RANDOM MUSINGS

Newsletter of the IADVL SIG Clinical Trials

E-Newsletter

Issue 02, December 2017

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Welcome to the second edition of *Random musings*, the newsletter of the SIG Clinical trials. This issue of the newsletter offers the readers an interesting potpourri of articles related to clinical trials and research. We have tried to address common issues in a manner that we hope is simple and informative, but above all practically useful. A special thanks to all the authors for their valuable contributions.

Dr Sanjay Singh gives an excellent brief summary of general aspects of randomized controlled trials. Nicole Stefanko and Dr Robert Dellavalle give an interesting overview of bias associated with clinical trials. Publication is usually the final step for all good clinical trials and Dr Dipankar De takes the readers through the dynamics of publication. We all complain that research requires too much paperwork…more so for clinical trials. Dr Amrita Sil and Dr Nilay Kanti Das will be updating you with the latest in terms of Government regulations related to clinical trials in India. Last, but not the least, Dr Brijesh Nair will keep you quizzing antennae alert with the second edition of the Random musings quiz.

I hope you enjoy this second issue and do let us know if there are any topics you would like to see covered in the future. For any suggestions please feel free to drop in a note to ferozkal@hotmail.com or drdasnilay@gmail.com

Keep musing!

Feroze and Nilay

Understanding the Publication Dynamics

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Researchers in India often rue that their articles are not accepted in a journal and this is also often accompanied by the lament that such rejection decisions are biased. It is imperative to have a clearer understanding of the publication industry from the perspective of a researcher/author. If there is an industry, there should be a market to sell the product. Here we will discuss the "publishing industry" and the "publication market."

In the era of consumerism, it is probably easier to understand these concepts in commercial terms. Imagine that you want to buy a new mobile phone. What are the parameters based on which you will finalize your choice? New features, quality, ease of use, brand value, and of course, cost, would probably be important factors. The same concepts can be extrapolated to scientific publication to some extent.

We as researchers do research and it is our responsibility to let others know about the findings of our research. It is an altogether different story if one wants only to pass an examination. Since the product of research need to be marketed, it must pass through quality controls. Members of the editorial board and reviewers for a journal are quality controllers who check on the quality of research. Usually, all the members of the editorial board and the reviewers are experts on the field of research that is being considered. Those who are experts in an area should ideally promote scientific progress and scholarship in their area and encourages publications, if it matches the expected quality standards. Most reputed scientific journals tend to go the extra mile to ensure these minimum quality benchmarks, which can lead to a high number of rejections when manuscripts are submitted to these journals. So, it is not fair to criticize editorial decisions and cry bias without a proper objective analysis.

Anything that is novel sells … at least for some time! If there are several products of a similar type in the market, competition increases and eventually some may not sell. For example, if someone is trying to publish a general study on types of cutaneous fungal infections or a study on the species of dermatophytes causing infections in a specific region of the country, chances of publication in a good journal would be bleak today as compared to a couple of decades earlier. However, if someone does research to unearth the cause of current problems of resistant dermatophytosis, the research has a good chance to be published in a good journal (provided it satisfies other quality criteria—study design, quality of writing, etc.). Whenever a research is planned, try to ensure that there is some novelty in the study. If you are planning a routine research due to paucity of funds, try to identify novel areas that can be explored within the constraints.

Everyone tends to consider their research good and novel. To each their own. However, after a thorough literature search if you find more than

handful of references on the core topic, perhaps you are not undertaking a novel research.

Whatever is novel and of good quality lasts in the market. The role of members of editorial board and the reviewers is to decide on issues like—Is the claim of the study being novel true? Is the study based on a solid research question? Are the findings relevant, accurate and the aspects related to the primary hypothesis properly presented? Are research methodology and statistical analyses justified to address the research question? Are the results likely to be reproducible in a similar study following similar methodology?

The other important thing is whether the research fits into the scope of the journal (shop) and will be liked by the readers of the journal (consumers). As fruits cannot be sold in a stationery shop, the likelihood of molecular research being published in a clinical journal (or vice versa) is low. Another common concern is "I submitted the manuscript as case report but the journal has asked to convert it to letter to editor." This also comes with the market considerations. When someone chooses a hotel online, they look on the rating of the hotels assessed on several parameters. Journals are also rated and then ranked. As everyone wants to improve and appear at the top, journals also try to do the same. Journal rating is presented in the form of various metrics like the journal impact factor. The journal impact factor is a ratio with the numerator being the number of times its articles published in the preceding 2 years have been cited in another article, and the denominator is represented by the number of articles published during the same period. However, the interesting part is that some sections like "letters to the editor," if cited, is counted in the numerator but is not counted as published article in the denominator. Thus, more the number of citable letters to editor, the merrier.

The likelihood of an article to be cited is highest with review articles and original articles. Case reports and letters to editors are generally published if the finding is uncommon, rare, or exceedingly rare depending on the genre of the journal. However, something that occurs rarely will be published rarely and thus similar research will also tend to be cited rarely. Hence, all journals promote publication of original articles and review articles and some journals have stopped or drastically reduced publication of shorter versions of scientific communications such as case reports. For example, discontinuation of publication of case reports in the Journal of the American Academy of Dermatology and focusing on original articles and review articles has perhaps helped it gain significantly on impact factor values. The journal tops the list among dermatology journals as per the latest journal ranking.

