Research Funding—Why, When, and How?

Abstract

Research funding is defined as a grant obtained for conducting scientific research generally through a competitive process. To apply for grants and securing research funding is an essential part of conducting research. In this article, we will discuss why should one apply for research grants, what are the avenues for getting research grants, and how to go about it in a step-wise manner. We will also discuss how to write research grants and what to be done after funding is received.

Keywords: *Research, research funding, research grant*

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Introduction

The two most important components of any research project is idea and execution. The successful execution of the research project depends not only on the effort of the researcher but also on available infrastructure to conduct the research. The conduct of a research project entails expenses on man and material and funding is essential to meet these requirements. It is possible to conduct many research projects without any external funding if the infrastructure to conduct the research is available with the researcher or institution. It is also unethical to order tests for research purpose when it does not benefit patient directly or is not part of the standard of care. Research funding is required to meet these expenses and smooth execution of research projects. Securing funding for the research project is a topic that is not discussed during postgraduation and afterwards during academic career especially in medical science. Many good ideas do not materialize into a good research project because of lack of funding.[1] This is an art which can be learnt only by practising and we intend to throw light on major hurdles faced to secure research funding.

Why Do We Need the Funds for Research?

It is possible to publish papers without any external funding; observational research and experimental research with small sample size can be conducted without external funding and can result in meaningful papers like case reports, case series, observational study, or small experimental study. However, when studies like multi-centric studies, randomized controlled trial, experimental study or observational study with large sample size are envisaged, it may not be possible to conduct the study within the resources of department or institution and a source of external funding is required.

Basic Requirements for Research Funding

The most important requirement is having an interest in the particular subject, thorough knowledge of the subject, and finding out the gap in the knowledge. The second requirement is to know whether your research can be completed with internal resources or requires external funding. The next step is finding out the funding agencies which provide funds for your subject, preparing research grant and submitting the research grant on time.

What Are the Sources of Research Funding? – Details of Funding Agencies

Many local, national, and international funding bodies can provide grants necessary for research. However, the priorities for different funding agencies on type of research may vary and this needs to be kept in mind while planning a grant proposal. Apart from this, different funding agencies

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have different timelines for proposal submission and limitation on funds. Details about funding bodies have been tabulated in Table 1. These details are only indicative and not comprehensive.

Application for the Research Grant

Applying for a research grant is a time-consuming but rewarding task. It not only provides an opportunity for

Table 1: Details of funding agencies

Funding agency	Timeline	Key thrust areas
	Local	
Institute	Variable, depends on institute	Not defined, mostly student research
University grants commission (UGC)[2]	Any time of year Evaluation in January and July	Retired or working teachers in college and university under section 2(f) and 12 (b) of the UGC act 1956. The list is available on UGC website. Major research project - up to 12 lacs Minor research project - 1 lac
	National	
Indian association of Dermatologist, Venereologist and Leprologist (IADVL)[3]	March - April	Basic sciences, clinical, laboratory based, epidemiological or quality of life studies. Up to Rs. 500,000 per project per Life Member of IADVL and one of the few grants in which private practitioners can also apply. Other grants available from IADVL are Post Graduate thesis grant and L'Oreal research grant.
Indian Council of Medical Research (ICMR)[4]	Oct - Nov	Basic science, communicable and non-communicable disease, nutrition
Short term studentship		To facilitate undergraduate research. Funding is 25,000 per student
Ad-hoc extramural research		Limit is up to 30 lacs per project
Task force research project		Multicentric projects
Financial support for thesis	Within 12 months of registration of MD	Anti-microbial resistance, tuberculosis, HIV/AIDS, malaria, diabetes, maternal and child health A total assistance of Rs 50,000/- will be given
Department of science and technology[5]		
Core research grant (extramural research grant)	Apr - May Notification on serbonline.in	Lifesciences
Early career research award	Notification on serbonline. in	Lifesciences. Maximum funding is 50 lacs per proposal Upper age limit is 37 years
Department of biotechnology[6]	Notification on dbtindia. gov. in	Vaccine research, nutrition and public health, stem cells and regenerative medicine, infectious and chronic disease biology
Council of scientific and industrial research (CSIR)[7]	Anytime of the year Evaluation twice a year	Project in collaboration with CSIR institutes are given priority
Defence Research and Development Organisation (DRDO) (Life sciences research board)[8]	Any time of year	Project of national/defence interest Call for proposal specify the key thrust areas
Department of Health Research (DHR) _ Grant aid scheme[9]	Any time of the year	Public health Translational research project Cost- effectiveness analysis of health technologies
	International	
National psoriasis foundation (NPF)[10]	Call for proposal available on website	Various research grants are available for psoriasis and includes: Psoriasis prevention initiative, milestone to a cure, Discovery, Translational, Early career research grant and Bridge grants
National Institute of Health (NIH)[11]	Call for proposal available online	Limited research grants applicable to researcher outside USA
	NGO	
Leo foundation[12]	Call for proposal available on website	Improve the understanding of the underlying medicinal, biological, chemical, or pharmacological mechanisms of dermatological diseases and their symptoms

designing a good study but also allows one to understand the administrative aspect of conducting research. In a publication, the peer review is done after the paper is submitted but in a research grant, peer review is done at the time of proposal, which helps the researcher to improve his study design even if the grant proposal is not successful. Funds which are available for research is generally limited; resulting in reviewing of a research grant on its merit by peer group before the proposal is approved. It is important to be on the lookout for call for proposal and deadlines for various grants. Ideally, the draft research proposal should be ready much before the call for proposal and every step should be meticulously planned to avoid rush just before the deadline. The steps of applying for a research grant are mentioned below and every step is essential but may not be conducted in a particular order.

1. Idea: The most important aspect of research is the idea. After having the idea in mind, it is important to refine your idea by going through literature and finding out what has already been done in the subject and what are the gaps in the research. FINER framework should be used while framing research questions. FINER stands for feasibility, interesting, novel, ethical, and relevant
2. Designing the study: Well-designed study is the first step of a well-executed research project. It is difficult to correct flawed study design when the project is advanced, hence it should be planned well and discussed with co-workers. The help of an expert epidemiologist can be sought while designing the study
3. Collaboration: The facility to conduct the study within the department is often limited. Inter-departmental and inter-institutional collaboration is the key to perform good research. The quality of project improves by having a subject expert onboard and it also makes acceptance of grant easier. The availability of the facility for conduct of research in department and institution should be ascertained before planning the project
4. Scientific and ethical committee approval: Most of the research grants require the project to be approved by the institutional ethical committee (IEC) before the project is submitted. IEC meeting usually happens once in a quarter; hence pre-planning the project is essential. Some institutes also conduct scientific committee meeting before the proposal can be submitted for funding. A project/study which is unscientific is not ethical, therefore it is a must that a research proposal should pass both the committees' scrutiny
5. Writing research grant: Writing a good research grant decides whether research funding can be secured or not. So, we will discuss this part in detail.

How to write a research grant proposal[13-15] The steps in writing a research grant are as follows

1. Identifying the idea and designing the study. Study design should include details about type of study, methodology, sampling, blinding, inclusion and exclusion criteria, outcome measurements, and statistical analysis
2. Identifying the prospective grants—the timing of application, specific requirements of grant and budget available in the grant
3. Discussing with collaborators (co-investigators) about the requirement of consumables and equipment
4. Preparing a budget proposal—the two most important part of any research proposal is methodology and budget proposal. It will be discussed separately
5. Preparing a specific proposal as outlined in the grant document. This should contain details about the study including brief review of literature, why do you want to conduct this study, and what are the implications of the study, budget requirement, and timeline of the study
6. A timeline or Gantt chart should always accompany any research proposal. This gives an idea about the major milestones of the project and how the project will be executed
7. The researcher should also be ready for revising the grant proposal. After going through the initial proposal, committee members may suggest some changes in methodology and budgetary outlay
8. The committee which scrutinizes grant proposal may be composed of varied specialities. Hence, proposal should be written in a language which even layman can understand. It is also a good idea to get the proposal peer reviewed before submission.

Budgeting for the Research Grant

Budgeting is as important as the methodology for grant proposal. The first step is to find out what is the monetary limit for grant proposal and what are the fund requirements for your project. If these do not match, even a good project may be rejected based on budgetary limitations. The budgetary layout should be prepared with prudence and only the amount necessary for the conduct of research should be asked. Administrative cost to conduct the research project should also be included in the proposal. The administrative cost varies depending on the type of research project.

Research fund can generally be used for the following requirement but not limited to these; it is helpful to know the subheads under which budgetary planning is done. The funds are generally allotted in a graded manner as per projected requirement and to the institution, not to the researcher.

1. Purchase of equipment which is not available in an institution (some funding bodies do not allow equipment to be procured out of research funds). The equipment once procured out of any research fund is owned by the institute/department

2. Consumables required for the conduct of research (consumables like medicines for the conduct of the investigator-initiated trials and laboratory consumables)
3. The hiring of trained personnel—research assistant, data entry operator for smooth conduct of research. The remuneration details of trained personnel can be obtained from the Indian Council of Medical Research (ICMR) website and the same can be used while planning the budget
4. Stationary—for the printing of forms and similar expense
5. Travel expense—If the researcher has to travel to present his finding or for some other reason necessary for the conduct of research, travel grant can be part of the research grant
6. Publication expense: Some research bodies provide publication expense which can help the author make his findings open access which allows wider visibility to research
7. Contingency: Miscellaneous expenditure during the conduct of research can be included in this head
8. Miscellaneous expenses may include expense toward auditing the fund account, and other essential expenses which may be included in this head.

Once the research funding is granted. The fund allotted has to be expended as planned under budgetary planning. Transparency, integrity, fairness, and competition are the cornerstones of public procurement and should be remembered while spending grant money. The hiring of trained staff on contract is also based on similar principles and details of procurement and hiring can be read at the ICMR website.[4] During the conduct of the study, many of grant guidelines mandate quarterly or half-yearly progress report of the project. This includes expense on budgetary layout and scientific progress of the project. These reports should be prepared and sent on time.

Completion of a Research Project

Once the research project is completed, the completion report has to be sent to the funding agency. Most funding agencies also require period progress report and project should ideally progress as per Gantt chart. The completion report has two parts. The first part includes a scientific report which is like writing a research paper and should include all subheads (Review of literature, material and methods, results, conclusion including implications of research). The second part is an expense report including how money was spent, was it according to budgetary layout or there was any deviation, and reasons for the deviation. Any unutilized fund has to be returned to the funding agency. Ideally, the allotted fund should be post audited by a professional (chartered accountant) and an audit report along with original bills of expenditure should be preserved for future use in case of any discrepancy. This is an essential part of any funded project that prevents the researcher from getting embroiled in any accusations of impropriety.

Sharing of scientific findings and thus help in scientific advancement is the ultimate goal of any research project. Publication of findings is the part of any research grant and many funding agencies have certain restrictions on publications and presentation of the project completed out of research funds. For example, Indian Association of Dermatologists, Venereologists and Leprologists (IADVL) research projects on completion have to be presented in a national conference and the same is true for most funding agencies. It is imperative that during presentation and publication, researcher mentions the source of funding.

Conclusion

Research funding is an essential part of conducting research. To be able to secure a research grant is a matter of prestige for a researcher and it also helps in the advancement of career.

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Conflicts of interest

There are no conflicts of interest.

References

1. Grant Proposals (or Give me the money!) – The Writing Center • University of North Carolina at Chapel Hill [Internet]. Available from: https://writingcenter.unc.edu/tips-and-tools/grant-proposals-or-give-me-the-money/. [Last cited on 2020 Jul 27].
2. UGC: Major Research Project (MRP) [Internet]. Available from: https://www.ugc.ac.in/mrp/. [Last cited on 2020 Jul 27].
3. IADVL - Indian Association of Dermatologists, Venereologists and Leprologists [Internet]. Available from:https://www.iadvl.org/. [Last cited 2020 Jul 27].
4. Indian Council of Medical Research [Internet]. Available from: http://icmrextramural.in/ICMR/. [Last cited on 2020 Jul 27].
5. Department Of Science & Technology [Internet]. [cited 2020 Dec 23]. Available from: https://dst.gov.in/. [Last cited on 2020 Jul 27].
6. Department of Biotechnology [Internet]. Available from: http://dbtindia.gov.in/. [Last cited on 2020 Jul 27].
7. Council of Scientific & Industrial Research | CSIR | GoI [Internet]. Available from: https://www.csir.res.in/. [Last cited on 2020 Jul 27].
8. Submission of Project Proposal | Defence Research and Development Organisation-DRDO | GoI [Internet]. Available from: https://www.drdo.gov.in/aeronautics-research-development/rules-grants-introductions. [Last cited on 2020 Jul 27].
9. Council of Scientific & Industrial Research | CSIR | GoI [Internet]. Available from: https://www.csir.res.in/. [Last cited on 2020 Jul 27].
10. The *p* is silent, but we are not! | National Psoriasis Foundation [Internet]. Available from: https://www.psoriasis.org/research/portfolio. [Last cited on 2020 Jul 27].

11. Grants & Funding | National Institutes of Health (NIH) [Internet]. Available from: https://www.nih.gov/grants-funding. [Last cited on 2020 Jul 27].
12. Apply for a grant-LEO Foundation [Internet]. Available from: https://leo-foundation.org/en/research-grants-awards/apply-for-a-grant/. [Last cited on 2020 Jul 27].
13. Wescott L, Laskofski M, Senator D, Curran C. Grant writing tips for translational research. Methods Mol Biol 2017;1606:367-78.
14. Liu JC, Pynnonen MA, St John M, Rosenthal EL, Couch ME, Schmalbach CE. Grant-writing pearls and pitfalls: Maximizing funding opportunities. Otolaryngol Head Neck Surg 2016;154:226-32.
15. Cuschieri S, Schembri-Wismayer P, Grech V. WASP (Write a Scientific Paper): Writing a research grant-2, drafting the proposal. Early Hum Dev 2018;127:109-11.

Practical Guidelines to Develop and Evaluate a Questionnaire

Abstract

Life expectancy is gradually increasing due to continuously improving medical and nonmedical interventions. The increasing life expectancy is desirable but brings in issues such as impairment of quality of life, disease perception, cognitive health, and mental health. Thus, questionnaire building and data collection through the questionnaires have become an active area of research. However, questionnaire development can be challenging and suboptimal in the absence of careful planning and user-friendly literature guide. Keeping in mind the intricacies of constructing a questionnaire, researchers need to carefully plan, document, and follow systematic steps to build a reliable and valid questionnaire. Additionally, questionnaire development is technical, jargon-filled, and is not a part of most of the graduate and postgraduate training. Therefore, this article is an attempt to initiate an understanding of the complexities of the questionnaire fundamentals, technical challenges, and sequential flow of steps to build a reliable and valid questionnaire.

Keywords: *Instrument, psychometrics, questionnaire development, reliability, scale construction, validity*

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Introduction

There is an increase in the usage of the questionnaires to understand and measure patients' perception of medical and nonmedical care. Recently, with increased interest in quality of life associated with chronic diseases, there is a surge in the usage and types of questionnaires. The questionnaires are also known as scales and instruments. Their significant advantage is that they capture information about unobservable characteristics such as attitude, belief, intention, or behavior. The multiple items measuring specific domains of interest are required to obtain hidden (latent) information from participants. However, the importance of questions or items needs to be validated and evaluated individually and holistically.

