RANDOM MUSINGS

Newsletter of the IADVL SIG Clinical Trials

E-Newsletter

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MUSINGS OF THE PRESIDENT

Dr Venkataram Mysore

President, IADVL

Research is and should be part of the job description of a doctor - after all every patient is a new source of information and a new challenge. Each patient is a source of learning something new, and if we document what we practice and what we learn, that is the beginning of research.

Our record in research however, is far from satisfactory,- though IADVL disburses nearly 45 lakhs every year for research, sufficient number of quality projects are not submitted and many submitted projects get rejected as they are not as per protocol. This suggests a lack of awareness of doing research and also lack of inclination.

Much has been done by IADVL to improve this –the Academy through SIG Clinical Trials organized a series of research methodology workshops throughout India in 2014 and 2015. All research projects are assisted by the SIG to bring them to required standards. A number of research projects have already been approved on different relevant areas.We earnestly hope that these will promote the research activities in our association.

I would also like to convey to our members that it is possible to do research in private practice. Several members already do this, and with recent emphasis on clinic software, photography and documentation for medicolegal purposes, enough material is available in all our clinics for research. This is particularly true for aesthetic and surgical practice. And we can hope to be world leaders if we focus on this part of our practice. I therefore urge all our members to think of utilizing the grants and engage in research.

This newsletter, the first of its kind, signifies the excellent work that has been done by the SIG Clinical Trials led by Dr Saumya Panda. My compliements to the editor Dr Feroze Kaliyadan, Dr Saumya Panda and all members of the SIG. I am sure members will find it useful.

MESSAGE FROM SECRETARY GENERAL IADVL

Dr Rashmi Sarkar

Secretary General IADVL

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Dear IADVL Members,

It gives me great pleasure that SIG IADVL Clinical Trials is coming out with an e-newsletter "Random Musings". This is truly innovative. I wish the SIG IADVL Clinical Trials Newsletter under President, Dr. Venkat's initiative and leadership of Dr. Saumya Panda and Dr. Feroze Kaliyadan all success. Happy reading!

MESSAGE FROM CHAIRMAN AND CONVENER IADVL ACADEMY

Dr Col Manas Chatterjee

Chairman, IADVL Academy

Dr Ameet Valia

Convener and Chairman designate,
IADVL Academy

IADVL Special Interest Group on Clinical Trials is coming out with its first newsletter. In several ways, it is path breaking in terms of being a newsletter with a foreword from none other than Professor Hywel Williams, the doyen of Evidence Based Dermatology. In this, almost all members of the SIG have actively participated in providing insightful material, under the watchful tutelage of Dr Saumya Panda, the highly active and potently effective coordinator of the Special Interest Group. All members of the SIG are well known authorities and group has been responsible for taking our Association and its members towards the path of discovery of what research and the conduct of clinical trials should be.

The SIG is involved in several areas such as preparation of two comprehensive research protocols, conduct of two years of country-wide Research Methodology workshops and assistance to the IADVL Academy in the evaluation and improvement of protocols submitted for allotment of research funds available to the Association, in addition to bringing out this intended quarterly newsletter.

The newsletter would be beneficial in the dissemination of useful information on the concepts of basic and clinical research, how to prepare research protocols for the purpose of grants, the ethics of clinical trials and the procedures of conduct of clinical studies. There can be no better source of information on these specialised areas than from material prepared by the best that the country has to offer. In this niche field, a lot of information needs to be disseminated rapidly to ensure that the quality of research performed, especially as it relates to the speciality of Dermatology, improves to match the best of the world. This would ensure that our work gets recognised for its worth and finds it rightful place in the pantheons of global literature at the apex of the evidence pyramid. In this area, the role of this SIG has been pivotal and they are performing the same with extraordinary alacrity.

We wish SIG Clinical Trials the very best in this ambitious venture and hope that our members are benefitted from the correct information that they would help disseminate.

All the best, Jai Hind

Hywel Williams FRCP, DSc, FMedSci

Professor of Dermato-Epidemiology and
Co-Director of the Centre of Evidence-Based Dermatology
at the University of Nottingham

Over the last 20 years, it has been my pleasure to travel the world giving talks that share my enthusiasm for evidence-based dermatology with colleagues. Sometimes the seeds that I scatter fall on stony ground. Those in the audience smile, but they do nothing. Some of the seeds grow too quickly yet they seem to fizzle out when something else "fashionable" comes along. But some seeds grow into sturdy saplings, and this is what I am witnessing with Saumya Panda and his colleagues with this Dermatology Clinical Trials Special Interest Group newsletter. The modestly titled "Random Musings" are neither random nor musings, but they are clear and coherent plans to promote understanding of how best to integrate the best external evidence in the care of patients and how to take some key research questions forward. It is such a joy to witness a new grove of evidence-based dermatology leaders growing in India – soon there will be a forest and one day you will be world leaders.

FROM THE EDITOR'S DESK

Saumya Panda

Co-ordinator,
Dermatology Clinical Trials SIG

We are unveiling 'Random Musings' – the e-newsletter of the Dermatology Clinical Trials Special Interest Group. We consider this to be a landmark event and a small, but significant, step forward in the field of academic dermatology in India. The newsletter has been designed to serve as a platform for the dermatologists in this country who are engaged or are interested in pursuing independent clinical research.

