Dermatology and Randomized Control Trials

Abstract

Well-designed and rigorously conducted randomized controlled trial (RCT) can produce most valid and precise scientific evidence. Any intervention, be it systemic or topical medicine, dermatology procedure needs to be tested for its efficacy in improving particular disease condition and RCT should come into mind of investigator. The biggest strength of RCT lies in two self-explanatory factors; they are randomized and controlled. Randomization of study subjects eliminates selection and confounding bias and controlling of study condition improves the internal and external validity of findings. "Blinding" eliminates assessment bias. If one starts a comparative study without stating proper hypothesis, he/she would end up collecting lots of data which does not make sense. PICOT format helps in formulating research question. Writing a detailed protocol based on hypothesis describing in detail methodology, sample size calculation, randomization method, and blinding procedure up to statistical analysis plan is very important step in planning of RCT. Trials registered prospectively contribute to transparency of the trial and are considered to reduce the publication bias by reducing selective publication of positive outcomes. Adverse events can occur at any time during conduct of an RCT and should be reported and kept track of. Physical injury resulting from clinical trial participation is entitled to financial compensation. During preparation of final manuscript of study, the CONSORT guidelines must be followed to improve the quality of reporting of RCTs. Clinical trials provide evidence-based approach in medicine and a designed and well-implemented trial can alter clinical dermatology practice for a healthier tomorrow.

Keywords: *Dermatology, randomized controlled trials, RCT*

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Introduction

In the last few decades, importance of evidence-based practice is increasing in dermatology like all other disciplines of medicine. When it comes to any intervention, may it be new drug, new dose regime, and newer dermatological procedure, importance of evidence-based dermatology for benefit of patients and legal safety of dermatologist cannot be underrated. The randomized controlled trial (RCT) is the most meticulous and robust research method of establishing whether a cause–effect relationship is present between intervention and outcome. Clinical trials give a broad idea about the safety and efficacy of a new agent/drug/device/lifestyle modification in treatment of a clinical condition.[1] Well-designed and rigorously conducted RCT can produce most valid and precise scientific evidences. Additionally well-conducted and well-reported RCT can easily yield itself to meta-analysis and systematic review which further help in generating evidence for particular intervention.[2] Negative trial reported on Patulin as a treatment for the common cold reported by Stansfeld *et al*. in 1944 is considered first reported RCT.[3] RCT loses its internal and external validity if not properly planned and conducted. In this article, we will briefly discuss salient points about designing good RCT.

When to think of RCT?

When any intervention, may it be systemic medicine, topical medicine, and dermatology procedure need, needs to be tested for its efficacy in improving particular disease condition, RCT should come into mind of investigator. The biggest disadvantage of observational studies like case report and case series as evidence of cause–effect analysis is their inherent bias.[4] Bias is defined as ability of any systematic factors related to design, data collection, and analysis of study to affect true estimation of cause–effect relationship of intervention. Bias

How to cite this article: Patel N, Sil A. Dermatology and randomized control trials. Indian Dermatol Online J 2021;12:400-7.

Received: 15-Sep-2020. **Revised:** 29-Nov-2020. **Accepted:** 25-Jan-2021. **Published:** 12-May-2021.

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Access this article online

Website: www.idoj.in

DOI: 10.4103/idoj.IDOJ_715_20

Quick Response Code:

