at the trial had no basis in law by which to prosecute the Nazi physicians. They developed 10 principles for this purpose, and these principles formed the basis of what came to be known as the Nuremberg Code for research involving human subjects. Few highlights of the Nuremberg Code include:

- Voluntary consent is essential. This requirement is at the heart of what the Nazis did wrong. They did not ask any of the people who were subject to their experiments if they wanted to participate.

- Research risks must be minimized and relative to the anticipated benefits of the research.

- The research must benefit society. It is unethical to needlessly endanger the well being of human volunteers if other methods of investigation exist. Poorly designed human subject research is unethical from its inception. Poorly designed research process, results in poor research outcome with possibility to endanger subjects' life.

- Research must be based on pre-clinical studies in animals and knowledge of the condition under study. Many of the Nazi experiments were performed just because the physicians found them interesting.

- Subjects have the right to end their participation in research. Unfortunately, the Nuremberg Code did not have much impact in the United States outside of the scholarly community. The reasons were simple. These then were mere codes and not legislation or laws.

The Belmont Report (1979)

This was produced secondary to the Tuskegee Syphilis study of 1932-1972. The study was to last for 6 months but due to the fact that the investigators were getting "good data", it continued for 40 years. To worsen the situation, the patients were denied treatment even when one was available (David, 2004)

The Belmont Report articulated three core ethical principles:

• **Respect for persons:** This principle concerns the ability of a person to direct his/her own actions. The requirement to obtain informed consent from prospective subjects is the practical translation of this ethical principle. Capacity to consent is also important. You must ensure that the person you are asking to undergo a clinical trial has the capacity to freely authorize his/her participation.

• **Beneficence:** This principle requires a balance between minimizing harms by good study design and maximizing any benefits that might accrue to study participants.

• **Justice:** This principle asks us to take a broader view of the research. There should be an equitable distribution of benefits and burdens, with equitable subject selection. Sometimes implementing this principle can be daunting due to entrenched social inequalities and disparities that exist in our country and in the world.

DECLARATION OF HELSINKI, (1964, AMENDED)

Chronological Revision of the Declaration of Helsinki (DoH)

Year	Month	City	Sections Revised	Revisions Made
1975	October	Tokyo, Japan	3rd, 4th and 5th paragraph 6th and 7th Paragraph Others Section 1.2, 1.5, 1.8, 1.9-1.11,1.12,11.2, 11.3,11.4,11.5	Nature and purpose of medical research Respect for environment and for animals used in research Review of research protocol by EC/IRB, interest of human subject to prevail over science, adherence to accuracy in publishing, enhanced requirement for informed consent, protocol to declare the adherence to DoH principles, best current therapy should be used, Assurance of access to best proven methods, patient's refusal not to affect doctor-patient relationship and when not to consider obtaining informed consent.
1983	October	Venice, Italy	Introduction, section 1.11,	Doctor changed to Physician Consent from minor to be obtained
1989	September	Hong Kong	Section 1.2	Specially appointed committee independent of the investigator and sponsor to review study protocol.
1996	October	Somerset West, South Africa	Section 11.3	The best available treatment should be given to study subjects or control group. Use of placebo even in the availability of proven standard treatment.

2000	October	Edinburgh, Scotland	Paragraph 8, 13, 16,21, 22,25,26,31,and 32.	Special consideration on research using vulnerable group, Ethics committee should monitor research and disclose all CoI, all studies should be publicly available, maintenance of confidentiality of subjects, provisions for obtaining consent other than in writing, consent changed to assent with research involving minors, provision where consent from subjects is not possible, disclose to subjects which aspect of care relates o research and use of all unproven treatment should be made available for research and results recorded and published accordingly.
2002**	October	Washington, DC, USA	Note of clarification added : section 29 Paragraph 30	"a placebo-controlled trial may be ethically acceptable, even if proven therapy is available" Post trial care of participants: Study participants should have access to proven therapies emanating from the study.
2004**	October	Tokyo, Japan	Same as above.	Same as above.
2008	October	Seoul, Republic of Korea	Paragrah 19, Paragraph 30	Listing of clinical trial in publicly accessible database, Publication of clinical research finding including 'Negative' result
2013	October	Fortaleza, Brazil	Pragraph 15, paragraph 20, & other minor changes	Increased protection for vulnerable groups, compensation for subjects harmed as a result of participating in the research, expanded requirements for post-study arrangements, use of placebo, scientific justification for

				the research.