This is another of the activities undertaken by the Dermatology Clinical Trials SIG since it was constituted in 2013 in the Ahmedabad DERMACON. This plan got impetus from the announcement earlier this year by the IADVL Academy for awarding grants to the SIGs for different projects.

The idea of having a newsletter was mooted by Feroze (Kaliyadan) as part of the internal discussion within the SIG. The initial outline for the newsletter consisted of details on recent trials, activities in India and general articles on concepts. Later on, as our content planning was further crystallized, this newsletter was designed to contain details on recent trials including a platform for repository of all independent/non-sponsored clinical trial protocols, periodic news on clinical research activities in India, recent updates of research regulatory issues in India, along with general articles on research methodology concepts.

The newsletter was christened 'Random Musings' on the basis of several suggestions forwarded by Brijesh (Nair). We hope that the newsletter will serve as a sounding board as well as a resource for those willing to undertake independent clinical research, as also facilitate the work of this SIG to serve as a nidus for the development of a network of clinical dermatologists who will pursue independent clinical research.

The problems facing independent clinical research are many. Only very recently, we have woken up and taken notice of the discipline called Evidence-Based Medicine (EBM) and the nuances of modern research methodology. The basics of medical statistics that is an integral part of the same, and imparting the training in which requires interdisciplinary interaction among the faculty, was out of the purview of medical education in our country. The Medical Council of India has started taking baby steps to correct this anomaly only now. This SIG is conducting Research Methodology Workshops in conjunction with the IADVL Academy and various State Branches of the IADVL since last year. In this scenario, having small capsules of practically oriented tips on methodology, including statistical methods, from time to time will go some way in sensitizing the novitiate, it is hoped.

The regulatory policies in clinical research in India have seen a radical change in trajectory. The Institutional Ethics Committees (IECs) had recently become, on the whole, extremely wary about approving trials on not only new interventions, but also novel (hitherto unapproved) uses of previously approved medications, including topical agents. In these situations, even well-designed and ethical studies were being approved by the IECs, by and large, only with a rider that recruitment of cases may only begin with the DCGI approval. This, in many instances, was proving to be an insurmountable bureaucratic bottleneck for independent (non-sponsored) interventional trials as such studies typically suffer from a lack of manpower and financial resources to do the bidding at the CDSCO offices in Delhi, unlike the industry-sponsored clinical trials. As such approvals are never obtained in black and white, as a matter of rule such studies had to be abandoned. A case in point is the topical timolol study in pyogenic granuloma, the protocol of which finds a place here. This study that was primarily designed by Feroze, was developed as a test case by the SIG to find out firsthand the feasibility of practically doing an independent multicentric study in this regulatory atmosphere which is not very conducive. So the choice of a potentially self-limited clinical condition with hardly any potentially serious sequelae, and also a topical medication, the safety parameters of which have

been previously established. Not entirely contrary to our expectations, in three of the sites of this multicentric study, only a conditional approval was obtained from the IECs, predicated upon clearance from DCGI. As a result, we were thinking in terms of limitingthe study to a single centre where unconditional approval from the IEC was obtained. Unless the regulatory environment got more pragmatic, such a situation would have spelt a doom for independent interventional clinical trials in this country.

As this Editorial was being written, the silver lining broke through the clouds in the form of a Circular dated 10.11. 2015 signed by the DCGI. The Circular pertained to permission for academic trials that are non-regulatory in nature, meaning that these trials are not for claiming permission of any new drug for marketing. The Circular specifically told that for these trials the permission of DCGI would not be needed. The onus of informing the DCGI about such trials has been put on the respective IECs. In the event of the DCGI not issuing any objection within 30 days of such information, it has to be presumed that there is no objection, and the trial may proceed. This is a huge step forward by the DCGI, and hopefully, will go a long way in promoting independent academic trials in this country.

Another protocol that has also been produced by our SIG during its tenure is a multicentric study to evaluate the host and pathogen factors in recurrent dermatophytoses. The SIG had been tasked by DrVenkataram Mysore, the President of the IADVL, to design a study to find out how much the current lack of response of dermatophytes to standard treatment is contributed by huge number of topical steroid-antifungal-antibacterial combinations that are freely available, over the counter. Sunil (Dogra) has primarily designed this protocol that is kind of all-encompassing and attempts to find out as many host and pathogen factors as possible behind this vexing problem that extends beyond our shores. It is expected that, once completed, the study will be of enormous relevance to a problem that is currently almost global in nature. Unfortunately, we have to withhold the publication of this protocol in this issue due to logistic reasons.

This newsletter will focus on such areas and issues which are of immediate interest to potential clinical researchers in dermatology in our country. Random Musings, which will be half-yearly to start with, will be the meeting ground of these researchers. Bon voyage!

SAMPLE SIZE – SIMPLE CONCEPTS

Dr Maninder Setia

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The present article is prepared to highlight explanations for some of the common statements we have heard during the course of discussions with students and researchers. A detailed discussion of sampling and sample size estimation will be covered in a series of articles in the Indian Journal of Dermatology next year.

1) One common statement that I have heard is that "Sample Size Depends on the Prevalence of the Disease"

   The quick response to this statement is: Yes and No. It will depend on the prevalence of the disease if 'prevalence' is your outcome. A general understanding should be that Sample size depends on the "outcome of interest". If the outcome of interest is prevalence of a disease, then of course, your sample size depends on the prevalence of this disease. However, this may not be the case in all studies.