Since we have compared a researcher with a manufacturer in an industry, one wonders what is the profit of the manufacturer in comparison to other industry. Not much. Practically, we as the researcher/author do not have any significant gains in financial terms but importantly we do gain "in kind." We in fact may lose in financial terms at times as some good journals charge a fee for article submission. Some journals in the other end of the spectrum charge publication fees!

To sum up, even before you start manufacturing a product, think about its novelty, the cost that will be required to manufacture, whether manufacturing is feasible with available resources, whether process of manufacture is sound enough to sustain the test of the quality controllers, whether it is practically relevant so that it is well accepted by the customers, and whether other manufacturers can get a lead from it. To choose the market where you intend to sell your product is also important. Refrain from selling your product in the market, which is not indexed and the marketing agency tells you that they will sell your product without quality control and by a specified date which is in a week or two. In that case perhaps you are dealing with a predatory market (read predatory journal) which has identified your weakness and trying to capitalize onto it. Since the earliest three parts in research are determining novelty, technical feasibility, and availability of funds, one needs to make thorough search of the market (read literature search) and discuss the issues out with as many seniors as possible. Guide of your thesis will always be there to guide you whenever guidance is required!

Happy researching and publishing!

RCT in a Nutshell

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Although all forms of data have their obvious importance in clinical research, barring exceptional circumstances, randomized controlled trial (RCT) is presently the best available scientific method to measure the efficacy (benefit) and harm arising from a treatment. In this article, the "why" and "how" of different steps of performing an RCT are discussed in a nutshell.

In an RCT, a new treatment (experimental treatment) is compared with another previously known effective treatment (active control) or a placebo. There can be more than two groups of patients receiving different treatments (multiple arms trial), but for the sake of simplicity an RCT with two groups of patients (two arms trial, one receiving the experimental drug and another placebo) is discussed here.

BIAS

RCT aims to avoid bias in assessment of treatment effects. Bias is the tendency of an estimate to deviate in one direction from a true value. Although there are several types of biases, the important ones are selection bias (patients of the two groups are different in baseline characteristics), performance (ascertainment) bias (difference in the care provided), detection bias (difference in how outcomes are determined), attrition bias (difference due to withdrawals), and reporting bias (difference between reported and unreported findings).

RESEARCH QUESTION

An RCT begins with a clearly defined research question. The question is usually expressed as null hypothesis (HO), which states that there is no difference in the efficacy of the two treatments. Alternate hypothesis (HA) is the opposite of HO, and states that the experimental treatment is more effective than the control treatment. In the end of the trial, the null hypothesis is either accepted or rejected.

SETTING AND LOCATION

Mentioning the setting (e.g., type of hospital in which the RCT is conducted) and geographical location provides proper perspective for the readers to decide whether the results may be applicable to their patients.

ETHICS COMMITTEE CLEARANCE

All RCTs have to be approved by appropriate ethics committees.

THE DISEASE

A clear definition of the disease or diagnostic criteria is to be mentioned. It has also to be mentioned how the diagnosis was arrived at. Was psoriasis diagnosed on the basis of clinical features or histopathology was performed? Was tinea diagnosed on the basis of clinical features or KOH microscopy and culture were also performed?

SELECTION CRITERIA

These will consist of inclusion criteria and exclusion criteria. Usually in testing the efficacy of new treatments exclusion criteria, among others, include pregnancy, lactation, children, and the elderly. Selection criteria must be clearly defined and should not be too narrow or restrictive. Too narrow selection criteria adversely affect the generalizability (the extent to which the results of an RCT can be generalized) of the results. Consider an RCT on psoriasis in which only those patients who had Psoriasis Area and Severity Index (PASI) scores between 5 and 10 were selected.

CONSENT

Patients or caregiver has to give informed, witnessed, written consent to be willingly included in the trial. Those patients who refuse to give consent should be provided appropriate treatment as any other patient.

SAMPLE SIZE

How many patients are to be included in the RCT? An ideal RCT will include all patients in the world with the disease of interest, but such an RCT will be logistically impossible to perform. Therefore, a prestudy sample size calculation is done to arrive at the minimum number of patients to be included in each group.

SEVERITY ASSESSMENT OF DISEASE

Clearly defined and validated method of assessing the severity of disease should be used. The method should be as objective as possible.

RANDOMIZATION

Who or what should determine which patient gets included in which group? Only chance should have a say in this matter. Randomization ensures that the known and (many) unknown prognostic variables are balanced between the groups. Thus, randomization prevents selection bias. Random allocation to the groups is usually done with the help of computer software or using online randomization tools.

THE CONTROL

Experimental treatment should preferably be compared with the best available treatment (active control). If an experimental treatment has been compared with placebo and found to be more effective than it, it in effect means that it is better than nothing. When no effective treatment exists for the disease of interest, placebo is an acceptable control.