Source: Robert et al (2004), Alexander (2013)

** Just note of clarifications made on the document.

ICH-GCP Regulation: (1996)

COUNCIL FOR INTERNATIONAL ORGANIZATIONS OF MEDICAL SCIENCES (CIOMS) RESEARCH GUIDELINES, (2002). *All regulations stipulated adherence to informed consent Process.*

What is Informed Consent?

Informed Consent is the process by which a person freely confirms their willingness to participate in clinical research after having been informed of all parts of the study that are relevant to the individual's decision to participate. (ICH-GCP, 1996).

What Constitutes Informed Consent?

- Competence/literacy level of the subject
- Disclosure of all information to the subject
- Understanding or comprehension of what has been thoroughly explained.
- Voluntariness of the decision

*What are the Elements of Informed Consent***:**

The Federal regulations require that 8 elements be included in each informed consent form. These are:

- Purpose and duration of participation
- Risks
- Alternatives
- Benefits
- Confidentiality of records
- Compensation for injuries
- Person to contact for answers to questions
- Voluntariness and right to withdraw

Abuse of Informed Consent

Prior to the enactment of ethical regulations governing clinical research, abuse of informed consent was a major problem. Many years after different regulations have been adopted all with a view to improving the ethical practices in clinical research and improving patients' safety and

right to full information in every research process, the regulations have not yielded the desired results. Abuse of informed consent has been a major problem in major trials conducted in Africa, Europe, America and Asia. Most clinical research studies have reported abuse of IC . The under mentioned case studies give some examples

CASE STUDIES

- **Gene Therapy :A case study with Jesse Gelsinger (**Stolberg **,1999)** : He was 18 years old. He suffered from an X-linked genetic disease. He was deficient of ornithine transcarbamylase. This enzyme is very important and critical for the conversion of ammonia, a poisonous gas in the body to urea, a deaminated product from ammonia, a reaction that takes place in the liver. The disorder is fatal in children due to the resulting metabolic acidosis secondary to the accumulation of NH_3. In Jesse's case, he did not inherit the disease from his parents, but was caused as a resultant of a spontaneous mutation of his gene which occurred after conception. His case was therefore not too fatal, but he was unable to metabolise certain foods containing protein and ammonia. On 13 September, 1999, Jesse joined a clinical trial for gene therapy run by the University of Pennsylvania. Jesse was injected with the deficient gene using a viral vector. He died during the process from injuries resulting from the trial, probably as a result of multiple organ failure. Investigations conducted showed that the gene therapy produced toxicities in human subjects used for the trial which the investigators did not disclose, but rather than terminate the study, the investigators continued with the trial .It was also discovered that the informed consent process was poorly conducted and risks associated with the trial was not properly disclosed. Jesse has high plasma ammonia and rather than excluded him from the study based on the pre determined selection criteria, he was still included in the trial.

- A research trial was carried out to check the level of malaria in children and according to the protocol, blood was to be collected once a day from each of the participating children in the clinical trial. However, rather than adhere to this protocol, the researchers went on and collected blood samples four times a day from each of the participating children. Participants were not informed of this and IRB saddled with the responsibilities to protect the subjects was also unable to detect and correct this unethical practice

- In a clinical research study that investigated the relationship between diabetes and sickle cell disease, a random check of the research process showed that: Patients were told to swallow a glucose solution and remain seated and immobile for 5 hours and blood samples were collected at timed interval over the 5hour period. Patients never knew they were being used for a research. Their consent was not sought. They were only promised a paltry sum of 3.0 USD which was neither disclosed, reviewed nor approved by the IRB.