   For example, if one is interested in estimating the mean levels of serum cholesterol in psoriasis patients, where will you fit in the prevalence of psoriasis? If you consider the formula for sample size calculation for one mean, some of the

important parameters included are 'standard deviation of the outcome', the 'designed error', or the 'difference between the null value of the mean and the hypothesized value of the mean'. So, the prevalence of psoriasis is not a component of this formula. Thus, knowledge about prevalence of psoriasis is not important in this study.

However, if we wanted to find out the prevalence of psoriasis in our population, then the expected prevalence of psoriasis (from literature) will be included in the formula. Thus, knowledge about prevalence of disease is important if we are interested in estimating the prevalence of the disease in our clinical study.

2) Another common statement I have heard is "Diseases which are common need larger sample sizes and diseases which are rare can be studied with smaller sample sizes"

I would like to highlight again, that such a blanket statement is not always correct. The sample size will depend on the 'outcome of the study'. For example, if a speaker has presented a study on acne, someone from the audience may stand up and comment – "Your sample size is so small. Acne is such a common condition. Don't you think you should have done a larger study?"

The best way to answer this question is: "We agree that acne is a common condition. However, we were not interested in estimating the prevalence of acne in our population. We were interested in estimating the proportion of metabolic syndrome in acne patients. From previous knowledge of literature, we used the given prevalence of metabolic syndrome in acne patients and inserted that proportion in the formula for 'sample size calculation for one proportion'. The other parameters (such as alpha values and Power) were set to acceptable levels (alpha=0.05 and Power=80%). Our sample size was estimated based on these aspects and we feel that our sample size has enough power to detect the outcome of interest".

3) Another common comment that you must have faced: "Your sample size is not adequate – Why don't you include 200 people in your study"

The researcher and the student may get this comment in response to a presentation or a manuscript that has been submitted to a journal.

To begin with, it is very difficult to comment on the adequacy of sample size by eyeballing. One has to formally calculate the sample size to comment on its adequacy. Thus, as a researcher and an author, you may reply to this comment using the sample size calculation formula that you may have used while designing the study.

However, some of the studies are secondary data analysis. For example, you may have analysed clinical data and presented the findings as manuscript. In such a scenario, you are not able to calculate the sample size, because the sample size is determined by the amount of clinical data that is available for analysis. Then, how do we answer the reviewer in this scenario? In this case, rather than calculating the sample size, you have to calculate the power of your study. If the power of the study is 80% or more, it is considered adequate. Thus, you may respond to the reviewer by stating 'According to formal power calculation, we found that the power to detect the outcome of interest is more than 80%; thus, we had adequate power in our study. Hence, the sample size is adequate'.

As stated earlier, the purpose of this discussion was to highlight some of the common concepts (or misconceptions) about sample size. A formal calculation of sample size and power analysis will be presented in a series of articles in the Indian Journal of Dermatology.

A SAMPLE RESEARCH PROTOCOL DEVELOPED BY THE SIG CLINICAL TRIALS TEAM

Authors: Feroze Kaliyadan, Saumya Panda, Maninder Singh Setia, Nilay Kanti Das, Sunil Dogra, Sujay Khandpur, Avijit Hazra, Amrita Sil

Effectiveness and safety of 0.5% Timolol long-acting solution in the treatment of pyogenic granuloma – A multicentric, randomized, double blind, placebo controlled pilot study

Summary of Proposal and Study Rationale

Pyogenic granuloma (lobular capillary hemangioma) is a relatively common benign vascular lesion of the skin and mucosa whose exact cause is unknown. Pyogenic granulomas are misnomers; they are neither infectious nor granulomatous. The lesion usually occurs in children and young adults as a solitary, glistening red papule or nodule that is prone to bleeding and ulceration. Pyogenic granulomas typically evolve rapidly over a period of a few weeks, most often on the head, neck, extremities, and upper trunk. Removal of pyogenic granuloma is indicated to alleviate any bleeding, discomfort, cosmetic distress, and diagnostic uncertainty. The precise mechanism for the development of pyogenic granuloma is unknown. Traumas, hormonal influences, virus, underlying microscopic arteriovenous malformations, the production of angiogenic growth factors, and cytogenetic abnormalities have all been postulated to play a role. Pyogenic granuloma is a benign lesion; however, discomfort and bleeding occasionally may be significant. Pyogenic granuloma lesions on the face can also be a cosmetic concern. [1, 2, 3]

Pyogenic granuloma at present does not have a standard line of care. Different modalities are used in the treatment like – surgical excision[1, 4], curettage, cauterization, cryotherapy[5, 6], CO2 laser[7], Pulsed dye laser[8] and sclerotherapy [9]. The present modalities are associated with a variable incidence of scarring and recurrence. [2]Lasers and sclerotherapy may require multiple sittings. Sclerotherapy has been shown to be associated with minimal scarring. Simple follow up (expectant management) may lead to spontaneous regression taking between 6-18 months, but may be associated with mild scarring. [2]The pathogenesis of pyogenic granuloma has similarities to infantile hemangiomas, where topical beta blockers have emerged as an effective and safe treatment option. The exact mechanism of action of beta blockers on vascular lesions is not known.It is hypothesized that vasoconstriction of the blood vessels within the hemangioma causes the observed softening of infantile hemangiomas. Beta blocker also have effects on vascular growth factor inhibition and promotion of apoptosis, which is how topical timolol is considered to be effective in small infantile hemangiomas.[10] It is proposed that since similar underlying factors may be involved in infantile hemangiomas and pyogenic granulomas, betablockers may be equally effective in both cases. There is data to indicate that gel-forming solution of timolol maleate may be the safest formulation in this regard because it has the least potential of systemic absorption. [11].