The item formulation is an integral part of the scale construction. The literature consists of many approaches, such as Thurstone, Rasch, Gutmann, or Likert methods for framing an item. The Thurstone scale is labor intensive, time-consuming, and is practically not better than the Likert scale.[1] In the Guttman method, cumulative attributes of the respondents are measured with a group of items framed from the "easiest" to the "most difficult." For example, for a stem, a participant may have to choose from options (a) stand, (b) walk, (c) jog, and (d) run. It requires a strict ordering of items. The Rasch method adds the stochastic component to the Guttman method which lay the foundation of modern and powerful technique item response theory for scale construction. All the approaches have their fair share of advantages and disadvantages. However, Likert scales based on classical testing theory are widely established and preferred by researchers to capture intrinsic characteristics. Therefore, in this article, we will discuss only psychometric properties required to build a Likert scale.

A hallmark of scientific research is that it needs to meet rigorous scientific standards. A questionnaire evaluates characteristics whose value can significantly change with time, place, and person. The error variance, along with systematic variation, plays a significant part in ascertaining unobservable characteristics. Therefore, it is critical to evaluate the instruments testing human traits rigorously. Such evaluations are known as psychometric evaluations in context to questionnaire development and

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validation. The scientific standards are available to select items, subscales, and entire scales. The researchers can broadly segment scientific criteria for a questionnaire into reliability and validity.

Despite increasing usage, many academicians grossly misunderstand the scales. The other complication is that many authors in the past did not adhere to the rigorous standards. Thus, the questionnaire-based research was criticized by many in the past for being a soft science.[2] The scale construction is also not a part of most of the graduate and postgraduate training. Given the previous discussion, the primary objective of this article is to sensitize researchers about the various intricacies and importance of each step for scale construction. The emphasis is also to make researcher aware and motivate to use multiple metrics to assess psychometric properties. Table 1 describes a glossary of essential terminologies used in context to questionnaire.

The process of building a questionnaire starts with item generation, followed by questionnaire development, and concludes with rigorous scientific evaluation. Figure 1 summarizes the systematic steps and respective tasks at each stage to build a good questionnaire. There are specific essential requirements which are not directly a part of scale development and evaluation; however,

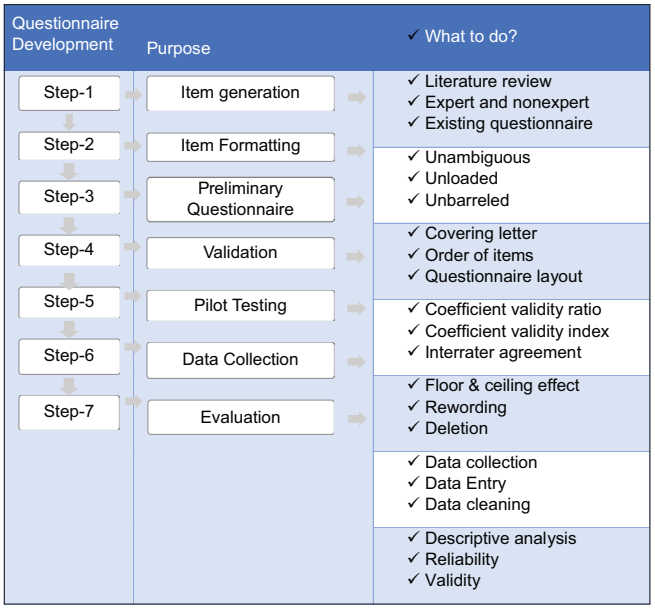

Figure 1: Flowchart demonstrating the various steps involved in the development of a questionnaire

Table 1: Glossary of important terms used in context to psychometric scale

Term	Definition
Psychometrics	A science which deals with the quantitative assessment of abilities that are not directly observable, e.g., confidence, intelligence
Reliability	Refer to the degree of consistency of instrument in measurements, e.g., is weighing machine giving similar results under consistent conditions?
Validity	Refer to the ability of an instrument to represent the intended measure correctly, e.g., is weighing machine giving accurate results?
Likert scale	A psychometric scale consists of multiple items that arrived through a systematic evaluation of reliability and validity, e.g., quality-of-life score
Likert Item	It is a statement with a fixed set of choices to express an opinion with the level of agreement or disagreement
Latent variable	Represent a concept or underlying construct which cannot be measured directly. Latent variables are also known as unobserved variables, e.g., health and socioeconomic status
Manifest variable	A variable which can be measured directly. Manifest variables are also known as observed variables, e.g., blood pressure and income
Double-barrel item	A question addressing two or more separate issues but provides an option for one answer, e.g., do you like the house and locality?
Negative item	It is an item which is in the opposite direction from most of the questions on a scale
Factor loadings	Demonstrate the correlation coefficient between the observed variable and factor. It quantifies the strength of the relationship between a latent variable (factor) and manifest variables. It is key to understand the relative importance of items in the final questionnaire. An item with high factor loading is more important than others
Cross-loading	An observed variable with loading more than threshold value on two or more factors, e.g., education level with value >0.35 for both teaching and research domains. The items with cross-loadings are candidates for deletion from a questionnaire
Reverse scoring	The practice of reversing the score to cancel positive and negative loading on the same factor, e.g., changing the maximum rating (such as strongly agree=5) to a minimum (such as strongly agree=1) or vice versa
Floor and ceiling effect	The inability of a scale to discriminate between participants in a study as the high proportion of participants score worst/minimum or best/maximum score, e.g., more than 80% responses are received by single option among the five options for a Likert item. Item is poorly discriminating between participants and is a candidate for deletion
Eigenvalue	An indicator of the amount of variance explained by a factor. The factor with the highest eigenvalue explains the maximum amount of variance and practically makes a factor most important. The eigenvalue is obtained by column sum of squares of factor loading

these improve the utility of the instrument. The indirect but necessary conditions are documented and discussed under the miscellaneous category. We broadly segment and discuss the questionnaire development process under three domains, known as questionnaire development, questionnaire evaluation, and miscellaneous properties.

Questionnaire Development

The development of the list of items is an essential and mandatory prerequisite for developing a good questionnaire. The researcher at this stage decides to utilize formats such as Guttman, Rasch, or Likert to frame items.[2] Further, the researcher carefully identifies the appropriate member of the expert panel group for face and content validity. Broadly, there are six steps in the scale development.

Step I

It is crucial to select appropriate questions (items) to capture the latent trait. An exhaustive list of items is the most critical and primary requisite to lay the foundation of a good questionnaire. It needs considerable work in terms of literature search, qualitative study, discussion with colleagues, other experts, general and targeted responders, and other questionnaires in and around the area of interest. General and targeted participants can also advise on items, wording, and smoothness of questionnaire as they will be the potential responders.

Step II

It is crucial to arrange and reword the pool of questions for eliminating ambiguity, technical jargon, and loading. Further, one should avoid using double-barreled, long, and negatively worded questions. Arrange all items systematically to form a preliminary draft of the questionnaire. After generating an initial draft, review the instrument for the flow of items, face validity and content validity before sending it to experts. The researcher needs to assess whether the items in the score are comprehensive (content validity) and appear to measure what it is supposed to measure (face validity). For example, does the scale measuring stress is measuring stress or is it measuring depression instead? There is no uniformity on the selection of a panel of experts. However, a general agreement is to use anywhere from a minimum of 5–15 experts in a group.[3] These experts will ascertain the face and content validity of the questionnaire. These are subjective and objective measures of validity, respectively.

Step III

It is advisable to prepare an appealing, jargon-free, and nontechnical cover letter explaining the purpose and description of the instrument. Further, it is better to include the reason/s for selecting the expert, scoring format, and explanations of response categories for the scale. It is advantageous to speak with experts telephonically, face to face, or electronically, requesting their participation before mailing the questionnaire. It is good to explain to them right in the beginning that this process unfolds over phases. The time allowed to respond can vary from hours to weeks. It is recommended to give at least 7 days to respond. However, a nonresponse needs to be followed up by a reminder email or call. Usually, this stage takes two to three rounds. Therefore, it is essential to engage with experts regularly; else there is a risk of nonresponse from the study. Table 2 gives general advice to researchers for making a cover letter. The researcher can modify the cover letter appropriately for their studies. The authors can consult Rubio and coauthors for more details regarding the drafting of a cover letter.[4]

Step IV

The responses from each round will help in rewording, rephrasing, and reordering of the items in the scale. Few questions may need deletion in the different rounds of previous steps. Therefore, it is better to evaluate content validity ratio (CVR), content validity index (CVI), and interrater agreement before deleting any question in the instrument. Readers can consult formulae in Table 2 for calculating CVR and CVI for the instrument. CVR is calculated and reported for the overall scale, whereas CVI is computed for each item. Researchers need to consult Lawshe table to determine the cutoff value for CVR as the same depends on the number of experts in the panel.[5] CVI >0.80 is recommended. Researchers interested in detail regarding CVR and CVI can read excellent articles written by Zamanzadeh *et al*. and Rubio *et al*.[4,6] It is crucial to compute CVR, CVI, and kappa agreement for each item from the rating of importance, representativeness, and clarity by experts. The CVR and CVI do not account for a chance factor. Since interrater agreement (IRA) incorporates chance factor; it is better to report CVR, CVI, and IRA measures.

Step V

The scholars require to address subtle issues before administering a questionnaire to responders for pilot testing. The introduction and format of the scale play a crucial role in mitigating doubts and maximizing response. The front page of the questionnaire provides an overview of the research without using technical words. Further, it includes roles and responsibilities of the participants, contact details of researchers, list of research ethics (such as voluntary participation, confidentiality and withdrawal, risks and benefits), and informed consent for participation in the study. It is also better to incorporate anchors (levels of Likert item) in each page at the top or bottom or both for ease and maximizing response. Readers can refer to Table 3 for detail.

Table 2: General overview and the instructions for rating in the cover letter to be accompanied by the questionnaire

Content	Explanation		
Construct	Definition of characteristics of the measurement		
Purpose	To evaluate the content and face validity		
How	Please rate each item for its representativeness and clarity on a scale from 1 to 4		
	Evaluate the comprehensiveness of the entire instrument in measuring the domain		
	Please add, delete, or modify any item as per your understanding		
Measure	**CVR**	**CVI**	
Characteristics	**Importance**	**Representative**	**Clarity**
Scoring	0-Not necessary	1-Not representative	1-Not clear
	1-Useful	2-Need major revisions to be representative	2-Need major revisions to be clear
	2-Essential	3-Need minor revisions to be representative	3-Need minor revisions to be clear
		4-Representative	4-Clear
Formula	$CVR = (N_E\text{-}N/2)/(N/2)$	$CVI_R=N_R/N$	$CVI_C=N_C/N$
	where N_E=number of experts rated an item as essential	where CVI_R=CVI for representativeness	where CVI_C=CVI for clarity
	N=Total number of experts	N_R=Number of experts rated an item as representative (3 or 4)	N_C=Number of experts rated an item as clear (3 or 4)
		N=Total number of experts	N=Total number of experts

Table 3: A random set of questions with anchors at the top and bottom row

Items	Strongly disagree (SD)	Disagree (D)	Neutral (N)	Agree (A)	Strongly agree (SA)
Duration of disease (since onset)	SD	D	N	A	SA
Number of relapse(s) of the disease	SD	D	N	A	SA
Duration of oral erosions (present episode)	SD	D	N	A	SA
Number of relapse(s) of oral lesions	SD	D	N	A	SA
Persistence of oral lesions after subsidence of cutaneous lesions	SD	D	N	A	SA
Change in size of existing lesion in last 1 week	SD	D	N	A	SA
Development of new lesions in last 1 week	SD	D	N	A	SA
Difficulty in eating normal food	SD	D	N	A	SA
Difficulty in eating food according to their consistency	SD	D	N	A	SA
Inability to eat spicy food	SD	D	N	A	SA
Inability to drink fruit juices	SD	D	N	A	SA
Excessive salivation/drooling	SD	D	N	A	SA
Difficulty in speaking	SD	D	N	A	SA
Difficulty in brushing teeth	SD	D	N	A	SA
Difficulty in swallowing	SD	D	N	A	SA
Restricted mouth opening	SD	D	N	A	SA
	Strongly disagree	Disagree	Neutral	Agree	Strongly agree

Step VI

Pilot testing of an instrument in the target population is an important and essential requirement before testing on a large sample of individuals. It helps in the elimination or revision of poorly worded items. At this stage, it is better to use floor and ceiling effects to eliminate poorly discriminating items. Further, random interviews of 5–10 participants can help to mitigate the problems such as difficulty, relevance, confusion, and order of the questions before testing it on the study population. The general recommendations are to recruit a sample size between 30 and 100 for pilot testing.[4] Inter-question (item) correlation (IQC) and Cronbach's α can be assessed at this stage. The values less than 0.3 and 0.7, respectively, for IQC and reliability, are suspicious and candidate for elimination from the questionnaire. Cronbach's α, a measure of internal consistency and IQC of a scale, indicates researcher about the quality of items in measuring latent attribute at the initial stage. This process is important to refine and finalize the questionnaire before starting the testing of a questionnaire in study participants.

Questionnaire Evaluation

The preliminary items and the questionnaire until this stage have addressed issues of reliability, validity, and overall appeal in the target population. However, researchers need to rigorously evaluate the psychometric properties of the primary instrument before finally adopting. The first step

in this process is to calculate the appropriate sample size for administering a preliminary questionnaire in the target group. The evaluations of various measures do not follow a sequential order like the previous stage. Nevertheless, these measures are critical to evaluate the reliability and validity of the questionnaire.

Data entry

Correct data entry is the first requirement to evaluate the characteristics of a manually administered questionnaire. The primary need is to enter the data into an appropriate spreadsheet. Subsequently, clean the data for cosmetic and logical errors. Finally, prepare a master sheet, and data dictionary for analysis and reference to coding, respectively. Authors interested in more detail can read "Biostatistics Series."[7,8] The data entry process of the questionnaire is like other cross-sectional study designs. The rows and columns represent participants and variables, respectively. It is better to enter the set of items with item numbers. First, it is tedious and time-consuming to find suitable variable names for many questions. Second, item numbers help in quick identification of significantly contributing and non-contributing items of the scale during the assessment of psychometric properties. Readers can see Table 4 for more detail.

Table 4: A sample of data entry format

(a) Illustration of master sheet

Participant	Age	Religion	Family	Height	Weight	Q1	Q2	Q3
1	25	1	1	185.0	85.0	1	5	2
2	26	3	1	155.0	63.0	2	5	1
3	22	2	2	155.0	57.0	4	2	1
4	35	2	1	158.5	67.5	3	2	2
5	49	1	2	175.0	64.0	2	4	3
6	40	4	1	159.0	78.0	2	4	3

Q*i*→*i*th Question in the questionnaire, where *i*=1,2,3, … *n*

(b) Illustration of coding sheet

Variable label	Description	Coding and valid range	Measurement scale
Participant	A random serial number to participant	None	String
Age	Age in years	None (30-70 years)	Interval
Religion	Religion of the participant	1=Hindu 2=Sikh 3=Muslim 4=Others	Nominal
Q	Level of agreement in the question	1=Strongly disagree 2=Disagree 3=Neutral 4=Agree 5=Strongly agree	Ordinal

Descriptive statistics

Spreadsheets are easy and flexible for routine data entry and cleaning. However, the same lack the features of advanced statistical analysis. Therefore, the master sheet needs to be exported to appropriate software for advanced statistical analysis. Descriptive analysis is the usual first step which helps in understanding the fundamental characteristics of the data. Thus, report appropriate descriptive measures such as mean and standard deviation, and median and interquartile/interdecile range for continuous symmetric and asymmetric data, respectively.[9] Utilize exploratory tabular and graphical display to inspect the distribution of various items in the questionnaire. A stacked bar chart is a handy tool to investigate the distribution of data graphically. Further, ascertain linearity and lack of extreme multicollinearity at this stage. Any value of IQC >0.7 warrants further inspection for deletion or modification. Help from a good biostatistician is of great assistance for data analysis and reporting.