GOING BLIND

The RCT may be single-blind (patients does not know which treatment he/she is receiving), double-blind (investigator also does not know), or triple-blind (statistician also does not know). To ensure adequate blinding, both treatments should be identical looking and identically packaged so that no visual differentiation is possible and the treatments are now identified only as A and B. Blinding, although admittedly not always possible, prevents performance and detection biases.

TREATMENT ALLOCATION CONCEALMENT

After a patient has been enrolled for the RCT, only then it should be known which treatment (A or B) he or she will receive. Randomization code is thus hidden from the investigators until a particular patient has been enrolled. There are many techniques available to ensure this.

OUTCOME MEASURES

Clinically relevant primary and secondary outcome measures are to be defined before the start of the RCT. Clinical relevance is important, a 75% reduction in severity of psoriasis will be a good outcome measure for an RCT on psoriasis, but what about tinea? Will you or your patient be satisfied with 75% reduction in severity of tinea?

STOPPING GUIDELINES

One does not have to continue with an RCT irrespective of whatever happens during the course of its performance. Stopping guidelines are an advance commitment about what course of action will be taken if something unexpected occurs (examples could be no decrease in severity of psoriasis in 1 month, occurrence of serious adverse events). Trial is also stopped midway if anything serious/life-threatening happens.

ASSESSMENT OF TREATMENT ADHERENCE (COMPLIANCE)

It goes without saying that any treatment is likely to work only when it is taken! Some method of assessing adherence to treatment, such as pill counting, should be employed.

RESULTS: PRETREATMENT CHARACTERISTICS

When mentioning the results, pretreatment characteristics (important patient-related variables which may influence outcome) of the patients of the two groups should be mentioned. The groups should preferably be balanced in this regard.

INTENTION-TO-TREAT VERSUS PER-PROTOCOL ANALYSIS

In intention-to-treat analysis (ITT), all patients who were enrolled are included in final analysis whether or not they completed the treatment. This prevents attrition bias. ITT is the preferred analysis for RCTs. In per-protocol analysis, only those patients who completed the treatment are included in analysis.

THE TWO ERRORS

Type 1 error (α) means incorrect rejection of null hypothesis (i.e. there was no difference between treatments, but the study concluded a difference, "false positive"). This is avoided by calculating the P value. A P value of <0.05 means that the probability of the result being by chance is less than 5%. In contrast, type 2 error (β) is incorrect acceptance of null hypothesis (i.e. there was a difference, but the study failed to find it, "false negative"). Type 2 error is usually taken care of by a good sample size.

REPORTING ALL RESULTS

All results of an RCT should be reported to prevent reporting bias, irrespective of whether they look desirable or not and whether or not they are statistically significant.

Clinical Trials in Dermatology: Ethics and Bias

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When conducting clinical trials in dermatology, it is important to adhere to ethical principles, while at the same time eliminating bias. Two landmark documents—the Declaration of Helsinki and the Belmont Report—have shaped the way that we view the treatment of human subjects in medical research. In 1964, the World Medical Association (WMA) developed the Declaration of Helsinki, "a statement of ethical principles for medical research involving human subjects."[1] As part of this declaration, an emphasis is placed on individual subject rights, including the right to privacy, confidentiality, health, integrity, and dignity.[1] These rights are not to be swept aside for the attainment or generation of future knowledge; the declaration states that it is only appropriate to conduct medical research with human subjects "if the importance of the objective outweighs the risks and burdens to the research subjects."[1] The Declaration of Helsinki also discusses the practice of obtaining informed consent from research participants and states that this consent must be voluntary; study participants shall be free to withdraw consent or refuse to participate at any time and may do so without reprisal.[1] According to the declaration, when studying new interventions, they must be tested against the best proven intervention when possible; if no best proven intervention exists, "the use of placebo, or no intervention, is acceptable."[1]

The Belmont Report was created by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research and published in 1979.[2] The report presents guidelines for research involving human subjects and discusses three basic principles essential to the conduction

of ethical research, including respect for persons, beneficence, and justice.[2] Respect for persons refers to the need to acknowledge the autonomy of individuals while also protecting those individuals who have decreased autonomy.[2] The opinions and decisions of research subjects should be respected, and their actions should not be obstructed "unless they are clearly detrimental to others."[2] To conduct clinical trials with beneficence, researchers should strive to maximize benefits while minimizing potential risks/harms of studies.[2] This entails maximizing benefits to research subjects directly and also maximizing long-term benefits more broadly, such as the enhancement of medical knowledge.[2] The principle of justice refers to a "fairness in distribution" regarding the benefits of research; according to the principle of justice, attempts should be made to treat equals equally.[2] This principle also applies to the selection of study participants.[2] For instance, different groups of people, including people of different races and socioeconomic classes, should not be selected as research participants based on their manipulability or position of compromise and should not be coerced.[2]

When conducting clinical research involving human subjects, we need to keep in mind that our own secondary gain is not more important than the rights and well-being of our research subjects.[3] For instance, it is important that conflicts of interest (such as a company donating a new drug for a clinical trial) not influence the way that patients are treated. In other words, we must strive to eliminate bias from our studies to produce truly meaningful results that can be used to enhance patient care.