Very recently, an uncontrolled trial was carried out in seven children with pyogenic granuloma with β-blockers, of whom six were given topical timolol.[3]

We therefore hypothesize that topical beta-blockers could be effective in the treatment of pyogenic granuloma also. If proven effective, the use of topical beta-blockers could avoid unnecessary surgical intervention and avoid scarring in cases of pyogenic granuloma, especially the pediatric cases. The study will evaluate the safety and effectiveness of topical timolol in the treatment of pyogenic granuloma.

Aims and Objectives

1. To assess and compare the effectiveness of the two treatment modalities
2. To evaluate and compare the safety of the two treatments

Materials and Methods

1. Study area and population

   The study is a multicentric study and will be carried out in 5 medical colleges.

The study subjects to be included are patients clinically diagnosed with pyogenic granuloma and reporting to the out patient department of the Department of Dermatology in the Medical Colleges.

2. Study period

Individual study subjects will be followed up for a period of 6 weeks. The study is to be concluded within a year of its initiation.

3. Sample size

20 patients will be recruited in either treatment arms. The sample size was calculated considering 71% resolution[3] in the treatment arm and 20% resolution in the control arm, 80% power and α as 0.05 and a drop out rate of 10%. The primary effectiveness measure ie, Global assessment scale (5 point Likert scale) was used to calculate the sample size.

4. Sample design

The study population will be randomised into two parallel groups with one group receiving Timolol 0.5% long-acting aqueous solution and the other group receiving placebo solution (dilute glycerine solution). Randomisation will be done by a computer generated random number table into two parallel groups of 20 patients each by balanced unstratified randomization using Winpepi software ETCETERA version 2.32. is a WINPEPI (PEPI-for-Windows) program.

- Allocation concealment will be done by sequentially numbered opaque sealed envelope (SNOSE) technique.
- Blinding will be done at both the patient and the investigator end. Both the medications will be supplied in similar looking containers. The medications will be coded into "A" and "B" by a person not involved in the trial and a weeks' supply of drugs will be made available in the coded box to be dispensed by the investigator. The coding will be revealed only at the end of the study rendering the trial double-blind.

5. Study design

It is an institution based double-blind prospective randomised comparative trial. All patients diagnosed as pyogenic granuloma will be included in the trial as per inclusion and exclusion criteria given below.

Inclusion criteria

i. Clinically diagnosed cases of pyogenic granuloma over skin

ii. Age 2 years to 65 years

iii. Patients consenting/ assenting to participate in the trial and come for follow – up visits

iv. Duration of skin lesion not more than 8 weeks

Exclusion criteria

i. Age less than 2 years or more than 65 years

ii. Mucosal pyogenic granuloma

iii. Pregnant or lactating patients

iv. Systemic comorbidities like cardiac problems (sinus bradycardia, 2nd or 3rd degree AV block, overt cardiac failure, cardiogenic shock), bronchial asthma, COPD, persistent hypoglycemia

v. Patients on systemic beta-blockers, calcium channel blockers, quinidine, which have a significant interaction with topical timolol.

vi. Use of any other treatment modality previously

Each patient will be followed up for 6 weeks. The follow-up timeline is given below:

0 weeks (Baseline visit):

- Patient diagnosed clinically as a case of pyogenic granuloma will be screened. General and physical examination will be conducted.
- Informed consent will be obtained.
- Patient included in the study as per inclusion criteria.
- Patient will be randomised using the random number table.
- The pyogenic granuloma once diagnosed will be measured and photographed. The size of the lesion will be recorded in terms of maximum diameter. The color of the lesions will be recorded. VAS on Likert scale will be employed and the information will be recorded in a standard case record form (CRF).
- Patients will be provided boxes with medicines either code "A" or "B" (according to randomisation) for two weeks, explained about the dosage (topical application of 1 to 2 drops over the lesion twice daily).
- There will be a provision for rescue medication throughout the study. Electrosurgery of the lesion is to be considered as the rescue treatment. If there is any change in the lesion or any complication including but not restricted to increase in size or significant bleeding, the patients will be withdrawn from the trial.
- Baseline investigations will be done – Routine haemogram, random blood sugar, urea, creatinine, liver function tests (LFT).
- The patient will be asked to come for follow-up after two weeks.

2 weeks (1st follow –up):

- The granuloma will be measured and photographs will be obtained. The size of the lesion will be recorded in terms of maximum diameter.
- A global assessment of improvement will be done based on photographic evaluation – into 4 grades Grade 1- > 75% improvement, grade 2 – 50-75% improvement, grade 3- 25-50% improvement and grade 4 - <25% improvement from baseline
- Patient's global assessment regarding the improvement with the treatment (or parent's in the case of patients less than 18 years) will be done on a five point scale – Grade 1 –Excellent, Grade 2- Very good, Grade 3- Good, Grade 4 – Poor, 5- No change
- Physicians's global assessment regarding the improvement with the treatment (or parent's in the case of patients less than 18 years) will be done on a five point scale – Grade 1 – Excellent, Grade 2 - Very good, Grade 3 - Good, Grade 4 – Poor, 5 - No change
- The patient will be inquired about the side effects of the drug using a check list.
- Patient will be provided with the same coded drug for another 14 days.
- The patient will be asked to come for follow-up next week.