Missing data analysis

Missing data is the rule, not the exception. Majority of the researchers face difficulties of finding missing values in the data. There are usually three approaches to analyze incomplete data. The first approach is to "take all" which use all the available data for analysis. In the second method, the analyst deletes the participants and variables with gross missingness or both from the analysis process. The third scenario consists of estimating the percentage and type of missingness. The typically recommended threshold for the missingness is 5%.[10] There are broadly three types of missingness, such as missing completely at random, missing at random, and not missing at random. After identification of a missing mechanism, impute the data with single or multiple imputation approaches. Readers can refer to an excellent article written by Graham for more details about missing data.[11]

Sample size

The optimum sample size is a vital requisite to build a good questionnaire. There are many guidelines in the literature regarding recruiting an appropriate sample size. Literature broadly segments sample size approaches into three domains known as subject to variables ratio (SVR), minimum sample size, and factor loadings (FL). The factor analysis (FA) is a crucial component of questionnaire designing. Therefore, recent recommendations are to use FLs to determine sample size. Readers can consult Table 5 for sample size recommendations under various domains. Interested readers can refer to Beavers and colleagues for more detail.[12] The stability of the factors is essential to determine sample size. Therefore, data analysis from questionnaires validates the sample size

Table 5: Sample size recommendations in the literature

Sample size criteria		
Subject to variables ratio	**Minimum sample size**	**Factor loading**
Minimum 100 participants + SVR ≥5	At least 300 participants	At least 4 items with FL >0.60 (minimum 100 participants)
51 participants + number of variables	At least 200 participants	At least 10 items with FL >0.40 (minimum 150 participants)
At least SVR >5	At least 150-300 participants	Items with 0.30 ≤ FL ≤0.40 (minimum 300 participants)

SVR→Subject to variable ratio, FL→Factor loading

after data collection. The Kaiser–Meyer–Olkin (KMO) criterion testing the adequacy of sample size is available in the majority of the statistical software packages. A higher value of KMO is an indicator of sufficient sample size for stable factor solution.

Correlation measures

The strength of relationships between the items is an imperative requisite for a stable factor solution. Therefore, the correlation matrix is calculated and ascertained for same. There are various recommendations of correlation coefficient; however, a value greater than 0.3 is a must.[13] A lower value of the correlation coefficient will fail to form a stable factor due to lack of commonality. The determinant and Bartlett's test of sphericity can be used to ascertain the stability of the factors. The determinant is a single value which ranges from zero to one. A nonzero determinant indicates that factors are possible. However, it is small in most of the studies and not easy to interpret. Therefore, Bartlett's test of sphericity is routinely used to infer that determinant is significantly different than zero.

Validity

Physical quantities such as height and weight are observable and measurable with instruments. However, many tools need regular calibration to be precise and accurate. The standardization in context to the questionnaire development is known as reliability and validity. The validity is the property which indicates that an instrument is measuring what it is supposed to measure. Validation is a continuous process which begins with the identification of domains and goes on till generalization. There are various measures to establish the validity of the instrument. Authors can consult Table 6 for different types of validity and their metrics.

Exploratory FA

FA assumes that there are underlying constructs (factors) which cannot be measured directly. Therefore, the investigator collects the exhaustive list of observed variables or responses representing underlying constructs. Researchers expect that variables or questions in the questionnaire correlate among themselves and load on the corresponding but a small number of factors. FA can be broadly segmented in exploratory factor analysis (EFA) and confirmatory factor analysis. The EFA is applied on the master sheet after assessing descriptive statistics such as tabular and graphical display, missing mechanism, sample size adequacy, IQC, and Bartlett's test in step 7 [Figure 1]. The value of EFA is used at the initial stages to extract factors while constructing a questionnaire. It is especially important to identify an adequate number of factors for building a decent scale. The factors represent latent variables that explain variance in the observed data. First and the last factor explain maximum and minimum variance, respectively. There are multiple factor selection criteria, each with its advantages and disadvantages. It is better to utilize more than one approach for retaining factors during the initial extraction phase. Readers can consult Sindhuja *et al*. for the practical application of more than one-factor selection criteria.[14]

Kaiser's criterion

Kaiser's criterion is one of the most popular factor retention criteria. The basis of the Kaiser criterion is to explain the variance through the eigenvalue approach. A factor with more than one eigenvalue is the candidate for retention.[15] An eigenvalue bigger than one simply means that a single factor is explaining variance for more than one observed variable. However, there is a dearth of scientifically rigorous studies to declare a cutoff value for Kaiser's criterion. Many authors highlighted that the Kaiser criterion over-extract and under-extract factors.[16,17] Therefore, investigators need to calculate and consider other measures for extraction of factors.

Cattell's scree plot

Cattell's scree plot is another widespread eigenvalue-based factor selection criterion used by researchers. It is popularly known as scree plot. The scree plot assigns the eigenvalues on the *y*-axis against the number of factors in the *x*-axis. The factors with highest to lowest eigenvalues are plotted from left to right on the *x*-axis. Usually, the scree plots form an elbow which indicates the cutoff point for factor extraction. The location or the bend at which the curve first begins to straighten out indicates the maximum number of factors to retain. A significant disadvantage of the scree plot is the subjectivity of the researcher's perception of the "elbow" in the plot. Researchers can see Figure 2 for detail.

Percentage of variance

The variance extraction criterion is another criterion to retain the number of factors. The literature recommendation varies from more than a minimum of 50–70% onward.[12] However, both the number of items and factors

Table 6: Scientific standards to evaluate and report for constructing a good scale

Psychometric properties	Component	Definition	Indices
Validity	Content validity	The items are addressing all the relevant aspect of construct	Content validity ratio Content validity indices Interrater agreement
	Face validity	The test appears to measure the intended measure	Expert opinion (qualitative)
	Construct validity	The strong (r_s) and weak (r_w) correlation between same and different construct, respectively	Exploratory factor analysis Correlation coefficient
	Criterion validity	The correlation between a predictor measure (teamwork) and criterion measures (actual performance in team)	Correlation coefficient
	Convergent validity	The correlation between a scale and conceptually similar scales or subscales of a scale	Correlation coefficient Multitrait-multimethod matrix
Reliability	Internal consistency	The cohesiveness of items in measuring the same variable consistently	Coefficient α Coefficient β Coefficient Ω
	Test-retest	Consistency of score for stable characteristics on separate times	Correlation coefficient Intra-class correlation coefficient
	Alternate forms	Consistency of scores among the same sample for similar tests	Correlation coefficient
Descriptive analysis	Tabular display	Display of essential data characteristics in rows and columns	Mean (SD) Median (IQR)
	Graphical display	Visual display of large data to exhibit trends, patterns, and relationships	Box plot Bar graph
Missing mechanism	MCAR	Missing data is independent of observed or unobserved data	Little's MCAR
	MAR	Missing data is related to observed but not unobserved data	Listing and Schlittgen (LS) test
	NMAR	Missing data is related to unobserved data	No standard test (based on assumptions)
Factorability	Sample size	Minimum number of participants required to measure study outcomes	KMO criteria
	Correlation matrix	A matrix displaying the inter-correlations among the variables	Determinant
	Sphericity	Refers to equality of correlations between different items	Bartlett's test

MCAR: Missing completely at random; MAR: Missing at random; NMAR: Not missing at random; KMO: Kaiser-Meyer-Olkin; SD: Standard deviation; IQR: Interquartile range

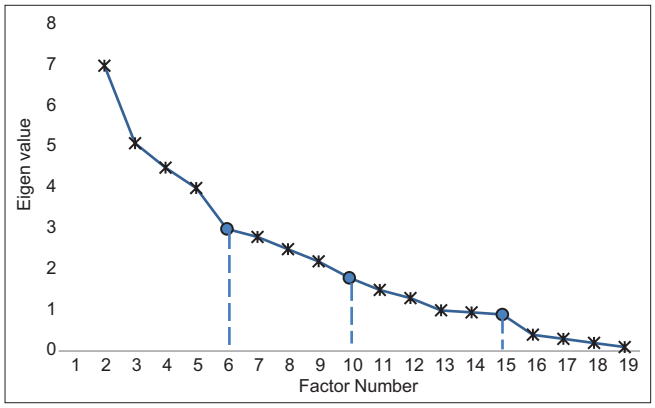

Figure 2: A hypothetical example showing the researcher's dilemma of selecting 6, 10, or 15 factors through scree plot

will increase dramatically if there are a large number of manifest (observed) variables. Practically, the percentage of variance explained mechanism should be used judiciously along with FL. The FLs with greater than 0.4 value are preferred; however, there are recommendations to use a value higher than 0.30.[3,15,18]

Very simple structure

Very simple structure (VSS) approach is a symbiosis of theory, psychometrics, and statistical analysis. The VSS criterion compares the fit of the simplified model to the original correlations. It plots the goodness-of-fit value as a function of several factors rather than statistical significance. The number of factors that maximizes the VSS criterion suggests the optimal number of factors to extract. VSS criterion facilitates comparison of a different number of factors for varying complexity. VSS will be highest at the optimum number of factors.[19] However, it is not efficient for factorially complex data.

Parallel analysis

Parallel analysis (PA) is a statistical theory-based robust technique to identify the appropriate number of factors. It

is the only technique which accounts for the probability that a factor is due to chance. PA simulates data to generate 95th percentile cutoff line on a scree plot restricted upon the number of items and sample size in original data. The factors above the cutoff line are not due to chance. PA is the most robust empirical technique to retain the appropriate number of factors.[16,20] However, it should be used cautiously for the eigenvalue near the 95th percentile cutoff line. PA is also robust to distributional assumptions of the data. Since different techniques have their fair share of advantages and disadvantages, researchers need to assess information on the basis of multiple criteria.

Reliability

Reliability, an essential requisite of a scale, is also known as reproducibility, repeatability, and consistency. It identifies that the instrument is consistently measuring the attribute under identical conditions. Reliability is a necessary characteristic of a tool. The trustworthiness of a scale can be increased by increasing and decreasing the systematic and random component, respectively. The reliability of an instrument can be further segmented and measured with various indices. Reliability is important but it is secondary to validity. Therefore, it is ideal to calculate and report reliability after validity. However, there are no hard and fast rules except that both are necessary and important measures. Readers may consult Table 6 for multiple types of indices for reliability.

Internal consistency

Cronbach's alpha (α), also known as α-coefficient, is one of the most used statistics to report internal consistency reliability. The internal consistency using the interitem correlations suggests the cohesiveness of items in a questionnaire. However, the α-coefficient is sample-specific; thus, the literature recommends the same to calculate and report for all the studies. Ideally, a value of α >0.70 is preferred; however, the value of α >0.60 is also accepted for construction of new scale.[21,22] Researchers can increase the α-coefficient by adding items in the scale. However, a value can either reduce with the addition of non-correlated items or deletion of correlated items. Corrected interitem correlation is another popular measure to report for internal consistency. A value of α <0.3 indicates the presence of nonrelated items. The studies claim that coefficient beta (β) and omega (Ω) are better indices than coefficient-α, but there is a scarcity of literature reporting these indices.[23]

Test–retest

Test–retest reliability measures the stability of an instrument over time. In other words, it measures the consistency of scores over time. However, the appropriate time between repeated measures is a debatable issue. Pearson's product-moment and intraclass correlation coefficient measure and report test–retest reliability. A high value of correlation >0.70 represents high reliability.[21] The change in study condition (recovery of patients after intervention) over time can decrease test–retest reliability. Therefore, it is important to report the time between repeated measures while reporting test–retest reliability.

Parallel forms and split-half reliability

Parallel form reliability is also known as an alternate form of consistency. There are two types of option to report parallel form reliability. In the first method, different but similar items make alternative forms of the test. The assumptions of both the assessment are that they measure the same phenomenon or underlying construct. It addresses the twin issues of time and knowledge acquisition of test in test–retest reliability. In the second approach, the researcher randomly divides the total items of an instrument into two halves. The calculation of parallel form from two halves is known as split-half reliability. However, randomly divided half may not be similar. The parallel from and split-half reliability are reported with the correlation coefficient. The recommendations are to use a value higher than 0.80 to assess the alternate form of consistency.[24] It is challenging to generate two types of tests in clinical studies. Therefore, researchers rarely report reliability from two analogous but separate tests.

General Questionnaire Properties

The major issues regarding the reliability and validity of scale development have already been discussed. However, there are many other subtle issues for developing a good questionnaire. These delicate issues may vary from a choice of Likert items, length of the instrument, cover letter, web or internet mode of data collection, and weighting of scale. The immediately preceding issues demand careful deliberation and attention from the researcher. Therefore, the researcher should carefully think through all these issues to build a good questionnaire.

Likert items

The Likert items are the fixed choice ordinal items which capture attitude, belief, and various other latent domains. The subsequent step is to rank the questions of the Likert scale for further analysis. The numerals for ranking can either start from 0 or 1. It does not make a difference. The Likert scale is primarily bipolar as opposite ends endorse the contrary idea.[2] These are the type of items which express opinions on a measure from strong disagreement to strong agreement. The adjectival scales are unipolar scale that tends to measure variables like pain intensity (no pain/mild pain/moderate pain/severe pain) in one direction. However, the Likert scale (most likely–least likely) can measure almost any attribute. The Likert scale can either have odd or even categories; however, odd categories are more popular. The number of classifications in the Likert scale can vary from anywhere between 3 and

11,[2] although the scale with 5 and 7 classes have displayed better statistical properties for discriminating between responses.[2,24]

Length of questionnaire

A good questionnaire needs to include many items to capture the construct of interest. Therefore, investigators need to collect as many questions as possible. However, the lengthier scale increases both time and cost. The response rate also decreases with an increase in the length of the questionnaire.[25] Although what is lengthy is debatable and varies from more than 4 pages to 12 pages in various studies,[26] the longer scales increase the false positivity rate.[27]

Translating a questionnaire

Many a time, there are already existing reliable and valid questionnaires for use. However, the expert needs to assess two immediate and important criteria of cultural sensitivity and language of the scale. Many sensitive questions on sexual preferences, political orientations, societal structure, and religion may be open for discussion in certain societies, religions, and cultures, whereas the same may be taboo or receive misreporting in others. The sensitive questions need to be reframed considering regional sentiments and culture in mind. Further, a questionnaire in different language needs to be translated by a minimum of two independent bilingual translators. Similarly, the translated questionnaire needs to be translated back into the original language by a minimum of two independent and different bilingual experts who converted the original questionnaire. The process of converting the original questionnaire to the targeted language and then back to the original language is known as forward and backward translation. The subsequent steps such as expert panel group, pilot testing, reliability, and validity for translating a questionnaire remain the same as in constructing a new scale.