Bias can be introduced into a study in virtually any step of the research process, including patient selection, data collection, and analysis of study results.[4] When the specifications or criteria used to assign patients to different study groups are inherently different, selection bias can occur.[4] One form of selection bias is membership bias; in this type of bias, study participants choose to be members of a group and may differ from nonmembers in a meaningful way.[5] Another type of selection bias is nonresponse bias, in which those subjects participating in a study differ from nonrespondents in meaningful ways.[5] This bias has been demonstrated in smokers; in one study using a mailed questionnaire, "cigarette smoker response rates were considerably lower than the other smoker categories."[6] Nonresponse bias has also been found among the elderly; in a study of elderly individuals, nonrespondents to a postal questionnaire were not only more disabled and more cognitively impaired than those who responded to the questionnaire, but they also had a higher 1-year mortality rate.[7] Thus, study participants may differ from nonparticipants in meaningful ways—for instance, by being healthier or younger or having different health-related habits—which can have an impact on study results. Strategies to reduce selection bias include increasing sample size in order to make the study as representative as possible and implementing randomization, where study participants are randomly assigned to different study groups.[8]

In the process of collecting data, several types of bias may alter study outcomes. Recall bias occurs when outcomes of an intervention shape the way study participants recall events during or before the interventional process; in other words, it occurs when research subjects in different study groups describe past events differently.[4,9] Better recall may be found among study participants with the disease being studied than among those participants who are healthy, as those who are burdened with a disease are more likely to spend time searching for a potential cause.[5] One such example of recall bias is parental recollection of the time at which his or her child received the measles, mumps, and rubella (MMR) immunization in relation to the onset of regressive symptoms seen in autism.[10] Parents of children diagnosed with autism after a highly publicized paper alleging a link between the MMR vaccine and autism were more likely than parents of children diagnosed with autism before the paper to recall the onset of regressive symptoms in their children shortly after MMR vaccine administration.[10] Recall bias has also been found to be related to exposures that are not socially acceptable, such as cigarette smoking, leading to underreporting of undesirable behaviors.[11] One strategy to reduce recall bias is to decrease the amount of time between exposure and follow-up; "the longer the interval, the higher the probability of incorrect recalls."[9] Additionally, research subjects and data collectors can be blinded to the study hypothesis to further reduce the potential for recall bias.[9]

Other forms of bias that can occur during data collection include performance bias and observer bias. Performance bias can occur when the performance of interventions or procedures is not the same, and thus, research subjects in different groups are treated differently.[12] This is especially common in surgical studies.[12] In addition, observer bias can occur when a researcher influences the study through his or her beliefs or predispositions.[13] One form of observer-expectancy bias is referred to as the Pygmalion effect or self-fulfilling

prophecy; subjects perform better or worse based on how they are expected to perform.[14] In order to reduce these biases, blinding of both research subjects and researchers can be effective.[12] This ensures that researchers are not aware of the allocation of subjects to different groups and prevents manipulation of data in favor of one group or the other.[12] It also prevents patients/study participants from producing better results based on expectations or trust in treatments.[12] Other possible remedies include limiting interactions between observers and experimenters, having well-defined variables, and limiting the observer's awareness of the experiment's purpose.[15]

Bias can also be brought into a study during the analysis of results. One such form of bias is lead-time bias, where early detection of a disease process can be confused with increased survival.[16] For instance, if patients with cancer are identified earlier with a screening study, researchers may inappropriately conclude that patients are living longer due to screening, when, in fact, the survival time did not change; the length of time between cancer detection and death was simply increased. It is important to be aware of the potential for lead-time bias both when conducting experiments and when analyzing study results.

In conclusion, researchers must be aware of the potential for the introduction of bias into studies, and efforts should be made to reduce these biases. Bias can be introduced into a study during patient selection, data collection, and data analysis, and many strategies may be employed to prevent these biases.[4] If at all possible, the allocation of research participants to different study groups should be randomized, and researchers and study participants alike should be blinded to reduce the influencing of results based on preconceived ideas or expectations. The interactions between observers and experimenters should be kept to a minimum, and sample size should be sufficiently large so as to make the sample as representative as possible. Finally, to decrease the probability of recall inaccuracy, efforts can be made to decrease the interval of time between exposure and follow-up.

Importantly, clinical trials in dermatology must strive to be ethically sound to protect the rights of study participants. We must strive to apply the ethical principles of respect for persons, beneficence, and justice to our research involving human subjects.[2] In addition to treating study participants equally, we must respect the choices of our study participants and minimize potential harm.[2] We must always remember that it is only appropriate to involve human subjects in our research "if the importance of the objective outweighs the risks and burdens to the research subjects."[1]

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Recent Government Circulars Regarding Clinical Trials and Their Relevance

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Carrying out academic clinical trials in India has been facilitated with the introduction of three government circulars. These circulars are discussed as below:

I. **Audio visual recording of informed consent process (Annexure I)**

Audio visual recording of the informed consent process was previously made mandatory for all clinical trials from November 2013 by the office of the Drug Controller General of India (DCGI).[1] DCGI had found under many circumstances that a well-designed informed consent document did not necessarily translate to a proper and ethical informed consent process. However, in the fifth amendment of the Drug and Cosmetic Rules in the official gazette of Government of India, on December 21, 2015, it was stated that the investigator should obtain audio visual recording of the informed consent process only for vulnerable participants in clinical trials of new chemical entity or new molecular entity.[2] In cases where clinical trials were conducted on anti-human immunodeficiency virus (HIV) and antileprosy drugs, the investigator should only obtain an audio recording of the informed consent process.[2] The data of the audio visual recording were to be archived for at least 5 years.