4 weeks (2nd follow –up):

- The granuloma will be measured and photographs will be obtained. The size of the lesion will be recorded in terms of maximum diameter.

- A global assessment of improvement will be done based on photographic evaluation – into 4 grades Grade 1- > 75% improvement, grade 2 – 50-75% improvement, grade 3- 25-50% improvement and grade 4 - <25% improvement from baseline
- Patient's global assessment regarding the improvement with the treatment (or parent's in the case of patients less than 18 years) will be done on a five point scale – Grade 1 –Excellent, Grade 2- Very good, Grade 3- Good, Grade 4 – Poor, 5- No change
- Physicians's global assessment regarding the improvement with the treatment (or parent's in the case of patients less than 18 years) will be done on a five point scale – Grade 1 – Excellent, Grade 2 - Very good, Grade 3 - Good, Grade 4 – Poor, 5 - No change
- The patient will be inquired about the side effects of the drug using a check list.
- Patient will be provided with the same coded drug for another 14 days.
- The patient will be asked to come for follow-up next week.

6 weeks (3rd follow - up):

- The granuloma will be measured and photographs will be obtained. The size of the lesion will be recorded in terms of maximum diameter.
- A global assessment of improvement will be done based on photographic evaluation – into 4 grades Grade 1- > 75% improvement, grade 2 – 50-75% improvement, grade 3- 25-50% improvement and grade 4 - <25% improvement from baseline
- Patient's global assessment regarding the improvement with the treatment (or parent's in the case of patients less than 18 years) will be done on a five point scale – Grade 1 –Excellent, Grade 2- Very good, Grade 3- Good, Grade 4 – Poor, 5- No change
- Physicians's global assessment regarding the improvement with the treatment (or parent's in the case of patients less than 18 years) will be done on a five point scale – Grade 1 – Excellent, Grade 2 - Very good, Grade 3 - Good, Grade 4 – Poor, 5 - No change
- The color of the lesions will be recorded. Improvement in color will be expressed subjectively in terms of four grades:1, 2, 3 and 4 where grade 1 is complete improvement and return to skin color, while grade 4 is 'no change', with the lesion remaining red.
- The patient will be inquired about the side effects of the drug using a check list.
- Laboratory investigations will be repeated – Routine haemogram, random blood sugar, urea, creatinine, liver function tests (LFT).

6. **Study Tools and Techniques:**

- Clinical history
- General survey and systemic examination
- Case record form (CRF)
- Adverse effect check list and CDSCO ADR reporting form
- Measuring scale
- Digital camera

7. **Study Parameters**

- Parameters for 1st primary objective (Effectiveness parameters):

1. Change in size of the lesion in millimeters (At each visit – size of the lesion will be recorded in terms of maximum diameter)
2. A global assessment of improvement based on photographic evaluation – into 4 grades

   Grade 1- > 75% improvement, grade 2 – 50-75% improvement, grade 3- 25-50% improvement and grade 4 - <25% improvement
3. The color of the lesions will be recorded at the baseline and the final visit after 6 weeks Improvement in color will be expressed subjectively in terms of four grades:1, 2, 3 and 4 where grade 1 is complete improvement and return to skin color, while grade 4 is 'no change' , with the lesion remaining red.
4. Patient's global assessment regarding the improvement with the treatment (or parent's in the case of patients less than 18 years) will be done on a five point scale –

   Grade 1 – Excellent, Grade 2 - Very good, Grade 3- Good, Grade 4 – Poor, 5- No change
5. Physicians's global assessment regarding the improvement with the treatment (or parent's in the case of patients less than 18 years) will be done on a five point scale –

   Grade 1 – Excellent, Grade 2 - Very good, Grade 3- Good, Grade 4 – Poor, 5- No change

- Parameters for 2ndprimary objective (safety and tolerability parameters):

1. Baseline investigations and investigations at the end of the 4 weeks Routine hemogram – TC, DC, ESR, Hb Random blood sugar, serum urea, creatinine Liver function tests (LFT)
2. Check list for adverse effects

8. **Project schedule including dates of preliminary and final reports:**

Activity	Month											
	1	2	3	4	5	6	7	8	9	10	11	12
Ethics clearance	X											
Patient recruitment and follow up		X	X	X	X	X	X	X	X			
Data analysis										X		
Preparation of final report											X	
Presentation publication												X

9. Plan for Analysis of Data

Numerical data will be summarized as Mean ± Standard deviation (SD), when normally distributed, and also as Median (Interquartile range) when otherwise. Categorical data will be summarized as counts and percentages. Subgroup comparisons will be done with Student's independent sample t test and Mann-Whitney U test for normally distributed and skewed numerical variables, respectively, and by Chi-square test or Fisher's exact test, as appropriate, for categorical variables. For the improvement in color and global assessment within groups, Mann-Whitney test and Friedman's ANOVA will be used. Medcalc version 10.2 [Mariakerke, Belgium: MedCalc Software, 2011] will be used for statistical analysis. A p value < 0.05 will be considered statistically significant.