can occur during selection of participants and distribution into "study arm" and "control arm" (selection bias), due to presence of "confounding" factors (confounding bias) and during assessment of outcome (assessment bias). RCT by virtue of its study design tries to overcome selection and confounding bias by the process of "randomization" and the assessment bias by "blinding." The biggest strength of RCT lies in two self-explanatory factors; they are randomized and controlled. Randomization of study subjects eliminates selection and confounding bias and controlling of study condition improves the internal and external validity of findings. While testing a research question with RCT, there should be sufficient uncertainty or ambiguity about effectiveness of intervention, also known as "clinical equipoise."[5] It is to be remembered that observation of your study should always have some usefulness to broader scientific community. For example, there is little point in conducting RCT to know efficacy of topical retinoid versus placebo in the management of mild-to-moderate acne vulgaris, as it is well established. A double-blind RCT to know efficacy of Azithromycin with oral isotretinoin versus oral isotretinoin only in the treatment of moderate-to-severe acne vulgaris is well-warranted RCT as information from such study has potential of changing existing treatment practice of acne vulgaris. Safety of participant is always paramount when planning RCT. One cannot expose study subjects to unjustifiable harm for sake of conducting study. Review of present safety evidence from preclinical and clinical studies, safety of intervention in other conditions, and risk–benefit assessment in context of nature of disease need consideration when evaluating this aspect of study. RCT to evaluate effectiveness of rituximab in the treatment of extensive and refractory subcutaneous lupus erythematosus might have some ethical justification, whereas rituximab for localized discoid lupus erythematous has none. For investigating etiology or natural history of disease, case-control and cohort studies are better than RCTs. Rare outcome and those that take a very long time to develop are not suitable for RCT.

Figures 1 and 2 highlight advantages and limitations of RCT.

RCT designs: Parallel group study design where subjects are allocated to two different intervention arms after randomization is most commonly used RCT design in routine practice. This is relatively simple to conduct RCT design for inexperienced researcher. There are other RCT designs like cross-over study design and its variations; factorial study and randomized withdrawal design [enrichment enrolment randomized withdrawal (EERW)] can be selected depending upon type of intervention and type of disease condition to be investigated. Readers can refer to article by Nair B previously published in this journal for further information on various RCT study designs.[6]

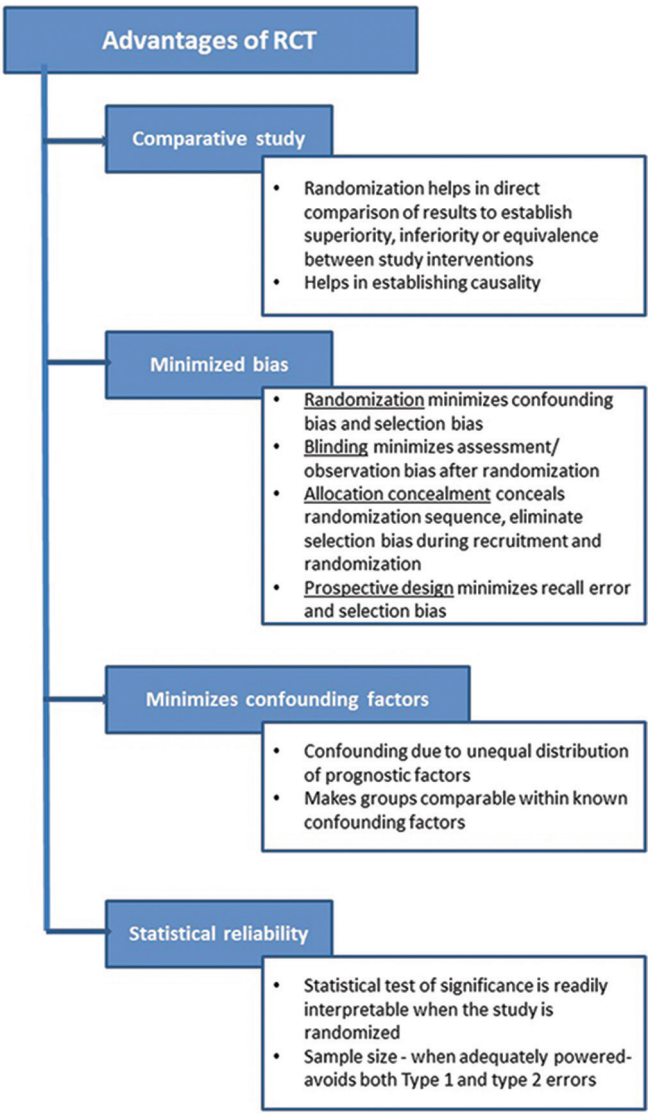

Figure 1: Advantages of RCTs

Crossover study design: In this trial design, participants receiving Drug A are switched to Drug B after giving adequate washout. Similarly, participants receiving Drug B are switched to Drug A. The results are compared at the end of the switch. To conduct such trial, the disease must be chronic and stable and the effect of the drug must not be irreversible. The advantage of this trial design is that a smaller sample size is required and each individual under research serves as his or her own control, limiting the variation within the study subjects.