The gazette notification does away with the arrangement of logistics for conducting audio visual recording and eases out the informed consent process.

II. **Requirement of permission for conduct of clinical trials for academic/research purposes that are nonregulatory in nature (Annexure II)**

A circular regarding the permission for conduct of clinical trials for academic/research purposes was published by the Central Drug Standards

Control Organization (CDSCO) on November 10, 2015. It said that if such trials were non-regulatory in nature, which is not seeking marketing approval of a drug, the permission of the DCGI was not mandatory to carry out these trials. Instead, the Ethics Committee (EC) of the respective institute was given an added responsibility of approving the initiation of the academic trial. If the EC has any doubts regarding the protocol, it can forward the protocol to the DCGI for approval. In the event of nonreceipt of any reply from the office of the DCGI by 30 days, the trial can be initiated, but also the record of the communication must be retained by the EC.

This circular is a breather for the conduct of academic trials, which are in essence postgraduate thesis or investigator-initiated trials in academic institutions.

III. **Restriction of the number of clinical trials that can be conducted per investigator (Annexure III)**

CDSCO previously restricted the number of clinical trials that could be conducted by an investigator to three in number. In a circular on 02.08.2016, CDSCO has decided to remove this restriction and has given the responsibility to the EC of the institute to judge the complexity, nature, and the risk involved with the trial and decide the number of trials the investigator can undertake.[3]

Previous restriction of maximum three clinical trials per investigator would not allow the supervisor/guide to undertake investigator-initiated/sponsored trials, if he is supervising three clinical trials as thesis of his/her postgraduates trainees. As per the recent Medical Council of India (MCI) guidelines of professor being able to supervise/guide two theses/dissertations per year, emergence of such situation was not unlikely. The present order lifts the ban and is a welcome sign for undertaking clinical as thesis/dissertation by postgraduate trainees.

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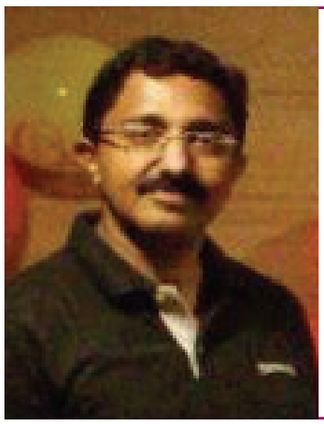
Quiz



DR. BRIJESH NAIR

Consultant Dermatologist

INHS, Sanjivani, Kochi

Hi to the discerning audience of the second newsletter of SIG Clinical Trials called "Random Musings." This quiz aims at introducing the history, progress, and new developments associated with personalities who have enhanced the field of evidence-based dermatology (medicine) and biostatistics, which is a key component to evidence-based medicine (EBM) and research methodology. So kindly give it a try to find out your evidence quotient (EQ).

QUESTIONS

1. Named after a Colombian physician who worked as a research fellow at the Oxford Pain Relief Unit, the Jadad Score or the Oxford scoring system sets out to measure:
   a. Trial heterogeneity in a systematic review
   b. Conflict of interest
   c. Positive results of a trial
   d. Methodological quality of a clinical trial
2. Recently, in an observational study, sunscreens were controversially implicated to a clinical entity, which led to lots of controversy regarding the study design of the trial and the consequent outcomes
   a. Psoriasis
   b. Seborrheic dermatitis
   c. Rosacea
   d. Lupus miliaris disseminata faciei
   e. Frontal fibrosing alopecia
3. Research with unethical concealment of risk can be of disastrous consequences. This is delineated in a botched gene therapy trial, which led to the demise of a trial subject, which was described in "Wilson RF. The death of _____: new evidence of the influence of money and prestige in human research. Am J Law Med 2010;36:295–325." This led to the coruscating conclusion that it "came to signify the corrosive influence of financial interests in human subject research." The primary researcher had financial conflicts of interest for the pharmacological firm initiating research. Name the infamous human casuality.
4. United States statistician and psychologist best known for his work on statistical power and effect size, which helped to lay foundations for current statistical meta-analysis. He was a critic of reliance on significance testing procedures used in statistics, especially misunderstandings of null hypothesis significance testing. In particular, he identified the "near universal misinterpretation of **P" as the probability that if H0 is false, the misinterpretation that its complement is the probability of successful replication, and the mistaken assumption that if one rejects H0 one thereby affirms the theory that led to the test. He revived the Fisherian argument of** recognition of single studies as merely exploratory and a reliance on replication for support. Interrater variability is measured by a statistic named after him.
5. This is a metric designed to measure stability of a meta-analysis. It can be calculated in any meta-analysis and may be defined as the

number of new, unpublished, or unretrieved nonsignificant or "null result" studies that would be required to exist to lower the significance of a meta-analysis to some specified level, for example, to barely significant or nonsignificant. To put it into correct context, for a meta-analysis in which 300 studies showed a large average effect size it would take 32,960 unpublished null result studies to bring the new combined P to a nonsignificant level. The existence of that many unpublished studies is improbable, and hence this adds greatly to the confidence it is possible to attach to that particular result of meta-analysis. What is this metric?