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THE ETHICS OF CLINICAL RESEARCH- PART 1 – HISTORY AND GENERAL PRINCIPLES

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"Ethics is not definable, is not implementable, because it is not conscious; it involves not only our thinking, but also our feeling" – Valdemar W. Setzer

Medical practice is bound by code of ethics (Greek word Ethos meaning Custom or Character) that is existent since fifth century BC when Greek physician, Hippocrates drafted the code of conduct for physicians, famously known as Hippocratic oath. This oath guides the physician to prescribe only beneficial treatments, according to his abilities and judgment and to refrain from causing harm or hurt to his patients,[1] they will place the interests of their patients above their own interests.[2] The Hippocratic oath has paved the road for the evolution of code of ethics in modern era, which is otherwise known as Good Clinical Practice (GCP). The GCP guidelines are framed by different countries with different names, but the guiding principles remains as do no harm to the patients. These principles of ethical guidelines were found to be breached and morality took the back-seat when need for gain-in-knowledge was felt by some researchers as the need-of-the-hour.

Science vs. Ethics

Medical science is one discipline where the advancement of knowledge is guided by research and there are instances when the zeal for research blurred the moral values. In clinical practice doctors pledge to treat every individual equally, irrespective of their age, disease or disability, creed, ethnic origin, gender, nationality, political affiliation, race, sexual orientation, social standing or any other factor;[3] but when it comes to research there are instances when it is forgotten that a subject for research is also a patient who has put his/her faith in thyself. This is reflected by the statement of a first century physician, Celsius who justified experiments on condemned criminals in Egypt by saying that "It is not cruel to inflict on a few criminals sufferings which may benefit multitudes of innocent people through all centuries".[4] By making this statement, the researcher has taken for granted that they are given the liberty of being reckless because criminals can be sacrificed (like guinea pigs in laboratory).

There is another face of research, where researchers who were selfless and did not hesitate in experimenting on self or family members as subject for research. Edward Jenner (1749-1823) first tested smallpox vaccines on his son and on neighbourhood children and Johann Jorg (1779-1856) swallowed 17 drugs in various doses to record their properties, are only two among many such instances.

Mankind has benefitted from many of such experiments but it must be remembered that benefit and risk are two faces of the same coin. These experiments have contributed a lot to the society and mankind has benefitted; but the risk is assumed by

individuals and benefit is reaped by a population who did not have to bear the risk. The role of ethical guideline is to balance between benefit and risk.

Ethics is pluralistic. Individuals disagree among themselves about what is right and what is wrong, and even when they agree, it can be for different reasons. Despite these differences, the fundamental ethical principles is in tune with the basic human rights proclaimed in the United Nations Universal Declaration of Human Rights, which upholds right to life, to freedom from discrimination, torture and cruelty, inhuman or degrading treatment, to freedom of opinion and expression, to equal access to public services in one's country, and to medical care.[2]

World War II has witnessed the extreme examples of such atrocities where thousands of war prisoners were subjected to inhuman torture in the name of research and benefit of science. This was the time when mankind had learned that the whims and fancies of researchers need to be reined in and that evolved the first guidelines for researchers, the Nuremberg code.[5]

Evolution of Ethics Guidelines

After the World War II, trials were conducted on 23 Nazi doctors and scientists at Nuremberg for the murder of concentration camp inmates who were used as research subjects. Among the 23, 15 were convicted, 7 were condemned to death by hanging, 8 received prison sentences ranging from 10 years to life. The trial brought to light the tortures that were conducted and in 1947 the judgment culminated in the formulation of codes to guide research on humans, famously known as ***Nuremberg code.*** The code highlighted the need for informed consent, rior animal work, qualified scientists, risk justification by anticipated benefits, avoidance of physical and mental suffering, death or disabling injury. [5]

It was found that researchers ignored the code and continued to exploit the faith of the patients. In ***Willowbrook Hepatitis Study*** (1956), children were deliberately infected with mild form of hepatitis, and consent was obtained from parents without informing about the hazards and giving the opportunity of school admission on participation in the study.[6] In 1963, ***Jewish Chronic Disease Study*** was conducted where cancer cells were inoculated in senile subject without proper explanation on risk. Both these studies used vulnerable groups of patients who could not take independent decisions.[7] The situation was highlighted in the article published in 1966 which described 22 such examples of researches where there were controversies regarding the ethics and conducted by reputable researchers and published in major journals (Breecher article).[8]

In view of the emerging situation World Medical Association (WMA) General Assembly (Helsinki, Finland, 1964) developed a set of guidelines to safeguard the rights and wellbeing of subjects participating in clinical research. This is referred to as ***Declaration of Helsinki*** and was revised from time to time, the last amendment in 64th WMA general assembly in Brazil, 2013. The declaration of WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care." The declaration specifically defines that the duty of the physician who is involved in medical research is to promote and safeguard the health, well-being and rights of patients.[9]

In a very shocking turn of events, the ethical atrocities conducted in United States ***(Tuskegee Syphilis Study)*** surfaced in 1972. The study was initiated in 1932 to study the natural course of Syphilis, and even after the development of penicillin, the trial participants were denied the treatment and when it came to light, it had already claimed 28 lives and led to permanent disability in 100 subjects; along with 40 patients infecting their wives resulting in 19 cases of congenital syphilis. Not only denial, the study misinformed the subjects and claimed spinal tap as special treatment.[10] The sheer misconduct led the US government to set up 'International Ethical Guidelines for Biomedical Research Involving Human Subjects' that submitted the report ***(Belmont report)*** in 1979, which stressed on three basic ethical principles: respect for person, beneficence and justice. [11]