RECALL OF CLINICAL RESEARCH WITH ABUSED INFORMED CONSENT PROCESS:

In 2001, a clinical trial was conducted at a site in US on a drug, hexamethonium. This drug was previously used for the treatment of hypertension, but due to its inefficiency it was deregistered by the FDA and subsequently withdrawn from the circulation. Rather than discard the drug, the sponsors began to look at the other medical benefits of the drug on healthy volunteers using clinical trial. The drug was administered by inhalation to the healthy volunteers including Ellen Roche, a 24 year old employee of a company who died few days after the inhalation. Investigations into her dead were navigated to defective informed consent process. It was found that the informed consent document was deficient in many ways. Investigations showed that the side effects of the drug were not fully documented in the informed document. The section on risks stated that hexamethonium may reduce blood pressure and may make one dizzy especially when one stands up. The major cause of death which was pulmonary toxicity was neither mentioned in the document nor disclosed to the patient (Steinbrook,2003)

In 2003, a clinical trial, Letrozole trial was conducted in India. For any clinical trial to be approved in India, it should receive the approval of the Drugs Controller General, India (DCGI), Hospital Ethics Committees and informed consent of participating subjects. Regulations also stipulated that trials should be done in recognized institutes with adequate research facilities and compensation should be given for any mishap occurred due to the trial. In this trial, more than 400 women who were unable to conceive were enrolled for a trial without their knowledge/consent. The trial was to check the ability of Letrozole to induce fertility under the impression of an expensive fertility-inducing drug. This drug patented by Novartis is a breast cancer drug and is not approved for any other use in any country Gynaecologists in their private clinics termed as 'institutes' with no standard research facility did most of the trials. Though the sponsors and physicians that conducted the trial knew they violated the set standards, yet nothing was done to remedy the injustice and violations on patient's right and safety.(Indrajit Basu , 2004; Ketan, 2005)

Prevention of Mother to Child Transmission (PMTCT) trials was conducted in Uganda from 1997-2003 using Nevirapine (Viramune) . Reports emanating from the study showed that not only were the patients improperly informed about the study, their consent was neither sought nor received. To worsen the trial and the conditions of the patients, wrong doses of the experimental drug were administered. Records regarding the trial were poorly kept; none of the adverse events and the fourteen deaths occurred were reported. Serious Adverse Events (SAE) procedures were not followed, and Boehringer Ingelheim (BI), the sponsor of the trial pressured US National Institutes of Health (NIH) to destroy the earlier research records to avoid the audits by US Food and Drug Administration (FDA). In 2004, FDA issued warnings about the drug's side effects and the usage on certain patients was stopped (Nancy , 2007).

In Nigeria in 1996, the drug giant Pfizer, conducted a clinical trial using Trovan, a drug developed for the treatment of cerebral meningitis. Many innocent children were given the drug and it resulted in lots of death and deformations. The informed consent was neither administered

nor the consent sought from the subjects. The risks associated with the drug were not also disclosed. IRB was not properly constituted nor did it give a formal approval of the trial protocol.(Onyeaghala, 2008) .

SIGNS OF DEFECTIVE INFORMED CONSENT

- Poor understanding of research process by participants
- Defective informed consent process and documentation
- Lack of informed consent
- Withholding information about risks
- Placing patients in a coercive situation
- Exploitation of a vulnerable group of subjects
- Abuse of human Right
- Financial inducement/abuse
- Deviations /violations of protocol

WHY DOES IT OCCUR?

While regulatory agencies in the West and other developed countries are trying to reduce abuse of ICP in clinical research, a lot of factors make it to thrive in most parts of developing countries. These are:

- Poverty
- Weak regulatory environment
- Lack of oversight function of IRB/IEC
- Illiteracy
- Desire to get 'POSITIVE' findings from research and NOT 'NEGATIVE' findings
- Do – Not –question –me attitude of some physicians (common in some African countries)
- Inability to separate medical care from research (either way, IC is required)
- Research Fraud
- Desire to Publish

CONSEQUENCES OF POOR ICP

- Abuse of human right
- Placing participants on a greater risk
- Development of unethical drug
- Numerous Recalls of products already approved
- Legal issues – tort (civil wrong doing) or criminal law (lack of informed consent-assault & battery)
- Denial of publications from such studies

CAN INFORMED CONSENT PROCESS BE IMPROVED?