Web-based or paper-based

Broadly, paper and electronic format are the two modes of administering a questionnaire to the participants. Both techniques have advantages and disadvantages. The response rate is a significant issue in self-administered scales. The significant benefits of electronic format are the reduction in cost, time, and data cleaning requirements. In contrast, paper-based administration of questionnaire increases external generalization, paper feel, and no need of internet. As per Greenlaw and Welty, the response rate improves with the availability of both the options to participants. However, cost and time increase in comparison to the usage of electronic format alone.[27]

Item order and weights

There are multiple ways to order an item in a questionnaire. The order of questions becomes more critical for a lengthy questionnaire. There are different opinions about either grouping or mixing the issues in an instrument.[24] Grouping inflates intra-scale correlation, whereas mixing inflates inter-scale correlation.[28] Both the approaches have empirically shown to give similar results for at least 20 or more items. The questions related to a particular domain can be assigned either equal or unequal weights. There are two mechanisms to assign unequal weights in a questionnaire. In the first situation, researchers affix different importance to items. In the second method, the investigators frame more or fewer questions as per the importance of subscales in the scale.

Conclusion

The fundamental triad of science is accuracy, precision, and objectivity. The increasing usage of questionnaires in medical sciences requires rigorous scientific evaluations before finally adopting it for routine use. There are no standard guidelines for questionnaire development, evaluation, and reporting in contrast to guidelines such as CONSORT, PRISMA, and STROBE for treatment development, evaluation, and reporting. In this article, we emphasize on the systematic and structured approach for building a good questionnaire. Failure to meet the questionnaire development standards may lead to biased, unreliable, and inaccurate study finding. Therefore, the general guidelines given in this article can be used to develop and validate an instrument before routine use.

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Conflicts of interest

There are no conflicts of interest.

References

1. Streiner DL, Norman GR, Cairney J. Health Measurement Scales: A Practical Guide to their Development and Use. USA: Oxford University Press; 2015.
2. Chapple ILC. Questionnaire research: An easy option? Br Dent J 2003;195:359.
3. Boateng GO, Neilands TB, Frongillo EA, Melgar-Quiñonez HR, Young SL. Best practices for developing and validating scales for health, social, and behavioral research: A primer. Front Public Health 2018;6:149.
4. Rubio DM, Berg-Weger M, Tebb SS, Lee ES, Rauch S. Objectifying content validity: Conducting a content validity study in social work research. Soc Work Res 2003;27:94–104.
5. Lawshe CH. A quantitative approach to content validity. Pers Pschol 1975;28:563-75.
6. Zamanzadeh V, Ghahramanian A, Rassouli M, Abbaszadeh A, Alavi-Majd H, Nikanfar AR. Design and implementation content validity study: Development of an instrument for measuring patient-centered communication. J Caring Sci 2015;4:165-78.
7. Kishore K, Kapoor R. Statistics corner: Structured data entry. J Postgr Med Educ Res 2019;53:94–7.
8. Kishore K, Kapoor R, Singh A. Statistics corner: Data

cleaning-I. J Postgrad Med Educ Res 2019;53:130–2.
9. Kishore K, Kapoor R. Statistics corner: Reporting descriptive statistics. J Postgrad Med Educ Res 2020;54:66–8.
10. Jakobsen JC, Gluud C, Wetterslev J, Winkel P. When and how should multiple imputation be used for handling missing data in randomised clinical trials–A practical guide with flowcharts. BMC Med Res Methodol 2017;17:162.
11. Graham JW. Missing data analysis: Making it work in the real world. Annu Rev Psychol 2009;60:549–76.
12. Beavers AS, Lounsbury JW, Richards JK, Huck SW. Practical considerations for using exploratory factor analysis in educational research. Pract Assessment Res Eval 2013;18:6.
13. Rattray J, Jones MC. Essential elements of questionnaire design and development. J Clin Nurs 2007;16:234–43.
14. Sindhuja T, De D, Handa S, Goel S, Mahajan R, Kishore K. Pemphigus oral lesions intensity score (POLIS): A novel scoring system for assessment of severity of oral lesions in pemphigus vulgaris. Front Med 2020;7:449.
15. Costello AB, Osborne J. Best practices in exploratory factor analysis: Four recommendations for getting the most from your analysis. Pract assessment Res Eval 2005;10:7.
16. Wood ND, Akloubou Gnonhosou DC, Bowling JW. Combining parallel and exploratory factor analysis in identifying relationship scales in secondary data. Marriage Fam Rev 2015;51:385–95.
17. Yang Y, Xia Y. On the number of factors to retain in exploratory factor analysis for ordered categorical data. Behav Res Methods 2015;47:756–72.
18. Revelle W, Rocklin T. Very simple structure: An alternative procedure for estimating the optimal number of interpretable factors. Multivariate Behav Res 1979;14:403–14.
19. Dinno A. Exploring the sensitivity of Horn's parallel analysis to the distributional form of random data. Multivariate Behav Res 2009;44:362–88.
20. DeVon HA, Block ME, Moyle-Wright P, Ernst DM, Hayden SJ, Lazzara DJ, *et al*. A psychometric toolbox for testing validity and reliability. J Nurs Scholarsh 2007;39:155–64.
21. Straub D, Boudreau MC, Gefen D. Validation guidelines for IS positivist research. Commun Assoc Inf Syst 2004;13:24.
22. Revelle W, Zinbarg RE. Coefficients alpha, beta, omega, and the glb: Comments on Sijtsma. Psychometrika 2009;74:145.
23. Robinson MA. Using multi-item psychometric scales for research and practice in human resource management. Hum Resour Manag 2018;57:739–50.
24. Edwards P, Roberts I, Sandercock P, Frost C. Follow-up by mail in clinical trials: Does questionnaire length matter? Control Clin Trials 2004;25:31–52.
25. Sahlqvist S, Song Y, Bull F, Adams E, Preston J, Ogilvie D, *et al*. Effect of questionnaire length, personalisation and reminder type on response rate to a complex postal survey: Randomised controlled trial. BMC Med Res Methodol 2011;11:62.
26. Edwards P. Questionnaires in clinical trials: Guidelines for optimal design and administration. Trials 2010;11:2.
27. Greenlaw C, Brown-Welty S. A comparison of web-based and paper-based survey methods: Testing assumptions of survey mode and response cost. Eval Rev 2009;33:464–80.
28. Podsakoff PM, MacKenzie SB, Lee JY, Podsakoff NP. Common method biases in behavioral research: A critical review of the literature and recommended remedies. J Appl Psychol 2003;88:879-903.

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

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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]

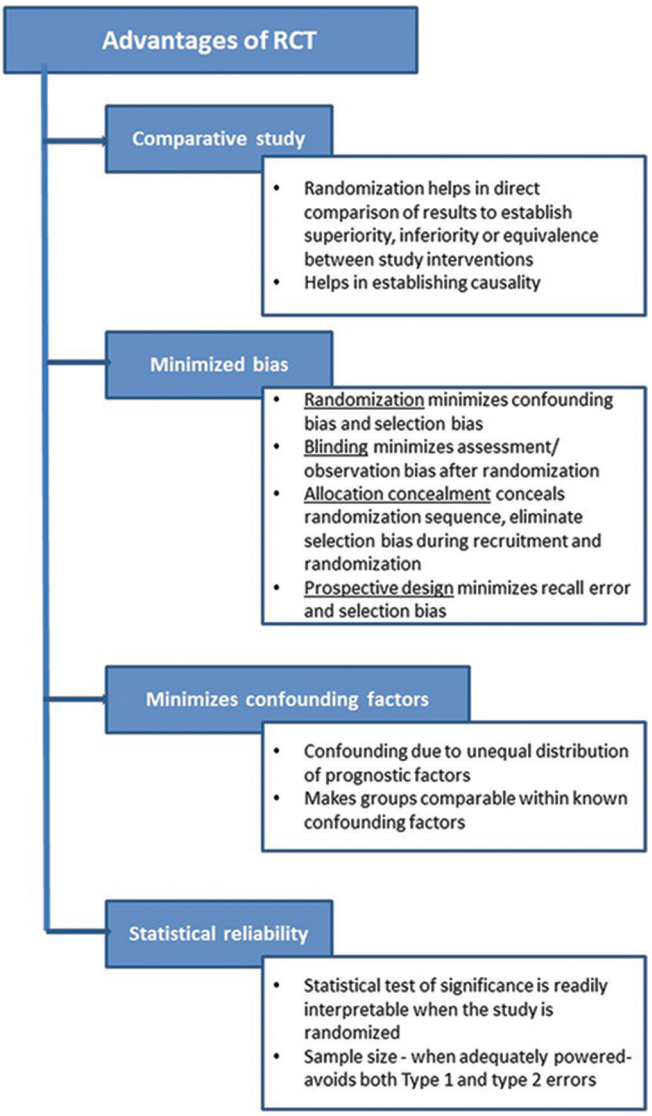

Figure 1: Advantages of RCTs

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

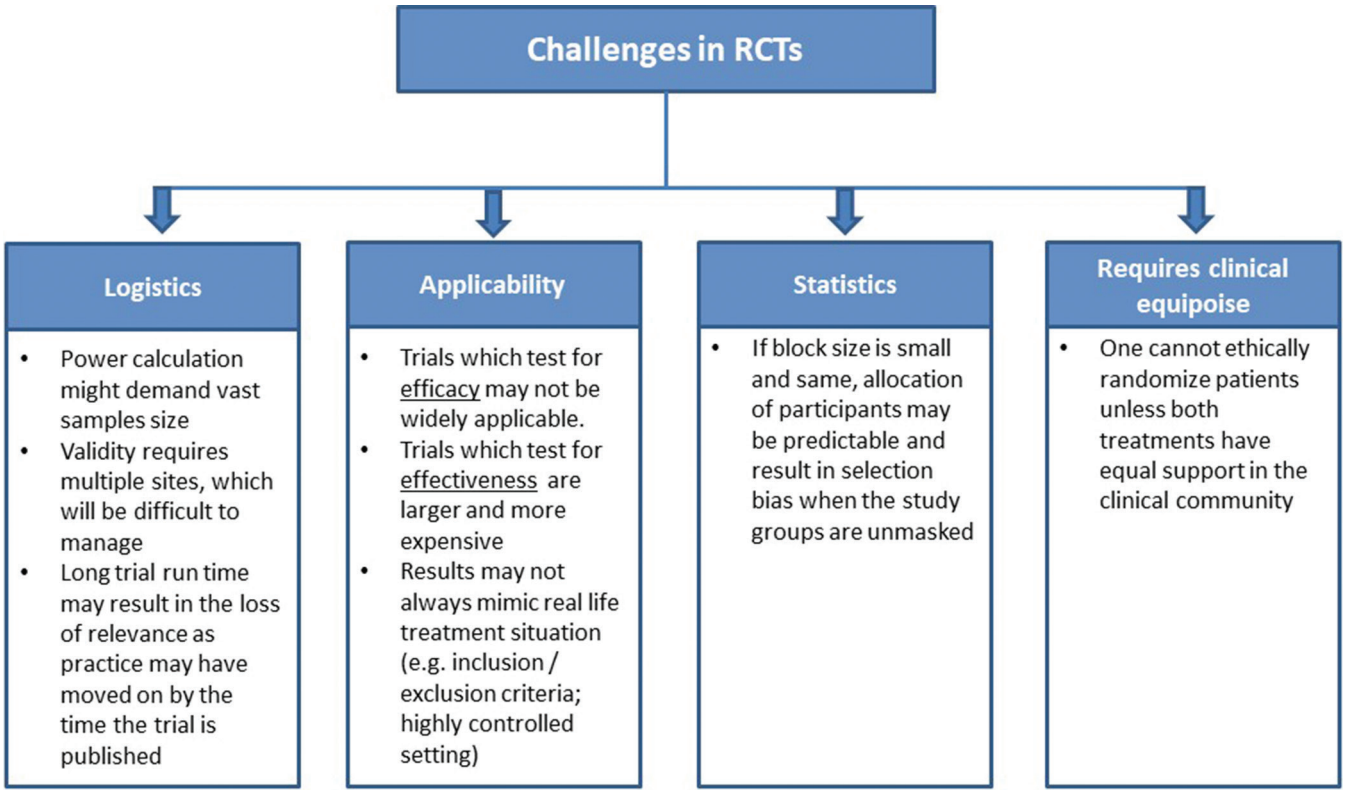

Figure 2: Drawbacks of RCTs

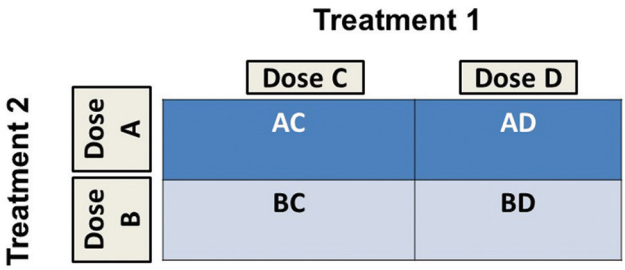

Figure 3: Pictorial representation of factorial study design

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]

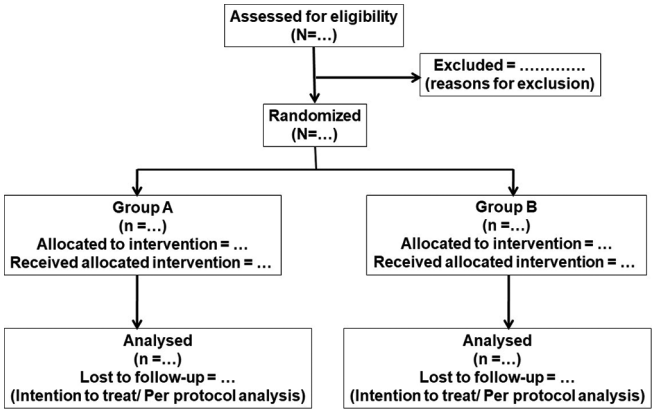

Figure 4: Flowchart as per CONSORT guidelines for reporting of RCT data

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.