Factorial study design: Two or more interventions and their combinations can be compared in a single trial. The trial also compares the interaction of the agents. The advantages are that the sample size is considerably reduced. However, there should be no interaction between the two or more treatments. A pictorial representation of factorial study design is given in Figure 3.

Randomized withdrawal designs (EERW): In this study design, all participants are assigned to receive intervention

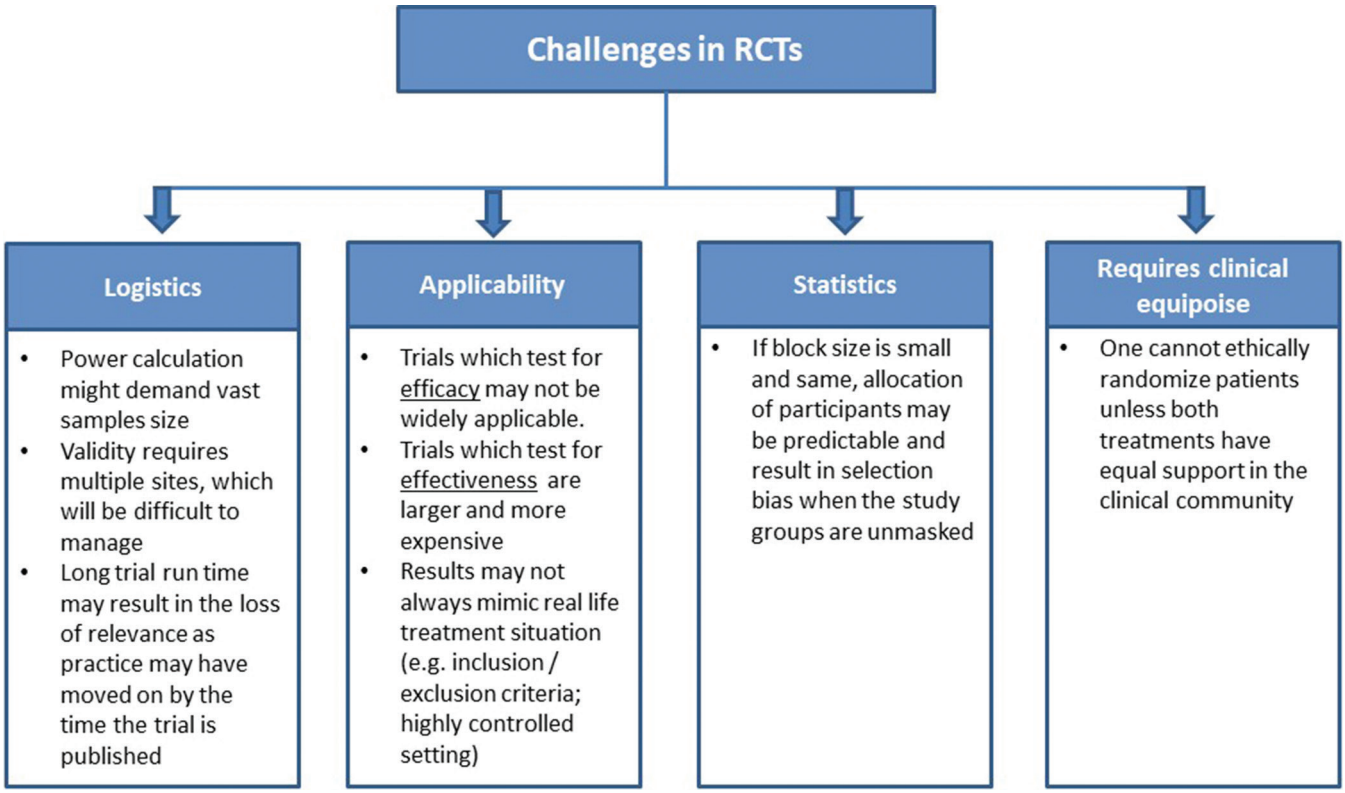

Figure 2: Drawbacks of RCTs

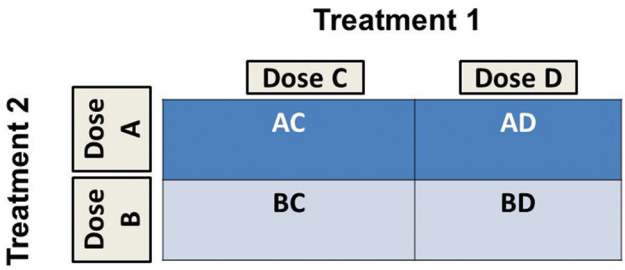

Figure 3: Pictorial representation of factorial study design

in the open-label enrichment period. Only the responders are carried forward and randomized. The nonresponders are withdrawn and are not randomized. This ensures acceptability to trial participants as the participants who have been withdrawn can restart effective therapy.

Planning RCT step by step

Developing research hypothesis and research question: Every analytical study must have hypothesis, which is statement of association or no association (as in null hypothesis) between intervention and outcome. Good hypothesis must be precise and stated in advance of commencement of study. First step in direction of formulating hypothesis is to formulate a research question. A sound research question should include the following components and is given as the acronym "PICOT": P (population of interest to be studied), I (intervention to be studied), C (comparator agent/intervention), O (outcomes to be evaluated), and T (time duration for intervention/outcome ascertainment).[7,8] If research question and specific hypothesis is not defined at start of study, researcher is more likely to end up having database with irrelevant data. Multiple statistical testing of associations from previously collected data could potentially lead to false-positive findings of association through chance alone.[9] One should also take into consideration that research hypothesis is vital first step on which study design, sample population as well as sample size is calculated.