6. This venture based out of the Institute for Health Metrics and Evaluation at the University of Washington and funded by the Bill and Melinda Gates Foundation is a comprehensive regional and global research program that assesses mortality and disability from major diseases, injuries, and risk factors. It set out to measure impact of disease using a metric that could also be used to assess the cost-effectiveness of interventions, called DALY (disability adjusted life years). Name this important epidemiologic venture.
7. X is an epidemiological measure used in communicating the effectiveness of a health-care intervention, typically a treatment with medication. It is defined as the **reciprocal of the absolute risk reduction or risk difference [1/(*p*1–*p*2)]**. It was described in 1988 by Laupacis, Sackett, and Roberts. It gives an easily comprehensible metric to determine effectiveness of medications. Name X.
8. The PRECIS tool is used to differentiate key domains that distinguish between:
   a. Randomized trial and nonrandomized trial
   b. Narrative review and a systematic review
   c. Parametric tests versus nonparametric tests
   d. Explanatory trial and pragmatic trial
   e. Observational study and interventional study
9. Which among the following modalities is rated as "Level 1 evidence, validated" in the British Association of Dermatology Bullous Pemphigoid Management Guidelines in 2014?
   a. Azathioprine
   b. Rituximab
   c. Topical potent steroids
   d. Omalizumab
   e. Mycophenolate mofetil
10. The STRATOS collaboration was initiated to help researchers cope with the methodological complexity arising from the broad range of issues potentially thrown up by _____.
    a. Observational study
    b. Qualitative study
    c. Equivalence trials
    d. Noninferiority trials
    e. n- of-1 trials
11. Nonmaleficence, autonomy, beneficence, and justice are the four pillars of?
12. A fun question: SnOUT and SpPIN are mnemonics for _____.
13. What does this graphic set out to summarize?

14. Identify this giant of EBM

15. All are confounder "breaking" strategies in a clinical trial except:
    a. Bootstrapping
    b. Stratified sampling
    c. Pair wise matching
    d. Exclusion
    e. Multivariate modelling

ANSWERS

1. d
2. e
3. Jesse Gelsinger

4. Jacob Cohen
5. Failsafe N
6. Global Burden of Disease Study (GBD)
7. Numbers needed to treat (NNT)
8. d
9. c
10. a
11. Principle of Medical Ethics
12. Sensitivity and specificity

    Sensitivity: SnOUT—a positive test in a diseased purpose, if the result is negative, disease is ruled out

    Specificity: SpPIN—a negative test result in a healthy person, positive result rules in(confirms) diagnosis
13. Bradford Hill Criteria for Causal Inference
14. Dr. David Sackett, father of EBM.
15. a

Annexure I: Government notification on audio visual recording of informed consent process

रजिस्ट्री सं० डी० एल०-33004/99 REGD. NO. D. L.-33004/99

भारत का राजपत्र
The Gazette of India

असाधारण
EXTRAORDINARY
भाग II—खण्ड 3—उप-खण्ड (i)
PART II—Section 3—Sub-section (i)
प्राधिकार से प्रकाशित
PUBLISHED BY AUTHORITY

सं. 489] नई दिल्ली, शुक्रवार, जुलाई 31, 2015/श्रावण 9, 1937
No. 489] NEW DELHI, FRIDAY, JULY 31, 2015/SHRAVANA 9, 1937

स्वास्थ्य और परिवार कल्याण मंत्रालय

(स्वास्थ्य विभाग)

अधिसूचना

नई दिल्ली, 31 जुलाई, 2015

सा. का. नि. 611(अ).—औषधि और प्रसाधन सामग्री नियम, 1945 का और संशोधन करने के लिए औषधि और प्रसाधन सामग्री अधिनियम, 1940 (1940 का 23) की धारा 33 के साथ पठित धारा 12 द्वारा यथापेक्षित कतिपय नियमों का प्रारूप भारत सरकार की स्वास्थ्य और परिवार कल्याण मंत्रालय (स्वास्थ्य और परिवार कल्याण विभाग) की अधिसूचना सं. सा.का.नि. 364(अ) तारीख 7 जून, 2013 द्वारा भारत के राजपत्र, असाधारण, भाग 2, खंड 3, उपखंड (i), तारीख 7 जून, 2013 में प्रकाशित किया गया था, उन पर उन सभी व्यक्तियों से जिनको उससे प्रभावित होने की संभावना है, उक्त अधिसूचना के राजपत्र की प्रतियां जनता को उपलब्ध होने की तारीख से पैंतालीस दिनों की अवधि के भीतर आक्षेप और सुझाव आमंत्रित किए गए थे ;