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Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Sil A, Kumar P, Kumar R, Das NK. Selection of control, randomization, blinding, and allocation concealment. Indian Dermatol Online J 2019;10:601-5.
2. Garg AX, Hackam D, Tonelli M. Systematic review and meta-analysis: When one study is just not enough. Clin J Am Soc Nephrol 2008;3:254-260.
3. Stansfeld JM, Francis AE, Stuart-Harris CH. Laboratory and clinical trials of Patulin. Lancet 1944;2:370-3.
4. Nissen T, Wynn R. The clinical case report: A review of its merits and limitations. BMC Res Notes 2014;7:264.
5. Fries JF, Krishnan E. Equipoise, design bias, and randomized controlled trials: The elusive ethics of new drug development. Arthritis Res Ther 2004;6:R250–5.
6. Nair B. Clinical trial designs. Indian Dermatol Online J 2019;10:193-201.
7. Riva JJ, Malik KM, Burnie SJ, Endicott AR, Busse JW. What is your research question? An introduction to the PICOT format for clinicians. J Can Chiropr Assoc 2012;56:167-71.
8. Farrugia P, Petrisor BA, Farrokhyar F, Bhandari M. Practical tips for surgical research: Research questions, hypotheses and objectives. Can J Surg 2010;53:278-81.
9. Hulley S, Cummings S, Browner W. Designing Clinical Research. 3rd ed. Philadelphia (PA): Lippincott Williams and Wilkins; 2007.
10. Hazra A, Gogtay N. Biostatistics series module 5: Determining

sample size. Indian J Dermatol 2016;61:496-504.
11. Elwood PC. Randomized controlled trials: Sampling. Br J Clin Pharmac 1982;13:631-6.
12. Zhong B. How to calculate sample size in randomized controlled trial. J Thorac Dis 2009;1:51–4.
13. Gupta KK, Attri JP, Singh A, Kaur H, Kaur G. Basic concepts for sample size calculation: Critical step for any clinical trials! Saudi J Anaesth 2016;10:328-31.
14. Debbarman P, Sil A, Bandyopadhyay D, Das NK. Autologous serum therapy in chronic urticaria: A promising complement to antihistamines. Indian J Dermatol 2014;59:375-82.
15. Ethical Guidelines for Biomedical Research on Human Subjects. New Delhi: Indian Council of Medical Research; 2006. Available from: http://www.icmr.nic.in/ethical_guidelines.pdf . [Last accessed on 2020 Jul 30].
16. Guidelines on Audio-Visual Recording of Informed Consent Process in Clinical Trial. Directorate General of Health Services Ministry of Health & Family Welfare Govt. of India 9th January, 2014. Available from: http://www.cdsco.nic.in/writereaddata/Guidance_for_AV%20Recording_09.January.14.pdf. [Last accessed on 2020 Jul 30].
17. Ovosi JO, Ibrahim MS, Bello-Ovosi BO. Randomized controlled trials: Ethical and scientific issues in the choice of placebo or active control. Ann Afr Med 2017;16:97-100.
18. Office for Human Research Protections (OHRP); Draft Guidance on Important Considerations for When Participation of Human Subjects in Research is Discontinued. 2008 Nov. Available from: http://www.hhs.gov/ohrp/requests/200811guidance.pdf. [Last accessed on 2020 Oct 06].
19. Dow A, Goldstein W. FDA and OHRP guidance on data retention and other considerations applicable to subjects who withdraw from clinical research. Available from: http://www.ebglaw.com/files/24854_CLIENT%20ALERT-FDA%20and%20OHRP%20Guidance%20on%20Data%20Retention.pdf. [Last accessed on 2020 Oct 06].
20. Sil A, Das NK. How to register a clinical trial in India?. Indian J Dermatol 2013;58:235-6.
21. Aslam A, Imanullah S, Asim M, El-Menyar A. Registration of clinical trials: Is it really needed? N Am J Med Sci 2013;5:713-5.
22. International Clinical Trials Registry Platform (ICTRP). Available from: http://www.who.int/ictrp/trial_reg/en/. [Last accessed on 2020 May 29].
23. Clinical Trials Registry- India. Available from: http://www.ctri.nic.in/Clinicaltrials/cont1.php. [Last accessed on 2020 May 29].
24. World Medical Association. World medical association declaration of Helsinki: Ethical principles for medical research involving human subjects. JAMA 2013;310:2191-4.
25. International Committee of Medical Journal Editors. Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals. Available from: http://www.icmje.org. [Last accessed on 2020 May 29].
26. Bowling A. Research Methods in Health: Investigating Health and Health Services. UK: McGraw-Hill Education; 2014.
27. Drugs and Cosmetics (Sixth Amendment) Rules, 2014 (DCR-6th Amdmt – English and Hindi/Hindī). (Effective Date: June 12, 2015) Department of Health, Ministry of Health and Family Welfare, Government of India; 12 December, 2014. Available from: http://www.cdsco.nic.in/writereaddata/Notificatiohn%20on%20Compensation%20on%20clincial%20trial%20(1).pdf. [Last accessed on 2020 Jul 30].
28. Sil A, Das NK. Ethics of safety reporting of a clinical trial. Indian J Dermatol 2017;62:387-91.
29. David M, Sally H, Kenneth FS, Victor M, Peter CG, Devereaux PJ, *et al.* CONSORT 2010 Explanation and Elaboration: Updated guidelines for reporting parallel group randomised trials. BMJ 2010;340:c869.
30. Taichman DB, Sahni P, Pinborg A, Peiperl L, Laine C, James A, *et al*. Data sharing statements for clinical trials: A requirement of the International Committee of Medical Journal Editors. Ann Internal Med 2017;167:63-5.

Informed Consent in Biomedical Research: Scopes and Challenges

Abstract

Medical science is evolving constantly and this evolution cannot happen without biomedical research involving human participant. Owing to a tumultuous history, importance of ethical research cannot be over emphasized in today's world and the concept of informed consent becomes the guardian of ethics, not only to improve the bonding between the participant and researcher aiding a wholehearted involvement but also ensuring safety for the participants from research related injury/loss. Subject information sheet (SIF) and Informed consent form (ICF) are the fundamental elements of informed consent document. Process of obtaining them from illiterate and vulnerable populations involves the legally authorized representative (LAR) and impartial witness. Audiovisual recording becomes important in case of clinical trials. Process of obtaining informed consent becomes challenging for vulnerable populations as well as during pandemic situations. A comprehensive informed consent is essential for a credible and ethical research.

Keywords: *Assent, consent, ethics, impartial witness, informed consent, legally authorized representatives*

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Prologue (Evolution of Informed Consent)

Advances in Medicine cannot be achieved without research involving human participants, but it is also of paramount importance that no harm is brought onto the research participants for the sake of research.[1] Thus, it is required that the researchers obtain permission or approval from the participants to understand their willingness to undertake the risk onto oneself for the sake of benefit to the society which can be achieved by way of research. In other word, *consent* (meaning in Merriam Webster Dictionary "to give assent or approval" *verb*; "compliance in or approval of what is done or proposed by another" *noun*)[2] becomes obligatory to ensure that *autonomy* of the patient is exercised. Autonomy is one of the primary pillar of ethics which decides research participants' *"right to self-governance, choice for care and the right to accept or refuse treatment;"* and the only way to establish self-governance is to make sure that before expressing the willingness the participants have complete information about what to expect, the benefit/risk of the process, and the alternative options.[3] Consent becomes futile if it's not complemented with detailed information regarding the entire research protocol in lay man's language *(vide infra)*; thus, *informed consent* evolved as the guardian of medical ethics. What is true for research is true for routine medical practice and law-of-the-land all over has evolved with time from historically practiced "doctor-focused" approach to a more "patient-focused" approach.[4] The history of medical research is marred with painful abuses, spanning nearly a century. Concept of "informed consent" is not just its outcome but has become an integral part of medical research to protect the interests of all the stakeholders. With advancements in understanding about pathogenesis, treatment, and various other aspects of different diseases and type of data being collected, the understanding of informed consent process undergoes a paradigm shift. The design of informed consent owes from tumultuous events in medical care and research involving human beings. A few historical landmarks with their repercussions are worth mentioning in this context

1. **The Duke of York's laws (1665)**: Under this law, physicians and surgeons were required to obtain a patient's consent prior to treatment. The law also said

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that as long as a treatment demonstrated no perceived risk or harm, physicians had the right to act without a patient's consent. The precise definition of harm was left to the judgement of the treating physician/surgeon.[5]

2. **The Case of Pratt vs. Davis (1905)**: A surgeon removed a woman's uterus and ovaries, without her knowledge, to treat her epilepsy. The court ruled in favor of the patient, arguing that a "Physician or Surgeon, however skillful […] [cannot] violate without permission the bodily integrity of his patient."[6]
3. **The Case of Schloendorff vs. Society of New York Hospital (1914)**: Upon accidental discovery of an abdominal mass, by physicians, in a woman complaining of stomach discomfort, the patient insisted against removal of that mass/tumor. But the physicians went on to perform a hysterectomy, followed by gangrene of her left arm because of surgical complications and some of her fingers had to be amputated. Additional surgeries for that hand had to be performed also because of an embolism from the original surgery. The verdict clarified that "Every human being of adult years and sound mind has a right to determine what shall be done with his own body […]."[7]
4. **The Nuremberg Code (1949)**: During the World War II, concentration camp victims were tortured and killed in the name of scientific research. The Nazi physicians, responsible for these heinous crimes, were tried by a tribunal of three American judges. They stated that "The voluntary consent of the human subject is absolutely essential." That research subjects "should be so situated as to able to exercise free power of choice," and that they "should have sufficient knowledge and comprehension of the elements of subject matter."[8]
5. **Declaration of Helsinki (1964):** Indirect influence of the Nuremberg code prompted the medical research community to frame its own guideline regarding behavior of researchers dealing with human subjects. These sets of guidelines by the World Medical Association has been the cornerstone of ethics in years to come and in its lifetime the "Declaration of Helsinki" has been revised many a times and has been constantly updated till October 2013. In most recent times, the area of ethical requirement in placebo-controlled trial and responsibilities of research participants at the end of study has been the focus of amendment.[9]
6. **The case of Salgo vs. Leland Standford Jr. University Board of Trustees (1957)**: The patient awoke paralyzed after a routine aortography, which proved permanent. The patient was never informed by the physicians and surgeons that such a risk even existed. The patient sued the hospital and was awarded $250,000 in damages.[10]
7. **Stanford Prison Experiment (1971):** The researcher, Philip Zimbardo, at Stanford University indulged in an experiment, where a group of students were to act either as prisoners or guards in a makeshift penitentiary setting, leading to enduring psychological trauma for the participants.[11]
8. **Tuskegee Syphilis Experiment (1931-72):** In one of the most gruesome human experiments, effects of untreated syphilis were observed in poor African-American land workers for over 40 years by denying them an access to curative medicine. This monumental violation of human rights along with the Stanford prison experiment established groundwork for Federal policy for protection of human subjects, also known as the common rule.[12]
9. **Belmont Report (1979):** It defined the basic principles for oversight on research process, basic ethical parameters involving human subject research leading to creation of informed consent.[13]
10. **HPV vaccine trial (2007):** In India, HPV vaccine trial was initiated among tribal women (vulnerable population) under the pretence of "observational study" or "Demonstration project" without taking mandatory permission from Drug Controller General of India. The trial resulted in the death of seven girls and in 2010 the Indian parliament's standing committee on health observed that "safety and rights of those children were highly compromised."[14]
11. **Regulatory requirement for conduct of clinical trials in India (2013):** In the wake of public interest litigations, the Supreme Court of India recommended stringent control in the conduct of clinical trials to safeguard the rights of trial participants. Following the directions and observations of Supreme Court, the Central Drugs Standard Control Organization (CDSCO) introduced three steps to streamline the conduct of clinical trials. The institutions that are involved in reviewing and approving clinical trials were strengthened, the rights of clinical trial participants were protected, and measures were taken to reduce uncertainty and delay for clinical trial sponsors and investigators.[15]

Definition of Informed Consent

It is the process by which a researcher/physician sensitizes a patient/participant about the nature of the study/research and what the patient/participant is supposed to go through (interventions and data collection) during the study/research, in their vernacular language that is non-technical and fully understandable by the patient/participant, in order to help them to participate with their complete willingness and without any coercion.[16]

Consent in research and medical care

Elements of Informed Consent Document: For any modern-day research to be undertaken, a written informed consent is the most important pre-requisite that must be obtained in accordance with the Good Clinical Practices (GCP), the Indian Council of Medical Research (ICMR) guidelines, and the New Drugs and Clinical Trials Rules 2019.[17-19] It is composed of "subject information sheet" and "informed consent form."

The Informed consent should highlight the Name of Investigator (s), Organization (s), Sponsors (in any), and the subject group on whom it is applicable.

1. **Subject Information Sheet (SIF)**: The subject information sheet needs to be drafted in a lucid, non-technical, and simple language that can be easily understood by the participants. There needs to be an introductory section of the SIF where they need to be invited to the research and given the freedom to ask about their doubts (to the investigator or anyone they confide) and also to exercise their autonomy should they choose to participate. It is also required that adequate time be given to the participant to read the SIF, if necessary discuss it with their family/friends, and seek clarification of her/his doubts from the researchers before confirming their participation in the research.[18] The elements of SIF are as follows:
   a. A statement that the study involves research: The SIF should clearly mention that the study is not a routine medical care to eliminate the perplexities that can shroud the mind of the participant with regard to "therapeutic misconception" *(vide infra)*.[1]

   Example: "This Informed Consent Form is for men and women who attend clinic Z, and who we are being invited to participate in research on 'X'. The title of our research project is "……."[20]

   b. Explanation about the purpose and expected duration of the subject's participation

   Example: In a trial of new drug "*abc*" on urticaria. The SIF need to explain the disease in layman's term (e.g. *wheals* or *hives*) with the details of the course of the medicine along with the number of visits to the clinic that will be required for the study.

   c. Description of procedures to be followed and identification of any that are experimental

   Example: "The participant has to take single tablet at bedtime for 6 weeks and record that in a daily diary that will be provided to him/her." The mention of venipuncture for routine investigation before and at the end of the study should also be mentioned. If biopsies are necessary, then it is important to mention which would be the site of biopsy and whether anesthesia will be given or not.

   d. Description of any foreseeable risk or discomforts to the subject, an estimate of their likelihood and a description of steps to be taken to prevent or minimize them. Unpredictable and/or serious adverse events are tricky matter and participants should be made aware about them too.

   Example: The known side-effects are to be mentioned with the note that the side-effects are sometimes unpredictable and may vary from person to person in its seriousness. If a new side-effect is noted during the course of the study, the SIF should be updated accordingly (change of version). It is important that the SIF should mention "We will follow you closely and keep track of any unwanted effects or any problems. We may use some other medicines to decrease the symptoms of the side effects or reactions. Or we may stop the use of one or more drugs. If this is necessary, we will discuss it together with you and you will always be consulted before we move to the next step."[20]

   e. Description of any benefits to the subject or to others that may reasonably be expected from the research. However, monetary compensation is not a benefit. The benefit from the disease symptoms to be mentioned.Also a mention of the benefit to mankind for the development of new therapeutic option/understanding or diagnosis of a disease. It is noteworthy that monetary benefit is not accounted in the description since that will amount to coercion.

   Example: "Any interim illnesses will be treated at no charge to you. If your child falls sick during this period, he/she will be treated free of charge. There may not be any benefit for you, but your participation is likely to help us find the answer to the research question. There may not be any benefit to the society at this stage of the research, but future generations are likely to benefit."[20]

   f. Disclosure of any appropriate alternative procedures or courses of treatment that might be advantageous to the subject along with the description of "rescue medication/treatment" as appropriate for the condition. This is the most vital aspect of offering the "autonomy" to the participant to exercise his/her free will to choose between options available.

   Example: The treatment options for urticaria need to be mentioned with a note that "If you do not wish to take part in the research, you will be provided with the established standard treatment available at the center/institute/hospital. People who have wheals/hives are given…"[20]

   The rescue treatment may be mentioned as "If we find that the medicine that is being used does not have the desired effect, or not to the extent that we wish it to have, we will use what is called a "rescue medicine." The medicine that we will use is called QRS and it has been proven to control wheal/hives. If you find that the drug we are testing does not stop your wheal/hives and it is very uncomfortable for you, we can use the rescue medicine to make you more comfortable."[20]

   g. Right to refuse or withdraw at any later date:

   Example: "You do not have to take part in this research if you do not wish to do so. You may also stop participating in the research at any time you choose. It is your choice and all of your rights will still be respected."[20]

   h. A statement describing to the extent of which, confidentiality of the records will be maintained,

including a description of who may have access to research records.