Illustrative example: Apremilast being new introduction in market, a dermatologist wants to know whether it is more efficacious in treating chronic plaque psoriasis compared to acitretin. First step would be through literature review using physical and electronic database like PubMed, Cochrane library, or Embase to see if there is already sufficiently powered RCT or meta-analysis available on this (you don't waste your time, energy, and funds on something which is already known). If by your literature review you feel that there is need of good RCT to know the difference, next step would be to frame research question, hypothesis, and protocol.

Research question: Is apremilast safer and more effective than acitretin in treatment of psoriasis?

If one starts a comparative study based on this question without stating proper hypothesis, he/she would end up collecting lots of data which does not make sense.

The PICOT format approach for summarizing the abovementioned research question is explained as follows:

P: Population: Implies the sample of participants you wish to recruit for your study, for example, patients of psoriasis attending the dermatology OPD.

I: Intervention: Refers to the treatment that will be provided to participants in the study, for example, apremilast 30 mg twice daily for 12 weeks.

C: Comparator group or control group: Identifies what you plan on using as a standard reference group for comparison to your treatment intervention, for example, acitretin 25 mg once daily for 12 weeks.

O: Outcome: They are the parameters of estimating effectiveness, for example, PASI score estimated at baseline, 4 weeks, 8 weeks of treatment, 12 weeks, and 16 weeks.

T: Time: Duration of study, for example, 1 year.

Research hypothesis: A significantly greater number of patients with moderate-to-severe chronic plaque psoriasis treated with apremilast 30 mg twice daily achieve reduction in PASI score more than 75% from baseline compared to acitretin 25 mg once day at end of 12 weeks of therapy.