- Physicians /PI should NOT administer informed consent – Conflict of interest and unnecessary coercion might be inevitable
- External ethical review of the research process other than institution's review should be sought
- Increased oversight functions of ERC and SMB should be enhanced
- Consider differences in culture (cultural component of IC)
- Use simple English and Limit number of pages to smaller volume
- Translate into subjects local language.
- Sponsors should insist on GCP compliant clinical research from all regions of the world
- Frequent audit of clinical research sites, procedures and processes.
- Quality assurance of process
- Use of multi-media interaction for illiterate group should be considered

CONCLUSION

Regulations may be made for every process, but it is within the purview of every Scientist to do that which is right. The decision to do what is right is a major part of human existence. No matter what regulations exist, when they are not implemented, it all becomes a piece of paper. Ethics have come a long way in research and to improve and advance scientific discoveries, increase translational research and medicine, the use of human subjects at various phases of the translational study becomes inevitable. All efforts should therefore be made to protect the subjects who have volunteered to improve the health of others.

REFERENCES

1) Alexander Gaffney, (2013). Revised Declaration of Helsinki Published for Comment, Earning Scathing Reviews.Regulatory Focus News, October, 2013. Retrieved from www.raps.org/focus.

2) David Perlman, (2004). Ethics in Clinical Research A History of Human Subject Protections and Practical Implementation of Ethical Standards. *Society of Clinical Research Journal, May, Pp 37-41*.

3) Indrajit Basuaddd, (2004). India's clinical trials and tribulations. *South Asia in Asia Times, July, 23.*

4) Ketan, D. (2005). The ethics of Clinical Trial in India: An Indian perspective. *Journal of Clinical Research Best Practice Vol 1, No.12*

5) Mitscherlich, A.., Mielke, F. (1992). Epilogue: Sever Were Hanged. In: *The Nazi Doctors and The Nuremberg Code - Human Rights in Human Experimentation*. Edited by Annas GJ, Rodin MA. New York: *Oxford University Press; pp: 105-107*.

6) Nancy, E. K. et al (2007): The structure and function of Research Ethics Committees in Africa: A Case Study. Retrieved from www.plosmedicine.org.

7) Onyeaghala, A..A.,(2008). Pharmaceutical companies, clinical trial in Africa and Good Clinical Practice. Retrieved from www.ibpassociation.org/IBPA_articles/april2008.

8) Rothman, D.J. (1991). Strangers At The Bedside: A History of How Law And Bioethics Transformed Medical Decision Making.: Basic Books; New York ,USA, ISBN : 0-465-08210-6 .

9) Robert, V., Carlson, Kenneth, M., Boyd and David Webb (2004). The revision of the Declaration of Helsinki: past, present and the future. *British Journal of Clinical Pharmacology, 57:6 PP 695-713*.

10) Shuster, E. (1997) Fifty Years later: The Significance Of The Nuremberg Code. *N Engl J Med , 337, 1436-1440.*

11) Steinbrook,(2003). Trial design and patient safety-the debate continues. *New England Journal of Medicine. 349:629-630.*

12) Stolberg, S. G. (1999): The biotech death of Jesse Gelsinger. New York Times Magazine, Novenmber,28.

LIFE (LOSARTAN INTERVENTION FOR END POINT REDUCTION) STUDIES IN HYPERTENSIVE PATIENTS IN REDUCING VARIOUS CV MORBIDITIES AND MORTALITIES INCLUDING STROKE COMPARED ATENOLOL

A Case Study by Manan K Trivedi, India
(Master of Science in Clinical Research, PhD in Clinical Research Student of Texila American University)
Email: mananmatrix@gmail.com

BACKGROUND

Stroke is the second leading cause of cardiovascular morbidity and mortality worldwide with long term disability in developed countries. Various risk factors lead to progression of stroke, they include hypertension, atrial fibrillation, new onset of diabetes, isolated systolic hypertension(ISH) & left ventricular hypertrophy. Among these risk factors, Hypertension is considered as major risk factor for myocardial infarction previously but now-a-days it is consider as the greatest risk factor for the stroke. Various antihypertensive agents which either as mono therapy or in combinations are use to reduce above cardiovascular (CV) morbidities and mortalities including different stroke outcomes.

Recently losartan, AT-2(angiotensin-2) receptor antagonist which is acting on renin angiotensin system (RAS) is considered as first line agent to reduce different CV morbidities and mortalities compared to other conventional B-blockers and Thiazide diuretic combinations. Various "LIFE (losartan intervention for end point reduction) studies" were conducted in hypertensive patients which show better efficacy profile of losartan in reducing various CV morbidities and mortalities including stroke compared to atenolol.