In the following years various countries drafted their own guidelines of Good Clinical Practice (GCP) and in India, ***the Indian Council of Medical Research (ICMR)*** first released a policy statement on ethical considerations involved in research on human subjects in 1980. ICMR revised the guidelines in 2000 in the face of controversies and introduced ***'Ethical Guidelines for Biomedical Research on Human Subjects'*** and latest amendments were done in 2006. [12] In India the ethics guidelines are given the legal status by way of ***Schedule Y Drugs and Cosmetics Rules, 1945.*** (rules l22A, l22B, 122D, 122DA, 122DAA and 122E).[13]

With the advent of multi-centric studies involving different countries, having a uniform GCP was a felt-need. For this purpose, ***International Conference on Harmonisation-GCP (ICH-GCP)*** was developed in 1996 in consideration of the current GCPs of the European Union, Japan, and the United States, as well as those of Australia, Canada, the Nordic countries and the World Health Organization (WHO).[14]

Principles of Ethics in research involving Human Subject

Ethics are the moral values of human behaviour and the principles which govern these values. The principles of ethics rest on the four pillars of ***autonomy, beneficence, justice, non-maleficence,***[15] and recently two more pillars are added which includes, ***confidentiality*** and ***honesty***.

Autonomy

Autonomy is the respect for the patient's 'right to self-governance, choice for care and the right to accept or refuse treatment'.[16,17]

The principle of autonomy states that the patient has the right to make his or her own choice as to what procedure he or she aspires to have. Thus, the patient's right to an informed consent must be respected. The patient must be given the right information as what to expect, the risks involved and the alternative options available.

Beneficence

The principle of beneficence requires the practitioner to act in the patient's 'best interest'. It is important for the practitioner to assess the risks versus the benefits of the procedure and maximize benefits, minimize harms. The motivation of the patient for having the procedure and how it will affect quality of life should be gauged by the physician. The physician should be specialized in the procedure and should be able to handle risks and side effects that might occur.

Justice

This principle seeks 'fair treatment'. Exploitation of the patient for the sole purpose of recruitment for the study and completion of research should be refrained. The practitioner should be respectful to the patients' wishes, understand the depth of the problem and educate the patient about the expectation from the procedure.

Non-maleficence

The principle of non-maleficence requires the practitioner to 'do no harm' to the patient. The practitioner should discuss of the possible side effects and complications of the trial procedure before including a person in the trial. At this point, the practitioner may suggest alternative procedures and treatments that may be more beneficial for the patient.

Confidentiality

It is essential to maintain confidentiality of all participating study patients, security of study data, photographs, biological samples, audio-visual records, etc.

Honesty

Investigator should be truthful to the study participants regarding the trial protocol, risk-benefits; and to co-investigators, sponsors, ethics committee and regulatory agencies regarding the adherence to trial protocol and outcome.

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TAKE A TRIAL !!!

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1. The letter T in the acronym 'PICOT' in respect to medical research stands for:

   (a) Target outcome (b) Therapeutic Efficacy (c) Time frame (d) Testing the results

2. PRISMA is a set of guidelines to carry out:

   (a) Randomized Control Trial (b) Cohort Studies (c) Therapeutic Guidelines (d) Meta-analysis (e) Cross over studies

3. Identify the diagram given below used to detect publication bias:

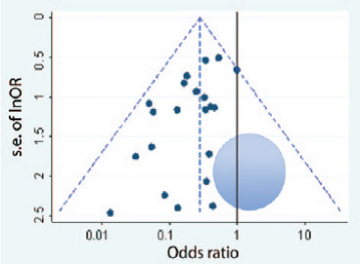
   (a) Forest plot

   (b) Cluster plot

   (c) Standard Error of Odds Ratio plot

   (d) Funnel plot

   (e) Circle plot



4. The summary measure best suited to measure time to event data or survival data (eg – the number of months till melanoma development) is:

   (a) Risk Ratio (b) Hazard Ratio (c) NNT (Numbers needed to treat) (d) absolute risk reduction (e) Odds ratio

5. The random effects model is used in meta-analysis when there is greater inter-study variability. All are random effects models,except:

   (a) Mantel Haenszel (b) Laird (c) DerSimonian (d) Bayes

6. For the purpose of calculation of sample size, the norm is to set statistical power at:

   (a) 50% (b) 70 % (c) 80% (d) 90 % (e) 95%

7. The association between an exposure and an outcome is best studied by:

   (a) Case control study (b) Cohort Study (c) Aggregate study (d) cross sectional study (e) Randomized control trial

8. The main potential pitfall of a case control study is:

   (a) Recall bias (b) Length time bias (c) sampling bias (d) zero time bias (e) confounding bias

9. The nine criteria of Hill (1965) is used to determine

(a) Sampling bias (b) Randomization technique (c) Association and causality relation (d) Confidence interval (e) results influenced by patient drop out

10. Blinding cases and controls regarding study hypothesis reduces chances of:

    (a) Sampling bias (c) Lead time bias (c) information bias (d) Referral bias (e) observer bias

11. Genetic association study design are recommended to follow which one of the following guidelines?

    (a) CONSORT (b) STROBE (c) STREGA (d) QUOROM (e) EQUATOR

12. The only drug which has undergone a randomized control trial for Toxic Epidermal Necrolysis is:

    (a) IVIg (b) Cyclosporine (c) Corticosteroids (d) N Acetyl Cysteine (e) Thalidomide