Writing a protocol: Writing a detail protocol based on hypothesis describing in detail methodology, sample size calculation, randomization method, and blinding procedure up to statistical analysis plan is very important step in planning of RCT. Well-written protocol is half of your manuscript ready even before study! One must peer review protocol before finalizing it. Peer review of protocol at early stage of study design provides investigator opportunity to ponder over constructive criticism from others and rectify if necessary, otherwise which may come during publication stage; by that time, it may be too late to address them. Seeking support from experienced researchers and biostatistics expert at designing stage of protocol is extremely necessary. Correcting errors at the design stage is preferred rather than the analysis stage.

Selection of study population/sampling method

The results of the RCT will finally be extrapolated to patients in general (also known as generalizability) and thus the nature of the selection of patients for a trial is highly critical. Ideally, all patients with disease condition should be in sampling frame and participants should be randomly selected from that, e.g., if you are conducting RCT on psoriasis, all patients of psoriasis in your area should be in sampling frame. This is hardly possible in real practice. So, in real-life situation, sampling frame is usually limited to patients attending particular clinic; so for the above example, patients attending psoriasis clinic in your institute would be your sampling frame. Inclusion and exclusion criteria will decide who qualify to be included in study. Most appropriate sampling technique for good generalizability of results would be consecutive sampling but this may draw unusually large sample. So, technique known as stratified sampling is used where the investigator draws sample from particular strata based on age, sex, or disease severity, for example, patient of chronic plaque psoriasis age between 18 and 60 years having PASI score more than 12. This is particular limitation of RCT where never a single RCT is generalizable to population as real patients in practice vary greatly in characteristic from studied subjects and multiple RCTs are advisable.[9]

Determining sample size

Ad hoc sample size determination is one of the biggest reasons why even a very well-planned clinical study failed to impress the scientific community. Sample size should always be calculated based on significance level in the study (type I error or α), power (1-type II error), effect size, and standard deviation.[10] Additional type of study design (superiority trials, non-inferiority trial, equivalence trial, etc.) will also affect the sample size calculation. It is understandable for a dermatologist to not have very detailed knowledge on sample size calculation. Taking help from biostatistician of institute or someone who is well versed with sample size calculation for various design is vital to study design of RCT.[11-13]

Randomization

Proper randomization allows study subject to equally allocate to both arms in respect to baseline characteristic and for any confounding factor. Randomization removes selection bias and confounding bias from study. There are two important steps in randomization process, first is generation of randomization sequence and second is allocation of subject to particular group in a way that this sequence remains unknown to both participant and investigator (allocation concealment).[1] Computer-generated random sequence developed by research support department (who will not participate in study enrollment), which is then sealed in consecutively/sequentially numbered opaque sealed envelopes (SNOSE technique), is perhaps most popular method of randomization. Multicenter study can have remote randomization facility (interactive voice response system) where the investigator calls after signing informed consent form and randomization number is allotted over phone. For other method of randomization like block and stratified, cluster randomization readers can access to previous article in this journal by Niar B and Sil A.[1,6]

Blinding

Blinding is a critical methodological feature of RCTs. Blinding seeks to eliminate selection bias during the process of recruitment and randomization, whereas allocation concealment seeks to reduce observation bias after randomization. The purpose of allocation concealment

is to conceal randomization sequence while that of blinding is to make both the participant and investigator unaware of the treatment being given. Role of hospital pharmacy is invaluable in creating foolproof system of packaging and labeling that does not compromise blinding. Independent drug dispenser who does not participate in any other study activity is desirable for good blinding.

The RCT can be open-labeled or unblinded, single blind (participant blind), double blind (participant and investigator/outcome assessor blind), or triple blind (participant, investigator/outcome assessor, and data analyst blind). Nowadays it is a good practice to express which persons are going to be unaware of the treatment instead of mentioning single, double, or triple blind.[1]

An example may clear the concepts as follows

"A study to evaluate the effectiveness and safety of autologous serum therapy (AST) in chronic urticaria (CU)."[14]

Research hypothesis

Whether AST + antihistamine cetirizine is effective and safer than cetirizine alone in chronic urticaria?