KEYWORDS : - Stroke, Losartan, Renin angiotensin system, Atenolol

INTRODUCTION OF LIFE STUDIES

LIFE studies were started in 1990. It analyzed difference between Angiotensin receptor blocker (losartan) and B-blocker (atenolol) in reducing risk of various cardiovascular morbidities and mortalities like stroke, myocardial infarction, sudden cardiac death, atrial fibrillation and new onset of diabetes as primary composite endpoint (CEP). Secondary composite endpoint of this

studies include up to what extent benefits of losartan can be expanded beyond blood pressure reduction in comparison to atenolol. These LIFE studies were an investigator-initiated, multicentre, double masked, randomized between losartan and atenolol as active control.

Hypertensive patients of age between 55 to 80 having evidence of electrocardiographic left ventricular hypertrophy were included in studies. Patients with previous history of stroke or myocardial infarction (MI) in the last six months; patients using B-blockers and calcium channel blockers and patients having cardiac output of less than 40%; hepatic or renal dysfunction were excluded from the study. Anti platelets, anti coagulant and thiazide diuretics were used as supplementary therapy during study.The mean follow-up time of 4.8 years obtained in study. Analyses of cardiovascular endpoints were based on intention to treat basis which include all randomized patients. Cost hoc regression model was used to assess difference between treatment groups.

OBJECTIVE

To analyze beneficial effects of losartanVs atenolol along with its safety and efficacy profile in different composite endpoints of CV morbidities and mortalities like MI, stroke, ISH (isolated systolic hypertension), Atrial fibrillation (AF) and new onset of diabetes and in comparison to atenolol group in hypertensive patients. Also to assess such beneficial effects in combination therapy of losartan and aspirin on the same outcomes.

LOSARTAN IN STROKE REDUCTION

"This study involved 9193 patients of ages 55 to 80 with hypertension and electrocardiographic evidence of left ventricular hypertrophy. LIFE study by Kizeret al (2004)" shows losartan attained 48% of systolic and diastolic targets compared to 46% of atenolol. In losartan group there was more reduction of 1.1 mmHg in systolic pressure compared to atenolol with almost no difference in diastolic pressure. Assessment of stroke was based on signs and symptoms, diagnostic imaging (MRI), computed tomography, or angiography, spinal fluid analysis, and autopsy. Stroke was classified into various categories which are developed in the "Framingham risk score". There were 541 incident of first strokes noted among all the participants, out of which ischemic atherothrombotic constitutes in 395 patients, ischemic embolic in 81, 55 incidence of hemorrhagic and 10 cases of other events.

Among strokes events 76 patients shows fatality. Atrial fibrillation also occurred in 55% of patients with embolic stroke. During follow-up 72 patients had recurrent stroke events. Statically significant benefits of losartan for stroke reduction were extended to ischemic, atherothrombotic and fatal strokes. But fatal stroke is reduced significantly in losartan group while results of other two strokes were similar in both the groups. There were significantly fewer stroke events in losartan arm on the basis of "Framingham risk score" classification as compared to atenolol. All the participants have achieved follow-up of 86% & 82% in losartan and atenolol group

respectively [1]. It was found that benefit of losartan versus atenolol on ECG regression of left ventricular hypertrophy and blood pressure reduction were independent which is supported by results of other LIFE studies [2-4]. Losartan shows overall 25% reduction in stroke outcomes compared to atenolol [1].

LOSARTAN IN ATRIAL FIBRILLATION WITH SUBSEQUENT STROKE REDUCTION

"LIFE study by wachtell et al (2005)" was conducted to check the benefits of losartan of new AF, as it is considered as major leading factor of stroke in 9193 patients. Results show that losartan attained 33% reduction in new onset ofAF with subsequent stroke as compared to atenolol [2]. The results of these study shows there were 48% reduction of composite endpoint (CEP) of CV morbidities and mortalities with 45% reduced rate of stroke events, supports the review study by Borghi et al (2007).

However, it was also found that randomization within patients with new onset of AF were might not be balanced. New-onset AF occurred in 150 patients randomized to losartan versus 221 to atenolol (6.8 vs. 10.1 per 1,000 person-years; relative risk 0.67, 95% confidence interval, $p < 0.001$) despite similar blood pressure reduction. Patients receiving losartan tended to stay in sinus rhythm longer (1,809 ± 225 vs. 1,709 ± 254 days from baseline, $p = 0.057$) than those receiving atenolol. [2].