और राजपत्र की प्रतियां जनता को 7 जून, 2013 को उपलब्ध करा दी गई थीं ;

और उक्त प्रारूप नियम के संबंध में प्राप्त आक्षेपों और सुझावों पर केन्द्रीय सरकार द्वारा विचार कर लिया गया है;

अतः, अब केन्द्रीय सरकार, औषधि और प्रसाधन सामग्री अधिनियम,1940 (1940 का 23) की धारा धारा 33 के साथ पठित धारा 12 द्वारा प्रदत्त शक्तियों का प्रयोग करते हुए, औषधि तकनीकी सलाहकार बोर्ड से

परामर्श करने के पश्चात्, औषधि और प्रसाधन सामग्री नियम, 1945 का और संशोधन करने के लिए निम्नलिखित नियम बनाती है, अर्थात् :-

1. (1) इन नियमों का संक्षिप्त नाम औषधि और प्रसाधन सामग्री (पंचम संशोधन) नियम, 2015 है।

(2) ये राजपत्र में उनके अंतिम प्रकाशन की तारीख को प्रवृत्त होंगे।

2. औषधि और प्रसाधन सामग्री नियम, 1945 की अनुसूची म में,-

(i) "नैदानिक परीक्षण" पर पैरा 2 के "संसूचित सहमति" से संबंधित उप पैरा (4) में खंड (iii) के पश्चात् निम्नलिखित अंतःस्थापित किया जाएगा, अर्थात् :-

"(iv) नए रासायनिक निकाय या नए अणु संबंधी निकाय की दशा में नैदानिक परीक्षणों में भेद्य व्यष्टियों की दशा में संसूचित सहमति प्रक्रिया का श्रव्य दृश्य अभिलेखन, जिसके अंतर्गत व्यष्टि को सूचना प्रदान करने की प्रक्रिया और उसकी सहमति की समझ भी है, का अन्वेषक द्वारा अभिलेख के लिए अनुरक्षण किया जाएगा:-

परंतु प्रतिरोधी एचआईवी और प्रतिरोधी कुष्ठ औषधियों के नैदानिक परीक्षण की दशा में व्यष्टि कर्ता की संसूचित सहमति प्रक्रिया का श्रव्य अभिलेखन, जिसके अंतर्गत व्यष्टि कर्ता को सूचना प्रदान करने की प्रक्रिया तथा ऐसी सहमति पर उसकी समझ भी है, का अन्वेषणकर्ता द्वारा अभिलेख के लिए अनुरक्षण किया जाएगा।";

(ii) परिशिष्ट 5 में "अनिवार्य तत्वों" से संबंधित उपशीर्षक 1.1 में "संसूचित सहमति" शीर्ष के अधीन क्रम संख्या 14 और उससे संबंधित प्रविष्टियों के स्थान पर निम्नलिखित क्रम संख्या और प्रविष्टियां रखी जाएंगी, अर्थात् :-

"14. यह विवरण कि आशयित चिकित्सा प्रभाव प्रदान करने में अन्वेषणीय उत्पाद के असफल रहने की संभावना है।

15. यह विवरण कि प्लेसबो नियंत्रित परीक्षण की दशा में व्यक्तियों को दिए गए प्लेसबो का चिकित्सीय प्रभाव नहीं होगा।

16. कोई अन्य संगत सूचना।"।

[फा. सं.एक्स-11014/1/2012-डीएफक्यूसी]

निकुंज बिहारी धल, संयुक्त सचिव

टिप्पण : मूल नियम राजपत्र में अधिसूचना संख्यांक एफ 28-10/45-एच(1), तारीख 21 दिसंबर, 1945 द्वारा प्रकाशित किए गए थे और सा.का.नि. 390 (अ) तारीख 18 मई, 2015 द्वारा उनका अंतिम संशोधन किया गया।

MINISTRY OF HEALTH AND FAMILY WELFARE

(Department of Health and Family Welfare)

NOTIFICATION

New Delhi, the 31st July, 2015

G.S.R. 611(E).—Whereas a draft of certain rules further to amend the Drugs and Cosmetics Rules, 1945, was published, as required by section 12 read with section 33 of the Drugs and Cosmetics Act, 1940

(23 of 1940), *vide* notification of the Government of India in the Ministry of Health and Family Welfare (Department of Health and Family Welfare), number G.S.R. 364(E), dated the 7th June, 2013, published in the Gazette of India, Extraordinary, Part II, section 3, sub-section (i), dated the 7th June, 2013, inviting objections and suggestions from all persons likely to be affected thereby before the expiry of a period of forty five days from the date on which the copies of the Official Gazette containing the said notification were made available to the public;

And whereas copies of the Gazette were made available to the public on 07th June, 2013;

And whereas, objections and suggestions received from the public on the said rules have been considered by the Central Government;

Now, therefore, in exercise of the powers conferred under section 12 read with section 33 of the Drugs and Cosmetics Act, 1940 (23 of 1940), the Central Government, after consultation with the Drugs Technical Advisory Board, hereby makes the following rules further to amend the Drugs and Cosmetics Rules, 1945, namely:—

1. (1) These rules may be called the Drugs and Cosmetics (Fifth Amendment) Rules, 2015.