Randomization

A random number table is generated by WINPEPI software. Balanced (1:1), unstratified randomization technique was used. The patients received autologous serum therapy or normal saline as placebo in either treatment group along with cetirizine.

The computer-generated random number table of 120 subjects (sample size) to groups A and B:

1: B 2: A 3: A 4: B 5: B 6: B 7: A 8: A 9: B 10: B 11: A 12: B 13: A

14: B 15: B 16: B 17: A 18: A 19: B 20: B 21: A 22: B 23: B 24: B 25: A

26: A 27: B 28: B 29: A 30: A 31: A 32: B 33: B 34: B 35: B 36: B 37: B

38: A 39: A 40: B 41: B 42: B 43: A 44: A 45: A 46: A 47: A 48: A 49: A

50: B 51: B 52: B 53: B 54: A 55: A 56: A 57: B 58: A 59: B 60: B 61: B

62: B 63: A 64: B 65: A 66: B 67: A 68: A 69: B 70: A 71: B 72: A 73: A

74: A 75: B 76: A 77: A 78: B 79: B 80: A 81: A 82: A 83: B 84: B 85: A

86: B 87: B 88: B 89: A 90: A 91: B 92: B 93: A 94: A 95: B 96: A 97: A

98: B 99: A 100: A 101: A 102: B 103: A 104: B 105: B 106: B 107: B 108: A 109: B 110: B 111: B 112: A 113: A 114: A 115: A 116: A 117: A 118: A 119: A 120: B

Totals: Group A: 60, Group B: 60

Group A and Group B are designated as either treatment arms and are not revealed to the evaluating physician.

Blinding

For blinding in this project, since one treatment was injectable, the placebo also had to be an injectable one. The groups received either serum or normal saline injections. Since the color of serum and normal saline are different, leucoplast was covered over the syringes to make them opaque. Thus, all patients were blinded regarding the treatment received. The evaluator who assessed the outcome parameters at baseline and at follow-ups was another dermatologist who was seated in a separate room and not involved in randomization, drawing, centrifuging, or injection of serum/placebo, making the trial double blind.

Allocation concealment

Allocation was concealed using SNOSE technique. Opaque brown envelopes were serially numbered till 120 (since sample size was 120). Small cards (2 cm × 2 cm) were made and "Group A" was written in 60 cards and "Group B" was written in the next 60 cards. According to the random number sequence generated by computer above, envelope 1 will have "Group B" card and envelope 2 will have "Group A" card. This concealment should be done by a person not associated with the study. When the envelope was opened, treatment was given according to the groups.

Ethics clearance

Ethics clearance is mandatory for any research involving human subject. Practically even for asking a question to patients whose answer is going to be utilized for research, ethical clearance is mandatory. Institutional or independent ethics committee (IEC) constituted as per guidelines can evaluate research proposal for ethical issues. The informed consent document is one of the key documents that uphold the autonomy of the study participants and has to be submitted in English and vernacular to the IEC for approval. Any advertisements related to recruitment of participants in the trial, financial transactions related to reimbursement of participation in the trial are to be approved by the IEC.[15] Audiovisual recording of the informed consent process has to be done in case the RCT involves a new molecular entity or vulnerable populations.[16] Trials involving vulnerable population are likely to face stiff ethical scrutiny. Placebo use is permitted only under circumstances where standard care of the disease does not exist. Use of placebo is always going to be questioned by ethics committee, so one must prepare sufficient scientific data before presentation.[17]