LOSARTAN VS ATENOLOL

LIFE study by Ruwaldet al (2012) includes total of 9193 hypertensive patients with LVH aged 45-83 years were followed for a mean of 4.8 years.Patients were divided into two age groups according to the median age of 67 years and the effects of losartan versus atenolol-based antihypertensive treatment on the primary composite endpoint (CEP) consisting of cardiovascular death, nonfatal stroke or nonfatal myocardial infarction were investigated. The beneficial effect of losartan versus atenolol-based treatment was greater in the group of patients older than 67 years [hazard ratio 0.79 (0.69-0.91), P=0.001] compared to the group of patients younger than 67 years [hazard ratio 1.03 (0.82-1.28), P=0809], P=0.045 for interaction. The beneficial effects of losartan versus atenolol-based antihypertensive treatment on pulse pressure, HDL-C, UACR, and Cornell and Sokolow-Lyon voltage were not more pronounced in patients older than 67 years compared to patients younger than 67 years. Study showed a greater beneficial effect of losartan versus atenolol-based antihypertensive treatment in the group of patients older than 67 years compared to the group of patients younger than 67 years. This difference was not explained by a more pronounced effect of losartan-based treatment on any of the cardiovascular risk factors demonstrated to have independent prognostic importance.[5]

SYSTOLIC LEFT VENTRICULAR FUNCTION IN LIFE STUDY

LIFE echocardiography sub-study byBanget al (2013) includes 939 patients had measurable LVM at enrolment. At baseline, 12% had eccentric nondilated, 20% eccentric dilated, 29% concentric nondilated, and 14% concentric dilated LVH, with normal LVM in 25%. Compared with the concentric nondilated LVH group, those with concentric dilated LVH had significantly lower pulse pressure/stroke index and ejection fraction; higher LVM index, stroke volume, cardiac output, left ventricular midwall shortening, left atrial volume and isovolumic relaxation time; and more had segmental wall motion abnormalities (all $P<0.05$). Similar differences existed between patients with eccentric dilated and those with eccentric nondilated LVH (all $P<0.05$).[6]

HEMODYNAMIC MECHANISMS OF LOSARTANVS ATENOLOL

LIFE echocardiography sub-study byGreve*et al*(2012) involved 801 patients with at least two echocardiographic examinations. Atenolol- and losartan-based therapy reduced BP similarly (cumulative difference in mean brachial blood pressure 0.3 mm Hg, $P = 0.65$). After 4 years the cumulative means of SI and heart rate were 1.8 ml/m(2) higher and 5.7 beats/min lower on atenolol-based treatment, respectively (both $P < 0.001$).This kept CI below baseline in atenolol-treated patients, whereas in the losartan group CI was unchanged from baseline throughout the study. [7]

SAFETY AND TOLERABILITY PROFILE OF LOSARTAN

"StudybyGoldberget*et al*(1995)of safety and tolerability of losartan potassium were compared with atenolol, felodipine, angiotensin converting enzyme(ACE) inhibitors" in 2900 hypertensive patients shows Increase in alanine amino transferase was the laboratory adverse event with the highest incidence of 1.9% in patients receiving losartan. But it was found that no laboratory adverse experience were unexpected or of clinical importance. Mainly dizziness was considered as "drug related adverse effect" in losartan (2.4%) compared to placebo (1.3%). Dry cough which were most significantly seen adverse effect in ACE inhibitors (8.8%) than in losartan (3.1%) & placebo group (2.6%).There were no clinically important difference in clinical or laboratory safety profiles in demographic subgroups for age, gender or race. In controlled clinical trials losartan shows excellent tolerability profile than other Antihypertensive agents which were determined by incidence of patient reporting any drug related adverse effect. [4]

COMBINATION THERAPY OF LOSARTAN WITH ASPIRIN

"LIFE study by Fossum *et al* (2005)" shows efficacy profile of losartan with aspirin group compared to losartan with atenolol group in various CV morbidities and mortalities. It was found that stastical significant interaction between losartan and aspirin shows better reduction in primary composite endpoints compared to atenolol with aspirin. Follow up in this studywere 74% and 68% in losartan and atenolol group respectively. There was greater reduction in stroke, MI, cardiovascular death in losartan group receiving aspirin compared to atenlol group with aspirin [5]. The similar blood pressure reduction found in both groups [1-2, 4].