13. Who is considered as the 'Father of Randomized Control Trials'?

    (a) BA Gilchrest (b) Bradford Hill (c) RS Stern (d) JPA Ioannidis (e) Jonathan Rees

14. The trial design used when investigational agent and the active control are dissimilar in appearance is:

    (a) Analytical study (b) Cluster trial (c) Double blind trial (d) Triple blind trial (e) Double dummy trial

15. Lehrs formula is a quick equation to determine

    (a) P-value (b) Numbers needed to treat (c) Statistical power (d) strength of causality (e) sample size

16. Homogeneity of variances of samples(samples have same variance) can be tested by:

    (a) normal probability plot (b) Kolmogorov –Smirnov test (c) Shapiro –Wilk test (d) Bonferroni adjustment (e) Levene's test

17. Intention To Treat Analysis helps reduce:

    (a) Sampling bias (b) Information bias (c) Recall bias (d) Attrition bias (e) Lead time bias

18. The statistical test used to compare 2 groups of Non parametric Quantitative data (numerical data) is:

    (a) Student's paired t –test (b) Gehan's test (c) Wilcoxon test (d)McNemar's test (e) Kruskal – Wallis test

19. The association between two parametric data variables is confirmed by which statistical test?

    (a) Spearmans coefficient (b) Kendall's π (c) Logistic Regression (d) G test (e)Pearson's r

20. Psoriasis Area Severity Index is an example of _____ variable.

    (a) Nominal (b) Ordinal (c) Continuous (d) discrete (e) Categorical

Answer Key

1 c, 2 d, 3 d, 4 b, 5 a, 6 c, 7 b , 8 a, 9 c, 10 c, 11 c, 12 e, 13 b, 14 e, 15 e, 16 e, 17 d, 18 c, 19 a, 20 c

IADVL RESEARCH METHODOLOGY WORKSHOPS, 2014 & 2015: A REPORT

Saumya Panda

Co-ordinator
Dermatology Clinical Trials SIG

These workshops were proposed by Dr Deepak Parikh, the Immediate Past President of the IADVL in 2014 in a bid to sensitize our members to, what for many, are the new language and methods of research methodology, and the rudiments of biostatistics, so that a new cadre of dermatologists may come up in the near future who are well-versed in the methods of clinical research.

The Co-ordinator, Dermatology Clinical Trials SIG was entrusted to plan and execute this series of workshops as the National Scientific Co-ordinator. The Workshops were organized under the aegis of the IADVL Academy of Dermatology in association with various State Branches of the IADVL. The workshops were possible through a generous grant and logistic support provided by MSD.

In the first year, the workshops were held at Mumbai, Kolkata, Bengaluru and Delhi. This year, these were held at Ahmedabad, Hyderabad, Guwahati and Calicut.

Both the years saw DrManinder Singh Setia as the key faculty, ably assisted by others.

The following table summarizes the attendance and pre- and post-test questionnaire scores at each one of the workshops in the first year:

Venue (date)	No. of delegates	Pre-test score range (mean)	Post-test score range (mean)
TN Medical College, Mumbai (15th& 16th February, 2014)	100	0 – 27 (7.41)	13 – 27 (18.45)
Command Hospital, Kolkata (22nd& 23rd February, 2014)	127	2 – 25 (11.74)	3 – 37 (21.19)
Victoria Hospital, Bengaluru (8th& 9th March, 2014)	160	1 – 26 (8.21)	10 – 29 (19.21)
Maulana Azad Medical College, Delhi (3rd& 4th May, 2014)	26	2 – 18 (9)	11 – 26 (17.82)

In 2015, four research methodology workshops, with an average attendance of more than 100 at each one, were organized in close collaboration with the Gujarat, Telangana, North East and Kerala state branches at Ahmedabad (GMERS Medical College, Sola, June 27 and 28), Hyderabad (Deccan College of Medical Sciences, July 4 and 5), Guwahati(Guwahati Medical College & Hospital, August 8 and 9), Kozhikode (Government Medical College, August 22 and 23). DrSaumya Panda and DrManinder Singh Setia were the key faculty in this series of workshops as well, complemented by Dr Yogesh Marfatia (Ahmedabad), Prof G Venkata Ramana (Hyderabad), Prof Avijit Hazra and Col Manas Chatterjee (Guwahati), and Dr KP Aravindan (Calicut).

COMPOSITION OF DERMATOLOGY CLINICAL TRIAL (2013-15)

Co-ordinator

Dr Saumya Panda, Professor, KPC Medical College, Kolkata

Convener

Dr Nilay Das, Associate Professor, Department of Dermatology, Medical College, Kolkata

Members

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Dr Chitra Nayak, Professor & Head, BYL Nair Ch Hospital & TN Medical College

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Dr Feroze Kaliyadan, Assistant Professor, Faculty of medicine (Dermatology), College of Medicine, King Faisal University, Hofuf, Kingdom of Saudi Arabia

Dr K M Ajith Tharakan, Dept of Dermatology, Malabar Medical College, Calicut, Kerala (2013-14).

International Advisor

Hywel Williams, Professor of Dermato-Epidemiology, Centre of Evidence Based Dermatology, University of Nottingham

National Advisor

Avijit Hazra, Professor, Department of Pharmacology, Institute of Postgraduate Medical Education & Research, Kolkata