Example: "The information that we collect from this research project will be kept confidential. Information about you that will be collected during the research will be put away and no-one but the researchers will be able to see it. Any information about you will have a number on it instead of your name. Only the researchers will know what your number is and we will lock that information up with a lock and key. It will not be shared with or given to anyone except [name who will have access to the information, such as research sponsors, data safety monitoring board, your clinician, drug regulatory authorities, ethics committee members]."[20]

i. For research involving, more than minimal risk, an explanation and description of available compensation and medical treatments for research subjects if they are injured, where further information may be obtained and details of contact person in case of a research related injury.

j. Information on the amount of remuneration/ compensation, if any, to be provided to the subjects.

Example: "We will give you [amount of money] to pay for your travel to the clinic/parking and we will give you [amount] for lost work time. You will not be given any other money or gifts to take part in this research."[20]

k. Special aspects of research which the participants are not familiar with have to be explained in details. These includes "Randomization," "Blinding," and "Use of Placebo."

Example: "Because we do not know if the new anti-wheal/anti-hives drug is better than the currently available drug for treating wheal/hives, we need to compare the two. To do this, we will put people taking part in this research into two groups. The groups are selected by chance, as if by tossing a coin or decided by computer.

Participants in one group will be given the test drug while participants in the other group will be given the drug that is currently being used for wheal/hives. It is important that neither you nor we know which of the two drugs you are given. This information will be in our files, but we will not look at these files until after the research is finished. This is the best way we have for testing without being influenced by what we think or hope might happen. We will then compare which of the two has the best results."[20]

"A placebo or inactive medicine looks like real medicine but it is not. It is a dummy or pretend medicine. It has no effect on a person because it has no real medicine in it. Sometimes when we want to know whether a new medicine is good, we give some people the new medicine and some people the pretend or dummy medicine. For the research to be good, it is important that you do not know whether you have been given the real medicine or the pretend or dummy medicine. This is one of the best ways we have for knowing what the medicine we are testing really does."[20]

l. Details of contact person to answer pertinent questions about the research subject's rights (Contact details for the research center's patient representative and telephone number with email id)

m. A statement that participation is voluntary and that refusal to participate or discontinuing participation at any time will involve no penalty or loss of benefits to which the subject is otherwise entitled[21]

Example: "Your participation in this research is entirely voluntary. It is your choice whether to participate or not. Whether you choose to participate or not, all the services you receive at this clinic will continue and nothing will change. If you choose not to participate in this research project, you will offered the treatment that is routinely offered in this clinic/hospital for disease Z, and we will tell you more about it later. You may change your mind later and stop participating even if you agreed earlier."[20]

A very simplified acronym LASERS, although not exhaustive can summarize the important aspects of the information sheet, particularly useful for Dermato-surgical studies. It can be expanded as Liability waiver, type of Anesthesia, Surveillance, no Expectations/guarantee clause, Revocation of consent and Snapshots.[22]

2. **Informed Consent Form (ICF):** It should be in accordance with the Appendix V of Schedule Y (Annexure III).[23]

Practice of Obtaining Informed consent (with reference to Literate and Illiterate participant): A smooth informed consent process not only makes life easy for a researcher in terms of bonding with the participant and avoiding possible medico-legal confrontations but also ensures compliance and autonomy of the participant. The process can be simplified by following flow-charts as described in Figure 1 (for Literate Participants), Figure 2 (for Illiterate Participants), and Figure 3 (for both Illiterate Participants and Illiterate Legally Acceptable Representatives).[16]

Introduction to Legally acceptable representative (LAR) and impartial witness: A LAR is an individual or a legal body authorized under applicable law to provide consent on behalf of a prospective participant, toward his/her participation in a research, under such a scenario where a participant is unable to give informed consent (e.g. minor, insanity, disability, unconsciousness). In case the participant or LAR are unable to read/write, an impartial witness must be present during the entire informed consent process and sign the ICF. It is important to understand that legally acceptable representative (LAR) is different from **Legally authorized representative**, who are chosen by applicable law or judicial authority. An impartial witness is any person who is independent of the research and cannot be unduly

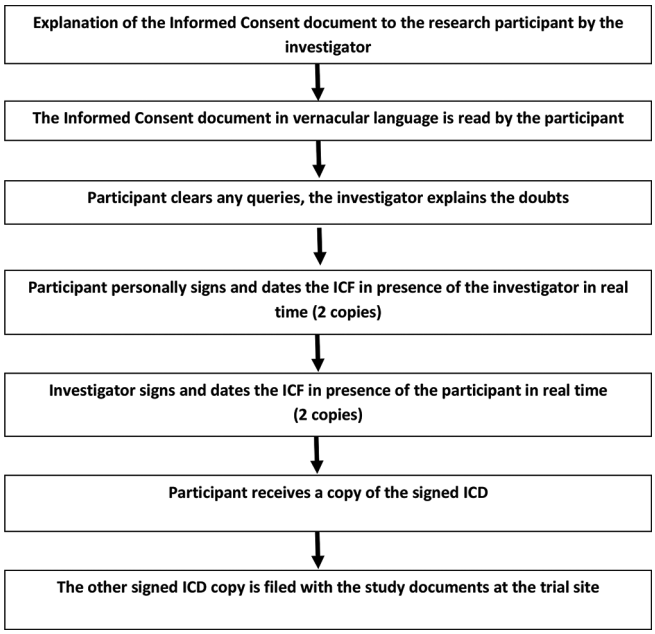

Figure 1: Process of obtaining written informed consent in case of a literate participant[16].

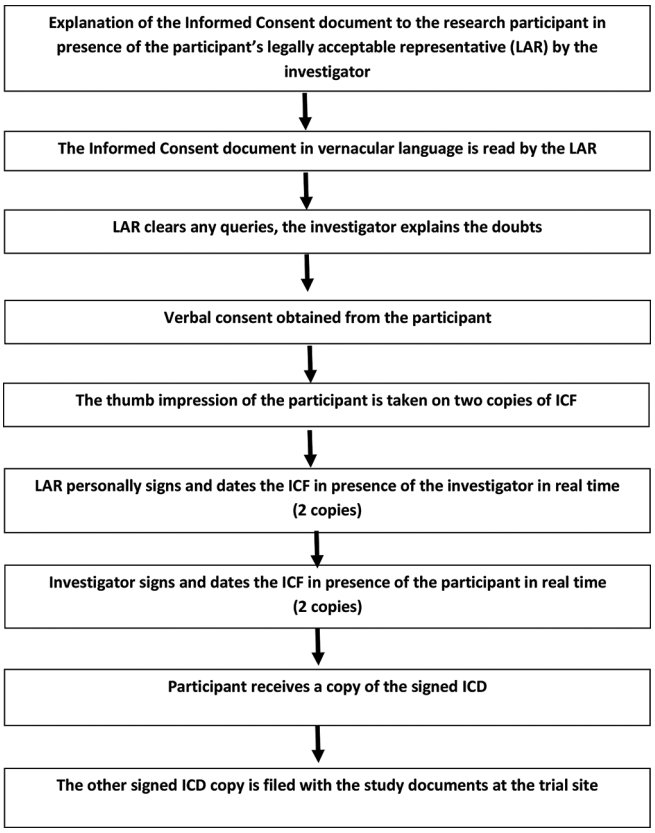

Figure 2: Process of obtaining written informed consent in case of an illiterate participant[16].

influenced by the stakeholders of the research and is able to read the SIF, ICF and any other written information supplied to the participant.[16]

Current Regulation

Audio Visual recording of Informed consent process: Current regulations in India mandate audiovisual (AV) recording of the informed consent process for all trials w.e.f 21st October 2013. On 31st July 2015, the original notification was modified, making AV recording mandatory only in cases of vulnerable populations and with research on new clinical entities.[24] Important elements of the AV recording are:

1. Documentation of Photo Identity for participant/LAR/ impartial witness
2. Adequate video camera to record facial details of participant/LAR/impartial witness and the investigator/ authorized person present during the consent process (Minimum resolution of 1280 × 780 pixels)
3. Logistic requirements (recordable memory of at least 4 GB, power backup for at least 2 h, microphone system, external hard disk, desktop/laptop computer, CD/DVD/ flash drives)
4. Disturbance free environment for both audio and video recording
5. Unrelated persons should not be present during the recording process

Audio recording in informed consent process: This is mandated only in case of clinical trials concerning drugs to treat leprosy and HIV infection.

Archiving of ICF and AV recording: AV recording of the informed consent process with all related documents must be preserved safely for at least a period of 5 years after completion/termination of the research, if not permanently. However, the sponsor for a trial/regulatory body may also request for preservation for > 5 years.

Challenges

Medical Emergencies: In such cases, saving life of a person if of prime importance and treatment is permissible for a research participant without his/her consent, in cases of unconsciousness, severe mental illness, grave sickness, and unavailability of another person authorized to give consent. If available, the guardian or LAR can give consent otherwise the consent is taken from the participant after he/ she regains the state of understanding the research. Such circumstances must explicitly be stated and addressed in the ICF.

Pregnant Women and Children: Pregnant or nursing women should only be included in a particular research when it intends to study any intervention for their benefit and data on non-pregnant women are not suitable. Risk to the developing fetus/feeding neonate should be minimal and no therapeutic or preventive benefits should be denied. The schedule Y and ICMR guidelines advocate against inclusion of an individual <18 years in a research. Though pediatric patients depend upon their guardian/LAR for providing consent, complete information in simple, common and understandable language has to be provided

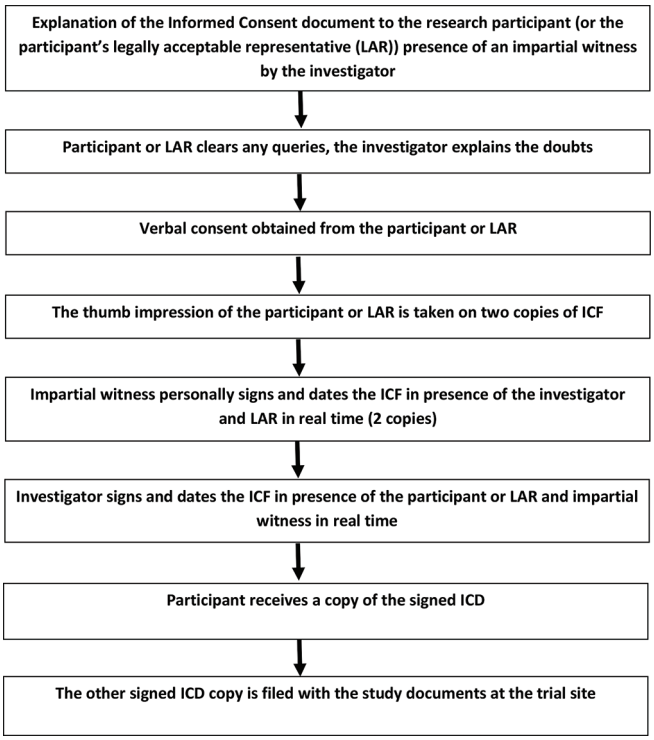

Figure 3: Process of obtaining written informed consent in case of an illiterate participant with illiterate legally acceptable representative[16].

with due respect to the refusal of the child despite consent from the guardian/LAR. Verbal consent from mature minors (7--18 years) after they read and understand a specially designed assent form, forms the concept of INFORMED ASSENT. Simplicity of the content is crucial in such a case. Therefore, 2 sets of consent forms are required for these mature minors, one being the informed assent form and other the ICF for guardian/LAR.

Vulnerable population: Research participants with reduced autonomy form the vulnerable population, for example, those suffering from terminal illness, undertrial persons, in detention, unemployed/poor socio-economic background, students, homeless/nomads, refugees and racial minority groups. Such population should not be included in a research unless they are specifically benefitted or the research cannot be carried out on other participants. Special ethical consideration is needed for such consent.

Mentally impaired participants: A proxy consent is obtained from the legal guardian or representative.[16]

Comprehension of the Informed Consent: It has been noted in real-life situations that participants were unaware of their participation in a clinical trial, in spite of their signing the informed consent document. This particularly happens in a society where there exists the atmosphere of "therapeutic misconception" (the trial is being considered as standard medical care)[1] and 'paternalism' (participants doctors to decide on their behalf)[25] clouds the decision-making capability of the participants. Translation of informed consent form in vernacular, if not properly done, can lose the essence of the informed consent document and can mislead the trial participants. In a patriarchal society, it is also not uncommon that the male member (father/husband) decides which piece of document the woman would or should sign. In such situation, it would be best to judge the comprehension of the participants regarding the informed consent document by using some existing validated questionnaires.[25] It needs to be mentioned that ensuring the comprehension is not a regulatory requirement but this exercise would help in strengthening the trust of the participants in the investigator.

Newer approaches with focus on COVID-19 era: The unprecedented wrath of COVID-19 pandemic has posed multiple challenges for biomedical research in terms of social distancing norms, travel restrictions for both the participants and investigators, interruption of logistic and sample transportation and risk of infection for the participant and investigator. Alternative methods for informed consent process during pandemic situation may include:

1. **Electronic consent:** Utilization of technology to create interactive formats, with tools, for example, text, graphics, audio, video, podcasts, interactive web platforms is encouraged to provide research related information and electronic documentation of informed assent/consent for the same.
2. **Digital signatures:** Important for both participant/LAR/impartial witness as well as the investigator, reviewed and approved by ethics committee *a priori*.
3. **Telemedical documentation:** Can be considered where AV recording is necessary.[26,27]

Epilogue: Validity and transparency in terms of including all possible information related to the research, risks which are anticipated as well as those beyond anticipation and benefits of enrollment in the research forms an informed consent, which is complete in true sense. The process of informed consent has well traversed the stage of a signed sheet of paper to become a multi-faceted bridge between the researcher and participant to ensure autonomy, justice, beneficence and non-maleficence on the participant's part and confidence, compliance and ethical research for the physician/researcher.

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Conflicts of interest

There are no conflicts of interest.