REVIEW OF GIVEN ARTICLE USING ABOVE REFERRED ARTICLES

LIFE studies shows similarity in similar blood pressure reductions and all of these studies also shows beneficial effect of losartan is independent of this blood pressure reductions [1-2, 4]. Besides this study by kizer et al (2004) shows outcomes of stroke results were independent of not only blood pressure but also on AF[1]. But study by wachtell *et al* (2005) shows losartan shows subsequent stroke reduction events by decreasing new onset of AF.These findings might be explained by the limitation of study by Kizer*et al*(2004) which had mentioned there was not properly adjustment of baseline characteristics for stroke and LVH, this might affects the results. In the given study there were also 55% new onset of AF found but study by wachtell et al(2005) shows 33% overall reduction in AF and subsequent stroke, this result can also be explained in similar manner as above [1,2].

Details of protocol and safety profile was given in study by Dahlof*et al* (2002) which was cited in the reference of given article. It shows better patient compliance in terms of safety and tolerability with less hospitalization in losartan group compared to atenolol [1]. These data of losartan's excellent safety and tolerability profile can also be supported by study of Goldberg*et al*(1995) in broader prospective. In controlled clinical trials losartan shows excellent tolerability profile than other Antihypertensive agents which were determined by incidence of patient reporting any drug related adverse effect. Rates of discontinuation of therapy were 2.3% in losartan group and 3.7% in placebo group.

In long term extension studies of 5 out of 16 double blind studies the most frequently occurring drug related clinical adverse experiences were headache (3.6%), dizziness (2.9%), and asthenia/fatigue (2.6%). These reported adverse experiences were consistent with those generally found in patients with essential hypertension. Losartan did not have any important adverse effects on lipids, glucose, or other metabolic parameters. Furthermore, the safety profile remained essentially unchanged during longer periods of treatment with losartan. Mainly dizziness was considered as "drug related adverse effect" in losartan (2.4%) compared to placebo (1.3%). Dry cough which were most significantly seen adverse effect in ACE inhibitors (8.8%)

than in losartan (3.1%) & placebo group (2.6%) [4].So in both studies losartan shows excellent safety and tolerability profile [1, 3].

In similar manner of losartan stroke reductions outcomes described in given study, Combination therapy of losartan with aspirin also shows 32% reductions in CEP compared to atenolol with aspirin. While result of Kizer*et al* (2004) shows only 13% improvements in CEP. So there might be significant interaction exist between losartan and aspirin which shows better efficacy in CEP. So combination therapy of losartan and aspirin shows more beneficial effects in different CEP. But to confirm its result which is either due to by chance or by protective action of aspirin is needs to be justified with future studies [1, 4].

Besides above review of given article few limitations of the LIFE study by Kizer*et al* (2004) also should be addressed with future research. Given studyof stroke reduction shows increase in stroke incidence in black & younger patients which could be might due to salt sensitive behavior of them or through other mechanism on RAS by losartasn. Another controversy exist between losartan AT-2 receptor antagonist and ACE inhibitors, "HOPE(heart outcomes prevention and evaluations)" trial shows greater reduction in stroke compared to LIFE trials. However after that another "ALLHAT (Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack)" trial shows exactly opposite effect i.e. increases in stroke events noted. So controversy between such trials and molecular targets of ACE inhibitors & AT-2 antagonist along with mechanistic explanation of losartan should be justified in future trials.Another limitation is of baseline characteristics of blood pressure and LVH regression, all the results of losartan found were independent of blood pressure reduction and LVH regression. So baseline characteristics should adjust in such a manner that result will not be deviate from the assessment criteria. In future rather than involving participants who are at high risk of cardiovascular events like LVH, AF selecting some baseline hypertensive patients in trials give exact picture of drug in broader view. This way data not only can be generalize to normal people but also gives better prediction of beneficial effect of drugs [1].