(2) They shall come into force on the date of their publication in the Official Gazette.

2. In the Drugs and Cosmetics Rules, 1945, in Schedule Y,—

(i) in paragraph 2 under the heading "CLINICAL TRIAL", in sub-paragraph (4) relating to "Informed Consent", after clause (iii), the following shall be inserted, namely:—

"(iv) An audio - video recording of the informed consent process in case of vulnerable subjects in clinical trials of New Chemical Entity or New Molecular Entity including procedure of providing information to the subject and his understanding on such consent, shall be maintained by the investigator for record;

Provided that in case of clinical trial of anti-HIV and anti-Leprosy drugs, only audio recording of the informed consent process of individual subject including the procedure of providing information to the subject and his understanding on such consent shall be maintained by the investigator for record.";

(ii) in APPENDIX V, under the heading "INFORMED CONSENT", in sub-heading 1.1 relating to "Essential Elements", for serial number 14 and the entries relating thereto, the following serial numbers and entries shall be substituted, namely:—

"14. Statement that there is a possibility of failure of investigational product to provide intended therapeutic effect.

15. Statement that in the case of placebo controlled trial, the placebo administered to the subjects shall not have any therapeutic effect.

16. Any other pertinent information.".

[F. No.X.11014/1/2012-DFQC]

NIKUNJA BIHARI DHAL, Jt. Secy.

Note : The principal rules were published in the Official Gazette *vide* notification No. F.28-10/45-H (1) dated the 21st December, 1945 and last amended *vide* notification number G.S.R. 390(E) dated the 18th May, 2015.

Printed by the Manager, Government of India Press, Ring Road, Mayapuri, New Delhi-110064
and Published by the Controller of Publications, Delhi-110054.

Annexure II: Government notification on requirement of permission for conduct of clinical trials for academic/research purposes that are nonregulatory in nature

File No. 12-01/14-DC (Pt. 47)
Central Drugs Standard Control Organization
Directorate General of Health Services
Ministry of Health and Family Welfare
FDA Bhawan, Kotla Road, New Delhi 110002

Dated 10.11.2015

CIRCULAR

Subject:- Requirement of permission for conduct of clinical trials for academic/research purposes that are non-regulatory in nature – regarding.

To deliberate stakeholders concerns and the way forward relating to some issues on conduct of clinical trials in India, two meetings were held on 20.08.2015 and 06.10.2015 under the Chairmanship of Secretary, Ministry of Health and Family Welfare in which experts including Secretary, D/o Health Research & Director General, ICMR and Director General Health Services were present.

As regards requirement of permission for conduct of clinical trials for academic/research purposes that are non-regulatory in nature, it was decided that the permission of DCG (I) shall not be required in such trials, provided that, the trials were approved by the respective Ethics Committee and they are not for regulatory submissions (i.e. if the trial are not for claiming permission of New Drug for marketing as per Drugs and Cosmetics Rules).

However, the Ethics Committee of the respective Institution may take a view in this regard. They should inform DCG (I) about the cases where permission of DCG (I) was not required. In case, no objection was received from DCGI within 30 days, the clearance of DCG (I) may be presumed.

This is communicated for information and necessary compliance by all concerned.

(Dr. G. N. Singh)
Drugs Controller General (India)

To:-

i) **All stakeholders through website of DCG (I).**
ii) **Zonal and Sub-zonal offices of CDSCO/ all officers of CDSCO (HQ).**

Copy to:-

i) **PS to Secretary, Ministry of Health and Family Welfare**
ii) **PPS to DGHS,**
iii) **PPS to JS(R).**

Annexure III: Government notification on restriction of the number of clinical trials that can beconducted per investigator

File No. 12-01/14-DC (Pt. 47)
Central Drugs Standard Control Organization
Directorate General of Health Services
Ministry of Health and Family Welfare
FDA Bhawan, Kotala Road, New Delhi 110002

Date: 02-08-16

CIRCULAR

Subject: - Restriction of conducting three clinical trials per investigator-regarding.

To deliberate stakeholders concerns and the way forward relating to some issues on conduct of clinical trials in India, two meetings were held on 20.08.2015 and 06.10.2015 under the Chairmanship of Secretary, Ministry of Health and Family Welfare in which experts including Secretary, D/o Health Research & Director General, ICMR and Director General Health Services were present.

As regards restriction that no investigator shall conduct more than three trials at any given period of time, it has been decided to remove this restriction & it is further decided that Ethics Committee after examining the risk and complexity involved in the trial being conducted/proposed shall decide about how many trials an investigator can undertake.

This is communicated for information and necessary compliance by all concerned.

(Dr. G. N. Singh)
Drugs Controller General (India)

To:-

I) All stakeholders through website of DCG (I).
II) Zonal and Sub-zonal offices of CDSCO/ all officers of CDSCO (HQ).

Copy to:-

I) PS to Secretary, Ministry of Health and Family Welfare,
II) PPS to DGHS,
III) PS to AS,
IV) PS to JS(R).

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