Subject withdrawal/dropouts from study

Investigator must ensure least possible "lost to follow up" or dropouts from study as it is one of the parameter of quality

of RCT and soundness of informed consent procedure being followed by the researcher. Despite all efforts, sometimes subject withdrawal become inevitable due to patient's factors like subject withdrawing consent (with or without siting reason) or changing residence. Principal investigator can withdraw subject due to worsening of clinical condition or unreasonable side effect. Criteria for subject withdrawal should be described well in advance in protocol by sponsor or principal investigator. Participant can withdraw from study completely or partially in which case he continues to participate from other study-related activity other than intervention like follow-up and safety analysis. Investigator can utilize data collected till time of withdrawal for final analysis. Though subject can revoke consent completely for any further use of his or her private information, for FDA submitted study it is mandatory to preserve data of withdrawn subject for maintaining integrity of data.[18,19] Intention to treat analysis model will help address problem of dropout at statistical level.

Registration of clinical trial

Clinical trials should be registered prospectively to maintain transparency of the trial. It is considered to reduce the publication bias by reducing selective publication of positive outcomes. The Declaration of Helsinki and International Committee of Medical Journal Editors (ICMJE) strongly recommend registration of clinical trials in publicly accessible database before enrollment of the first study participant. The ICMJE recommends registration in any primary register of the World Health Organization's International Clinical Trials Registry Platform (WHO-ICTRP) or in Clinicaltrials.gov. The Clinical Trials Registry of India (CTRI) is one of the primary registries of WHO-ICTRP. CTRI is a free and online public record system for registration of clinical trials conducted in India. It was initiated as a voluntary measure; however, registry was made mandatory by the Drug Controller General of India (DCGI) since June 15, 2009.[20] Registration of trials ensures transparency, accountability, and accessibility of clinical trials as the protocol, safety measures, and other details of the proposal are accessible online, even to the lay public. Registering just once before the commencement of the trial is not the end of the exercise and data (e.g., recruitment status, results, adverse events) are to be updated in the registry time to time as the trial progresses. Registration of clinical trial is minimum requirement by most leading biomedical journals.[21-25]

Statistical analysis plan

Ideally, electronic database format and statistical analysis plan should be ready well before study is commenced. Electronic datasheet should be as similar as physical case report form to avoid any mistake during data entry. Errors at entry stage can be minimized if the database is preprepared to accept only variables within given permissible ranges and to alert the user to missing values. It is necessary to randomly check selected physical case report forms with database to find out any error in data entry.

When using a one-tailed test, we are testing for the possibility of the relationship in one direction and completely disregarding the possibility of a relationship in the other direction. The one-tailed test provides more power to detect an effect; it is tempting to use a one-tailed test whenever you have a hypothesis about the direction of an effect. Before doing so, consider the consequences of missing an effect in the other direction. It is always good to use a two-tailed test. The two-tail test regardless of the direction of the relationship you hypothesize tests the possibility of the relationship in both directions. For example, we may wish to compare the mean of a sample to a given value x using a t-test. Our null hypothesis is that the mean is equal to x. A two-tailed test will test both if the mean is significantly greater than x and if the mean significantly less than x.

Further access to biomedical statistics may be made in the following article: Sil A, Betkerur J, Das NK. *P* Value Demystified. Indian Dermatol Online J. 2019;10:745-750.

Quality control

Quality control of all aspect of RCT once the study begins is extremely necessary. Data collection is repetitive and tedious phase of study. Small pilot for data collection before actual study begins will help to identify any problem and provide opportunity to rectify it. If more than one investigator are involved in the study, it is always advisable to develop the standard operation document for how to recruit subjects and how to capture different variables. Ideally, any outcome measurement taken on a patient should be precise and reproducible, with minimum inter-observer variability.[26] Training sessions should be arranged at the beginning of study by principal investigator for all the persons involved in the study. They should be thoroughly trained for their role. If the study is long, repetitive training sessions are advisable. Case report form should be well designed before study. It should be simple, user-friendly, self-explanatory, and should collect only data which are necessary. As already mentioned, testing of protocol on small pilot is always advisable. Any changes in the protocol after study commencement should be avoided. Protocol amendment should only be made if it deemed extremely necessary or any change that can improve the finding of study. In case for any changes in the protocol, the coinvestigators and ethics committee must be kept informed.