In addition to above studies, study by Ruwald*et al* (2012) showed greater beneficial effect of losartan versus atenolol-based antihypertensive treatment in the group of patients older than 67 years compared to the group of patients younger than 67 years. Study by Bang *et al* (2013) identifies dilated sub-groups with reduced left ventricular function among patients currently classified with eccentric or concentric LVH. Contrasting hemodynamics impacted cardiac response to similar reductions in brachial BP on losartan- vs. atenolol-based therapy in study by Greve*et al* (2012). []

CONCLUSION

LIFE studies justified efficacy and safety profile of losartan against atenolol in not only stroke but also other cardiovascular morbidities and mortalities with similar composite endpoint reduction in combination therapy of losartan with aspirin.

REFERENCES

1) Bang, C. N., Gerdts, E., Aurigemma, G. P., Boman, K., Dahlöf, B., Roman, M. J., Køber L., Wachtell, K., Devereux, R. B. (2013). Systolic left ventricular function according to left ventricular concentricity and dilatation in hypertensive patients: the Losartan Intervention For Endpoint reduction in hypertension study. *J Hypertens, 31(10), 2060-8.*

2) Fossum, E., Moan, A., Kjeldsen, S. E., Devereux, R. B., Julius, S., Snapinn, S. M., Edelman, J. M., Faire, U., Fyhrquist, F., Ibsen, H., Kristianson, K., Lederballe-Pedersen ,O., Lindholm, L. H., Nieminen, M. S., Omvik, P., Oparil, S., Wedel, H., Dahlöf, B. (2005). The Effect of Losartan Versus Atenolol on Cardiovascular Morbidity and Mortality in Patients With Hypertension Taking Aspirin The Losartan Intervention for Endpoint Reduction in Hypertension (LIFE)Study. *J Am Coll Cardiol;46:770 –775*.

3) Goldberg, A. I., Dunlay, M. C., and Sweet, C. S. (1995). Safety and Tolerability of Losartan Potassium, an Angiotensin II Receptor Antagonist, Compared With Htdrochlorothirrzide, Atenolol, Felodiprne ER. And Angiotensin-Converting Enzyme Inhibitors for the Treatment of Systemic Hypertension. *Am J Cardiol, 75,793-795.*

(1.) Greve, A. M., Olsen, M. H., Bella, J. N., Lønnebakken M. T., Gerdts, E., Okin P. M., Palmieri V., Boman K., Nieminen M. S., Omvik P., Dahlöf, B., Devereux, R. B., Wachtell, K. (2012). Contrasting hemodynamic mechanisms of losartan- vs. atenolol-based antihypertensive treatment: a LIFE study. *Am J Hypertens, 25(9), 1017-23.*

4) Kizer, J. R., Dahlof, B., Kjeldsen, S. E., Julius, S., Beevers, G., Faire, U., Fyhrquist, F., Ibsen, H., Kristianson, K., Lindholm, H. M., Nieminen, M. S., Omvik, P., Oparil, S., Wedel, H., Wachtell, K., Edelman, J. M., Snapinn, S. M., Harris, K. E., Devereux, R. B.,(2005). Stroke Reduction in Hypertensive Adults With Cardiac Hypertrophy Randomized to Losartan Versus Atenolol The Losartan Intervention For Endpoint Reduction in Hypertension Study. *J. Am. Heart Assoc. Hypertension, 45, 46-52.*

5) Ruwald A. C., Westergaard, B., Sehestedt, T., Kjeldsen, S. E., Lindholm, L. H., Wachtell, K., Devereux, R. B., Ibsen, H., Nieminen, M. S., Dahlöf, B., Olsen, M. H. (2012). Losartan versus atenolol-based antihypertensive treatment reduces cardiovascular events especially well in elderly patients: the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study. *J Hypertens, 30(6), 1252-9.*

6) Wachtell, K., Lehto, M., Gerdts, E., Olsen, M. H., Hornestam, B., Dahlöf, B., Ibsen, H., Julius, S., Kjeldsen, S. E., Lindholm, L. H., Nieminen, M. S., Devereux, R. B.(2005). Angiotensin II receptor blockade reduces new-onset atrial fibrillation and subsequent stroke compared to atenolol: The Losartan Intervention For End point reduction in hypertension (LIFE) study. *J. Am. Coll. Cardiol*, 45, 712-719.

Texila American University

Lot A, Goedverwagting, Sparendaam,
East Coast Demerara, Guyana,
South America.
Telephone: (+592) 2225224 / (+592) 2225225
E-mail: ejournal.assist@tau.edu.gy