References

1. Das NK. Ethical issues pertinent to current clinical research environment in India. Indian J Dermatol 2017;62:371-2.
2. Consent. Definition of Consent. Marriam Webstar. Available from: https://www.merriam-webster.com/dictionary/consent. [Last accessed on 2021 Jan 31].
3. Das NK, Sil A. Evolution of ethics in clinical research and ethics committee. Indian J Dermatol 2017;62:373-9.
4. Foy MA. Informed consent: Where are we in 2015? Bone Joint J 2015;97:1159-61.
5. The Duke of York's Laws, 1665-75. Available from: https://www.nycourts.gov/history/legal-history-new-york/documents/charters-duke-transcript.pdf. [Last accessed on 2021 Jan 31].
6. Pratt v. Davis, 118 Ill. App. 161, Ill. Appellate Court (1905). Available from: https://www.ravellaw.com/opinions/967d63e3e4aceb0c7ccc62e78af2d543. [Last accessed on 2021 Jan 31].
7. Consent and Informed Consent. Basic right to consent to medical care-Schoendorff v. Society of New York Hosp., 105 N.E. 92, 93 (N. Y. 1914). Available from: https://biotech.law.lsu.edu/cases/consent/schoendorff.htm. [Last accessed on 2021 Jan 31].
8. Shuster E. Fifty years later: The significance of the Nuremberg code. N Engl J Med 1997;337:1436-40.
9. Carlson RV, Boyd KM, Webb DJ. The revision of the Declaration of Helsinki: Past, present and future. Br J Clin Pharmacol 2004;57:695-713.
10. Salgo v. Leland Stanford etc., Bd. Trustees. [Civ. No. 17045. First Dist., Div. One. Oct. 22, 1957.] Available from: https://law.justia.com/cases/california/court-of-appeal/2d/154/560.html. [Last accessed on 2021 Jan 31].
11. Zimbardo P, Haney C, Banks WC, Jaffe D. The Stanford prison experiment: A simulation study of the psychology of imprisonment. Available from: https://web.stanford.edu/dept/spec_coll/uarch/exhibits/Narration.pdf. [Last accessed on 2021 Jan 31].
12. Paul C, Brookes B. The rationalization of unethical research: Revisionist accounts of the Tuskegee Syphilis Study and the New Zealand "Unfortunate Experiment". Am J Public Health 2015;105:e12-9. doi: 10.2105/AJPH.2015.302720.
13. Dankar FK, Gergely M, Dankar SK. Informed consent in biomedical research. Comput Struct Biotechnol J 2019;17:463-74.
14. Sharma DC. Rights violation found in HPV vaccine studies in India. Lancet Oncol 2013;14:e443. doi: 10.1016/S1470-2045 (13) 70420-0.
15. Roy Chaudhury R, Mehta D. Regulatory developments in the conduct of clinical trials in India. Glob Health Epidemiol Genom 2016;1:e4.
16. Sil A, Das NK. Informed consent process: Foundation of the researcher–participant bond. Indian J Dermatol 2017;62:380-6.
17. Good clinical practices for clinical research in India (IN-GCPs). Central Drugs Standard Control Organization, Ministry of Health and Family Welfare, Government of India; 10 February 2018. Availablefrom: http://www.cdsco.nic.in/. [Last accessed on 2021 Jan 23].
18. Handbook on national ethical guidelines for biomedical and health research involving human participants (ICMR Guidelines); 2018. Indian Council of Medical Research, Department of Health, Ministry of Health and Family Welfare, Government of India. Available from: https://ethics.ncdirindia.org//asset/pdf/ICMR_National_Ethical_Guidelines.pdf. [Last accessed on 2021 Jan 23].
19. The Drugs and Cosmetics Rules, 1945 (As amended up to the 31st December, 2016). Department of Health. Ministry of Health and Family Welfare. Government of India. Available from: https://cdsco.gov.in/opencms/export/sites/CDSCO_WEB/Pdf-documents/acts_rules/2016DrugsandCosmeticsAct1940Rules1945.pdf. [Last accessed on 2021 Jan 31].
20. Templates for informed consent forms. Research Ethics Review Committee (ERC). World Health Organization. Available from: https://www.who.int/groups/research-ethics-review-committee/guidelines-on-submitting-research-proposals-for-ethics-review/templates-for-informed-consent-forms. [Lastaccessed on 2021 Jan 31].
21. Nijhawan LP, Janodia MD, Muddukrishna BS, Bhat KM, Bairy KL, Udupa N, *et al*. Informed consent: Issues and challenges. J Adv Pharm Technol Res 2013;4:134-40.
22. Nirmal B, Sacchidanand SA. Informed consent in dermatology: What's known and what's new? Indian J Dermatol Venereol Leprol 2014;80:58-61.
23. International Conference on harmonization of technical requirements for registration of pharmaceuticals. ICH Harmonized Tripartite Guideline: Guideline for Good Clinical Practice E6 (R1), 2005. Available from: https://database.ich.org/sites/default/files/Q10%20Concept%20Paper.pdf. [Last accessed on 2021 Jan 23].
24. Shetty PA, Maurya MR, Figer BH, Thatte UM, Gogtay NJ. Audiovisual recording of the consenting process in clinical research: Experiences from a tertiary referral center. Perspect Clin Res 2018;9:44-7.
25. Shafiq N, Malhotra S. Ethics in clinical research: Need for assessing comprehension of informed consent form? Contemp Clin Trials 2011;32:169-72.
26. Sil A, Das NK, Gangopadhyay DN. Bio-medical research in COVID-19 times. Indian J Dermatol 2020;65:337-40.
27. National Guidelines for Ethics Committees reviewing biomedical and health research during COVID-19 pandemic. Indian Council of Medical Research; April 2020. Available from: https://ethics.ncdirindia.org//asset/pdf/EC_Guidance_COVID19.pdf.

How to Write a Case Report?

Abstract:
Case report is regarded as one of the first line of evidence in medical science. There have been numerous circumstances, where the initial dissemination (and breakthrough) of scientific knowledge had been done, with the help of case reports. Case report is a particular variety of manuscript that showcases the unusual features and management of a patient. The words of William Osler (Father of modern medicine) "Always note and record the unusual…publish it. Place it on permanent record as a short, concise note. Such communications are always of value," still hold relevance in today's era. In this article, we shall discuss the keys to draft a case report worthy of publication.

Keywords: *Case reports, tips, tricks*

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Case report is a distinct way of conveying a piece of information.[1] In addition, writing a case report provides a good opportunity to young physicians to get acquainted with the nitty gritties of writing a scientific article.[2] Case reports have more chances of acceptance if they provide a message which has the ability to alter clinical practice. They are also accepted if they add to the existing literature and/or raise a novel research question, which has the potential of generating a large-scale research.[3,4]

A case report is expected to be authentic and thought provoking. The use of propranolol for the management of infantile hemangiomas is an example; which came into limelight with the publication of case reports; and thereafter, large-scale experimental studies were designed.[5-7] Therefore, case reports aid in designing tenable protocol for performing good quality scientific research.[8] The CARE (CAse REport) guidelines for writing a case report are universally followed.[9]

Brevity and clarity, are the two pre-requisites for any case report.[9] The various components of a case report and the preferable formatting of the same have been summarized below:

1. **Title:** Authors should attempt to provide a short and crisp title, and ensure that the title attracts the reviewers, editors, and the readers, to go through the entire article. The title should be well-thought of and comprehensive. It should always give a fair idea of what lies within the article, and should not be vague and non-specific. The new message of the article should preferably be reflected in the title. Most importantly, the title should be scientifically sound. Abbreviations in the first place should be avoided, and authors should avoid the use of "superfluous words".
2. **Abstract:** The abstract must clearly state the new information and the key takeaway messages.[10] There should be adequate patient data in terms of relevant history, clinical findings, tests, and interventions. Both physician and patient assessed outcomes should be mentioned.[11] Abstract is one of the most crucial components of an article, because, the reviewers and the editors would be having a fair perception of the entire manuscript after reading the abstract, and many times, the articles get rejected due to a poorly written abstract (lack of flow and message). Abstract should be revised every time the manuscript is revised or changed.
3. **Keywords:** Choosing a proper keyword is very important, while writing a case report. Keywords aid the indexers and search engines find relevant papers. Keywords should represent the content of the manuscript, and should be specific to the entity in question

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4. **Introduction:** Introduction of a case report must initially address the magnitude and importance of the disease in question. Authors should highlight as to what is unknown about the entity and why they are reporting the case.
5. **Case report:** This section should describe all the necessary details of the patient including de-identified patient-specific information, concerns, and symptoms, relevant history (medical, surgical, and family), significant clinical examination findings (both positive and negative), diagnostic tests, differentials, provisional diagnosis, and prognosis. Authors should always mention how they ruled out the clinical and histpathological differentials (preferably in a tabular format) and how they arrived at the final diagnosis. If applicable, authors should also describe the details of therapeutic intervention (pharmacological name of drug, dose, frequency and duration). The response to treatment (objective and subjective parameters) must be mentioned clearly, without any ambiguity. When the authors are reporting a drug reaction, it is advisable to mention the details of Naranjo's adverse drug reaction probability scale, Hartwig's severity assessment scale and modified Schumock and Thornton scale. Besides, it is prudent to register the drug reaction under Pharmacovigilance Program of India (PvPI) and mention the necessary details about the same, in the case report.
6. **Discussion:** The discussion should include the relevant medical literature and the rationale for the conclusion. It is always advisable to add the perspective of the patients, whenever possible.[12] A thorough literature search must be done and the relevant references must be cited. Some widely used reference management and formatting software applications are BibTeX, Papers, Zotero, EndNote, RefWords, ReadCube, and Mendeley. Authors should always avoid the claims the first publication, because this is not possible to be verified by the reviewers and editors, and such claims are not desirable while publishing any article. Authors should summarize the key findings and unique points about their case, highlighting the need for publishing the case report (as to how this will add to the literature). The primary take-away messages of the case report should be given at the end of the article, in the form of a one-line conclusion.
7. **Images and figures:** The requirements are always mentioned in the website of the journal. Some of the vital considerations include a non-identifiable patient, high-quality JPEG or TIFF-centered clear and sharply focused images, and not exceeding 3-4 MB. Authors should never crop the original image, and ensure that the background is clean. If the figure has been published before, authors should acknowledge the original source and submit written permission from the copyright holder to reproduce the material. A credit line should appear in the legend for such figures. Low-resolution images, grainy images due to high ISO and pixelated images should never be submitted. The photographs must be clicked in a manner that makes it clear to the readers, as to which region is involved. If the authors are describing a case whose uniqueness lies in the unilateral distribution of lesions on the lower limb, the photograph must be clicked in a fashion which displays both the lower limbs. When it comes to therapeutic interventions, the pre-treatment and post-treatment photographs should have the same resolution, exposure, brightness and background. The figure legends must precisely mention about the stain and magnification for dermatopathology images; and the type of dermoscope used (and the magnification).[13]

Apart from the aforementioned things, some of the important issues which need to be taken care of, include informed consent by the patient, potential conflicts of interest, de-identification of patient-related data, and ethics committee approval, if obtained or necessary.[14,15] We propose the format as shown in Apppendix 1 for case report. This worksheet can streamline the process of writing, by providing a structure. Once completed, it can be quickly formatted into a manuscript for submission. We believe that this worksheet will serve as a handy tool for penning down case reports. The greatest barrier is paucity of time, and a certain anxiety about the process of publication. Following a structured standard approach to organizing and presenting clinical observations, may remove these barriers for busy physicians who are genuinely interested in writing case reports.

Most authors, reviewers and editors are of the opinion, that authors should strictly follow the instructions pertaining to preparation of manuscript so as to increase the probability of acceptance of manuscript. Authors may either follow the instructions which are available on the specific website of the journal, or they can also follow the guidelines which are uniformly followed by all biomedical journals (http://www.icmje.org/index.html). Manuscripts are often rejected outright by the journals, when the instructions are not followed properly.[10]

An accurate, thoroughly worked-up and well-written case report strengthens the medical literature. Therefore, authors must strictly follow the instructions while preparing the draft of the case report – comprehensive, crisp, and apt, and most importantly, the ability to add to clinical practice.

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Conflicts of interest

There are no conflicts of interest.

References

1. Green BN, Johnson CD. How to write a case report for publication. J Chiropr Med 2006;5:72-82.
2. McCarthy LH, Reilly KE. How to write a case report. Fam Med 2000;32:190-5.
3. Anwar R, Kabir H, Botchu R, Khan SA, Gogi N. How to write a case report. Student BMJ 2004;12:60-2.
4. Har-el G. Does it take a village to write a case report? Otolaryngol Head Neck Surg 1999;120:787-8.
5. Cohen H. How to write a patient case report. Am J Health Syst Pharm 2006;63:1888-92.
6. Bagatur AE, Yalçınkaya M. How to write a case report? Or. not write at all. Eklem Hastalik Cerrahisi 2014;25:165-7.
7. Al-Awqati Q. How to write a case report: Lessons from 1600 B.C. Kidney Int 2006;69:2113-4.
8. Ul Haq R, Dhammi IK. Effective medical writing: How to write a case report which Editors would publish. Indian J Orthop 2017;51:237-9.
9. Biswas S, Jones O. How to write a medical case report. BMJ 2016;355:h3731.
10. Greaves I. Write a case report. J R Army Med Corps 2001;147:348.
11. Carleton HA, Webb ML. The case report in context. Yale J Biol Med 2012;85:93-6.
12. Alsaywid BS, Abdulhaq NM. Guideline on writing a case report. Urol Ann 2019;11:126-31.
13. https://ijdvl.com/contributors
14. Calvache JA, Vera-Montoya M, Ordoñez D, Hernandez AV, Altman D, Moher D. Completeness of reporting of case reports in high-impact medical journals. Eur J Clin Invest 2020;50:e13215.
15. Vaishya R, Vaish A. Effective medical writing: How to write a case report which editors would publish. Indian J Orthop 2017;51:719.

Appendix 1: Case report check sheet

Authorship:
- ICMJE (International Committee of Medical Journal Editors) criteria
- Names should be listed in the sequence of their contribution to the manuscript

Patient Privacy:
- Identifying information should be deleted
- Informed consent from the patient to publish the case
- Written approval from the Institutional Review Board/privacy officer has been obtained

Title:
- Crisp description of the case in discussion

Abstract:
- ≤250 words
- Written in a properly organized design
- Clearly stated objective
- Details of management discussed in the case report subsection
- Discussion summarizes the contribution of the case to the literature
- Indexing terms from Pub Med are provided

Introduction:
- Clearly stated purpose
- Significance of the entity (in discussion) is mentioned
- Definitions of the relevant terminologies are mentioned
- It is mentioned as to how the case adds to the existing literature

Case Report:
- The case is outlined in a comprehensive style
- The course of events is presented chronologically
- Patient characteristics are described accurately
- Positive and noteworthy negative results are mentioned
- Newer investigational procedures are described properly, with properly cited references
- All unusual terms are defined precisely
- A diagnosis is provided, with a clear presentation of the treatment

Discussion:
- The case is weighed up against the existing knowledge, with a brief discussion of differential diagnoses
- Scientific basis for the management is provided
- The authors hypothesize a mechanism behind the findings
- Limitations are mentioned
- Authors suggest avenues for future research

Conclusion:
- The conclusion is relatable to the reason behind reporting the case.
- New information is well-summarized

Acknowledgements:
- Those who have contributed to the case, but they have not been included as authors in the manuscript, should be acknowledged

References:
- The authors provide relevant and suitable references
- References must be strictly written in accordance with the journal instructions
- Figures and Clinical Images:
- Figures conform to the specifications of the journal (mentioned in the instructions to authors)
- Authors must obtain permission from the publisher, if the figures have been published elsewhere

Pitfalls in Article Submissions for Publication

Abstract

The aim of every academician and clinical dermatologist is to publish their research in reputed biomedical journals. But from conceptualization to completion, myriad shortcomings creep into the article and by the time it is ready for publication, by default and certainly not by design, the article discourse gets flawed, sometime fatally so. The endeavor of this article is to discuss these pitfalls from conceptualization, statistical machinations, authorial misconcepts, article structuring, and final journal selection. The article can function as a prophylactic checklist, albeit not comprehensive, by any prospective author and is an appreciation of the most oft repeated fallacies usually detected in publication submissions.