Safety reporting of a clinical trial

Adverse events can occur at any time during the conduct of an RCT and should be reported and kept track of. An adverse event that is associated with death, inpatient hospitalization (in case the study was being conducted on outpatients), prolongation of hospitalization (in case

the study was being conducted on inpatients), persistent or significant disability or incapacity, a congenital anomaly or birth defect, or otherwise life-threatening is known as serious adverse event or serious adverse drug reaction (SAE). Such SAEs should be reported within 24 h of occurrence by the investigator to the IEC, sponsor of the trial, and the regulatory body (DCGI). Further to the initial intimation, a detailed report of the SAE is to be sent to the IEC and DCGI.[27]

Clinical trial-induced injury in research participants is subject to financial compensation. In case of death, the family of the deceased research participant is entitled to the compensation.[28]

Preparation of final report/manuscript

Short summary of study detail in regards to number of patients screened, randomized, and screen failed (with reason) should be prepared at the end of study and should be submitted to ethics committee as well as trial registry. Preparation of final manuscript of study must follow the consolidated standards of reporting trial (CONSORT) guidelines to improve the quality of reporting of RCTs.[29] A flowchart has to be supplemented with the trial report as per CONSORT and has been shown in Figure 4.

It is crucial that we continue to engage in RCTs to support advancement in dermatology and medicine. Clinical trials are important in the field of medical practice and a designed and well-implemented trial can alter clinical practice for better tomorrow. Transparency within the trial is another aspect we should take into consideration for effective future treatments. There is a need to improve quality of trials in the field of dermatology and other medical fields to discover more effective treatment options.

ICMJE encourages sharing of deidentified data of interventional clinical trials. Statement of detail data sharing plan should be incorporated at the time of trial registration to clinical trial registry. Data sharing plan should clearly mention what type of data (protocol, statistical analysis plan, ICF, clinical study report, etc.) will be shared, where it will be available (institute website, third party website, by e-mail on request, etc.), to whom it will be available (researcher, anybody, etc.), and how long it will be available (for 3 years, 5 years, indefinite, etc.) from date of publication. Clear statement of same should be published with manuscript.[30]

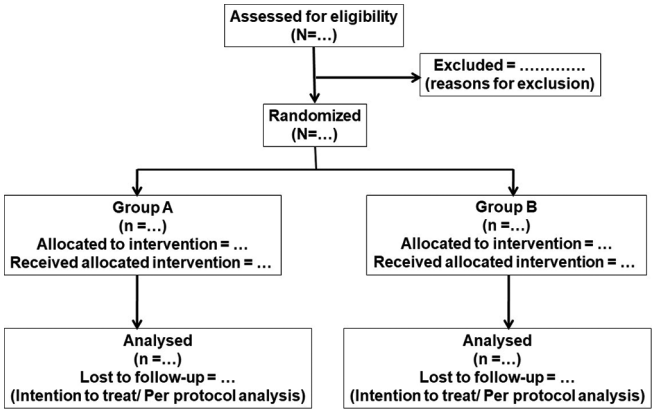

Figure 4: Flowchart as per CONSORT guidelines for reporting of RCT data

Common mistakes of researchers

1. When comparing two therapies, always attempt to randomize. Don't try to go for age and sex matching even in randomized trial (as randomization eliminates selection bias).
2. Random number sequence is generated but allocation is not concealed (vide supra).
3. Allocation concealment and blinding are confused (vide supra). Blind anybody who can be blinded: the participant, investigator, observer, data analyst.
4. Prior sample size calculation is essential to avoid Type II error (false-negative error). Avoid false-positive results (Type I error) by clearly stating the outcome parameters before conduct of the study.
5. Real-time filling of case report form (CRF) is often not done.
6. RCT is often not reported according to CONSORT guidelines.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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