Keywords: *Article, pitfalls, publication, submissions*

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The aim of every academician is to convert their innovative and novel ideas of research into a publication. Publication in a reputed indexed journal is the dream of many a researcher. This helps in academic furtherance, further research collaboration with like-minded academicians and also career promotion. But unfortunately, dermatological articles which are submitted having an honest innovative concept is 'lost in translation'. It is imperative that the viable novel research project get caught up due to certain common pitfalls in the conceptualization, methodology, translation into the final paper and deficiencies in the knowhow regarding publication dynamics. The aim of this article is to basically act as a checklist of sorts for any aspiring researcher. Certain general issues will be covered and specific section wise pitfalls will be highlighted in the subsequent sections.

Pitfalls in selection of research question

Novelty of the research project is the most important facet which the journal assesses. Not conducting an adequate literature review to assess the possible redundancy of the research question is a major deficiency. This is imperative to avoid the phenomenon of research waste. The following points are frowned upon by journals in general

(a) Rehash of established facts. For example, redox theory of vitiligo is a well appreciated pathogenetic concept. To prove the same again by using another oxidant marker to reinvent the wheel about the redox concept of vitiligo will be redundant.
(b) Irrelevant research topic selection
(c) Clinically non-translatable basic research and animal studies
(d) Selection of a non-generalizable research question

Pitfalls in conceptualization

The most important limiting step is the concept which fructifies into the research project. The following issues crop up in the conceptualization of the project

1. The aims and objectives have to be crystal clear and these things cannot be evolved as the study progresses.
2. Incorporating the biostatistician during conceptualization and estimation of sample size based on primary outcome measure depending on the primary outcome measure and anticipated effect size.
3. Taking on projects without critical evaluation of feasibility and availability of center resources is a common pitfall and needs to be addressed ab initio.
4. Not designating a primary outcome measure and ignoring the fact that

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anticipated sample size is dependent on the primary outcome measure is another common deficiency. Hence primary and the secondary outcome measures have to be clearly delineated

5. Non-registration of interventional trials in the Central Trial Registry of India once the protocol is approved by the institutional ethics committee before actual initiation of subject recruitment is a major pitfall which leads to article rejection. The locking of your aims, objectives, methods, and outcome measures in the form of a registered protocol prevents mid-stream switch of research prerogative. Reputed journals are recommending even systematic reviews to be registered with PROSPERO registry to enhance authenticity
6. Institutional Ethical Committee approval is mandatory for kinds of studies. Submission of the ethics committee approval document along with the article or on reviewer/editorial request during article processing is desirable.

Pitfalls in Title

An article title is extremely important facet which initiates the readership process. The following pitfalls may be avoided

(a) Title not reflective of the nature of study
(b) Non mention of study design in title. This is important for purpose of systematic review and meta-analysis. If the search parameters is for randomized control trials it will be easier for the systematic reviewers to pick up your research and use the data of your study in the meta-analysis if attempted. This increases the relevance of your data.
(c) Over-flowery grandiose titles can actually be detrimental and may not reflect what the article contains
(d) More than 16 words in title feels lengthy and may be undesirable
(e) The name of the nature of intervention and disability need to be definitely included.
(f) Whether to reflect the study outcome in the title or be outcome neutral in the title is author's choice. But actually, reflecting clearly the outcome of research may be a good idea but it is not mandatory
(g) Use of abbreviations, formulas and brand names in title is absolutely not recommended

Pitfalls in Abstract

The abstract is the bird's eye view that is the most publicly visible and initially evaluated facet of any article. Hence, a well-written abstract is absolutely imperative for consideration by editors.

(a) CONSORT statement for Abstracts is an essential requirement for interventional trials. Not structuring the abstract is a common pitfall. Even observational analytical papers can structure their abstract based on CONSORT
(b) The abstracts must be self-explanatory and must be a stand-alone viable synopsis of the article.
(c) Non reflection of confidence intervals along with *P* values is a common pitfall. *P* values alone carry no meaning without estimating confidence intervals.
(d) Abstracts need to be structured under these heads—Objective with one line on need of research, Design and Setting, Subjects, Measurements (What is being measured, what statistical tests were used, what outcome measures were evaluated), Results, Limitations, Conclusions, and Keywords.

Pitfalls in Introduction

The introduction is actually a run up into the actual research section of the article. A good introduction needs to be succinct, clear and must encourage the reviewers to approach the actual methods section with a feeling of anticipation and must convince them that this line of research was actually needed and the research question has been chosen with due diligence. Common pitfalls are as below

1. Including long passages on nature of disease, clinical presentation of disease, and pathogenesis in an interventional disease. The description of disease must be completed in 1-2 sentences.
2. Confusing introduction with discussion
3. Not discussing study hypothesis clearly or nebulous hypothesis
4. Not reflecting the aims and objectives of research in introduction
5. The introduction is best structured like this
    a. Significance of concept
    b. Magnitude and significance of the knowledge gap
    c. Discrepancy between previous studies in literature necessitating the research project (differences in results, conclusions, opinions)
    d. How does the study set out to clear the knowledge gap?
    e. Delineation of the research question
    f. Purpose statement (aims, objectives)

Pitfalls in Study Design

This is the most important aspect of any paper publication. And hence the generic comments and subsections shall be dwelled into in some length.

1. A common pitfall is the wrong naming of design. Calling a cross sectional study as a case-control study is a common observed pitfall. Another common pitfall is calling an interventional study as a case control study. Any kind of intervention whether therapeutic, counselling, etc., constitutes an interventional trial and not a descriptive analytic study (case-control study). Basic awareness of research designs can help avoid this common pitfall.
2. Choosing the correct research design is all important.

The appropriate design for the appropriate research question is reflected in Table 1
3. Vague/inadequate method description
4. Methods lacking sufficient rigor
5. Biased (stacked) protocol—This happens when a newer intervention at adequate dosage with another older intervention at lower than standard dosage (ineffective dosage) and thereby implying greater efficacy for the newer intervention is highly undesirable.
6. Small sample size/sample size calculation not done—This is the commonest pitfall in many research submissions.
7. The way to circumvent these pitfalls is to discuss with peers, reading of literature, interaction with experienced people in the said line of research and intervention of biostatistician ab initio.

Pitfalls in Materials and Methods

1. Inadequate description of intervention: Not mentioning dose, route of administration, frequency of dosage, duration of intervention, and duration of follow up
2. Inadequate mention of study period
3. Non clarity regarding study settings
4. Non-mention of sampling frame for cases and controls
5. How were the cases and controls defined—Clear inclusion and exclusion criteria
6. Not mentioning wash out period prior to intervention
7. Not confirming informed consent process for patients
8. Not describing standard of care if that is what is offered for control
9. Inadequate mention of co-interventions in case and control group

Table 1: Miscellaneous pitfalls in article submissions

Poor grammar, syntax, or spelling
Poor organization of methods and results section as well as discussion
Too long and verbose writing style, with too much jargon and empty bombastic words
Excessively self-promotional presentation with nots of self-citations
Proliferation of unauthorized abbreviations
Abbreviations at first instance of use should be avoided
Non submission of ink signed copyright form
Changing order of authors mid-stream during submission and review process
Repetition of statements for purported over-emphasis to hide vacuity of research effort
Not adhering to word count and image count
If there is an incoherence in thought flow, subheadings can be used in discussion
Efforts to covertly de-anonymize your institution name or details to bias reviewers/editors
Revealing patient details in print
Funding source/conflicts of interest not revealed

10. Not mentioning allocation concealment
11. Using quasi-randomization methods like alternate recruitments into case and control groups and claiming adequate randomization
12. No patient flow chart provided
13. Quantum of patients considered for recruitment but not randomized. This needs explicit mention as to why the subjects considered for recruitment were not ultimately randomized. This is an often-forgotten facet of materials/methods and may reflect the acceptability of the intervention by the patients and their apprehensions regarding the interventions offered.
14. Reasons for dropouts and crossovers—This needs to be clearly mentioned, preferably in the flowchart
15. Who all were blinded—This decreases risk of bias. If the interventions are unlike each other, blinding of investigators or patients may not be feasible. In such scenarios too, outcome assessor must be blinded. If the outcome measured is subjective, it will be important to have multiple outcome assessors and their agreement coefficient must also be assessed
16. In case of complex interventions, it is better to include innovative figures to describe the timing of intervention, interventional frequency and follow up
17. Using new non-validated scales, scores, instruments, and questionnaires. Adequate references must be provided for previous validation of the scales and instruments used
18. Lack of reproducible details. The materials and methods must be provided in exquisite detail without lacunae to facilitate any future researchers or readers of the article to recreate the same processes in case they want to extend the line of research or reproduce the same research with a larger sample size in the future
19. Lack of a control group in self-healing conditions like alopecia areata, warts, etc. This is a serious flaw and a control group to factor in the spontaneous healing is mandatory for any viable valid outcomes.
20. Not mentioning confounding variables and measures to reduce confounding.
21. Mention of institutional ethics committee approval is very important in the manuscript. It is ideal to submit a copy of IEC approval along with manuscript in additional files section
22. Any instrument used to assess outcomes must be ideally validated and validation references need to be cited (i.e., MASI, PASI). De novo instruments without adequate validation to measure outcome brings the results into question
23. It is ideal to include both objective physician assessment of outcome along with patient generated outcome measures (e.g., DLQI), which improves the patient-centricity of the research endeavor. Ultimately all biomedical research is not for academic furtherance, but for patient benefit and this needs to be remembered at every turn.

24. Factoring for confounding variables in observational analytic studies and adjustment for confounding variables in both methods and statistical planning is needed. There is always a risk of confounding as randomization has not been carried out, i.e., some other covariate is associated with both the risk factor or intervention and the outcome. If you know what the covariate is, you can "control" or "adjust" for it using regression analysis.
25. Propensity Score (PS) matched analysis is a tool to control for confounding and selection bias and must be resorted to at every probable instance. In the statistical analysis of observational data, propensity score matching (PSM) is a statistical matching technique that attempts to estimate the effect of a treatment, policy, or other intervention by accounting for the covariates that predict receiving the treatment. PSM attempts to reduce the bias due to confounding variables that could be found in an estimate of the treatment effect obtained from simply comparing outcomes among units that received the treatment versus those that did not. It allows us to take many different variables and condense them into a single variable that gives the probability that the intervention will occur in each individual. Thus we can find people or groups with similar propensity scores, and use this score to make the groups being compared more similar. By matching people with similar scores we can see if the results still show that the intervention is associated with the outcome of interest. In this way, PS looks like an attractive tool to simulate a RCT in which all the covariates end up being the same except the treatment. Thus, many biases of an observational study can be obviated by propensity score matching
26. Proliferation of submissions involving correlation of inflammatory markers and oxidative markers in dermatological studies. Of late, there has been a proliferation of observational (mostly, retrospective) analytic studies involving such non-specific parameters as Red Cell Width (RDW), Neutrophil: Lymphocyte Ratio (NLR), C-Reactive Protein and myriad markers of oxidant-antioxidant status in various dermatological conditions with the attendant allusions of diagnostic status for positive results gleaned from such studies. This can be patently mis-leading.
27. Labelling a single group observational descriptive study as cohort study or cross-sectional study is a common pitfall. A cohort study or cross-sectional study needs to have a control group.
28. Labeling a cross-sectional study (comparing two groups at a fixed snapshot in time) as a case-control study just because it has a case and control group is a common avoidable malady.
29. Selection bias needs to be avoided in observational studies. Selection bias arises when the study population is not a random selection from the target population which is subject of the observational study. Individuals are then recruited in such a way that they are not representative of the target population. The aim must be a high participation rate, in order to achieve a representative cross-section of the population if possible. Self-selection of participants also takes place when economic, linguistic or health barriers hinder participation. Cultural differences and social status can also influence readiness to participate, for example, in screening programmes. This all tends to reduce the possibility of generalizing the results.
30. Measurement error or misclassification may result from lack of care by the investigator or from poor quality of measuring or survey instruments. Collecting blood samples for cases in morning and controls in evening, for example, will bias results. An interviewer treats patients during an interview with more sympathy than the controls, as their status rapidly becomes clear to him during the interview. As a result, he obtains more, and more detailed, information from the patients. These tendencies needs to be eschewed.

Pitfalls in Results

Results are where you lay out the fruits of your research for reader perusal and has to be simply presented without ostentatious wording in the most ergonomic way possible with judicious combination of text and figures. Common pitfalls in results section noted are as follows:

1. Baseline characteristics table clearly lays out the data set for benefit of the interpreter and must always be included.
2. Combining results with baseline characteristics in one table is to be strictly avoided.
3. Results are where the results of your research endeavor are blandly laid out along with accompanied statistical analysis. Interpreting the results too much in the results section is not recommended.
4. Non-use of charts, tables and graphs makes interpretation of results tedious and must be used judiciously. Overuse of graphs and charts also can be counter-productive.
5. Repeating what you have said in text in form of tables also is overstating the obvious and needs to be eschewed. Tables must be used to judiciously reduce word count.
6. Selective omission of results to match your hypothesis is not justifiable. Sometimes studies omit to mention primary outcome results altogether or try to gloss over the primary outcome in favor of secondary outcome variables and certain post-hoc added variables which have attained the miraculous P value of <0.05. This is deemed avoidable at all costs.
7. Presenting results in the same logical order presented in methods makes sense and creates a smooth logical ergonomization of ideas.
8. Reduce usages of turn of phrase like "Almost significant. Tends to significance. Nearly significant"

to put a spin on results to favor a vested hypothesis. It easily catches a reviewer eye.

9. P values not accompanied by confidence intervals in the tables and text are an incomplete presentation of results. Presenting the confidence intervals helps reviewers and readers interpret the data in its totality and can also glean the clinical significance of the statistically significant results.
10. Do not include every statistical table generated by biostatistician as is. An article is not a thesis.
11. Do not embed tables and graphs in article text. Graphs and charts are submitted in "figures" section and Tables are included after references. Closely follow author instructions of the journal to which you intend to submit your article.
12. Another not so uncommon pitfall is that the results in main text and tables fails to match numerical values in abstract of the article. This is a glaring deficiency which raises doubts about the veracity of the results.
13. Inclusion of a patient flow chart both pre-randomization and post randomization in an RCT is must. Clear reasons must be stated for drop-outs in study and control arms both pre-randomization and post randomization.
14. Presentation of a table depicting results of both univariate and multivariate analysis is important in observational studies.
15. Interpreting correlation as causation in observational studies is a common pitfall. Correlation (Pearson's and Spearman's correlation coefficient) with significant values does not indicate causation but only hints at an association.
16. Submitting a STROBE checklist along with observational studies will enhance the chances of appreciation from evaluators. STROBE checklist is for observational studies akin to CONSORT checklist for RCTs.
17. Missing data has to factored in analysis of results and chances of data missing in observational analysis are much more likely than prospective interventional trials. Retrospective cohort studies and case control studies are more prone to this pitfall as data are retrieved from databases or based on individual memory and recall and are thus prone to bias and can result in chunks of data missing.

Common Pitfalls in Statistics

The section on statistics can be an article in itself. Hence for detailed discussion, other articles may be referred to. Only common pitfalls are discussed below.

1. Not having a statistical plan. Certain articles are submitted wherein authors interpret that treatment A cured 50 patients in Group A and treatment B cured 43 patients in Group B, and hence Drug A is better than Drug B without any formal statistical analysis. This is a cardinal mistake.
2. The concept that there is no clinically significant difference if *P* value magic mark is not attained. It must be remembered that absence of evidence is not evidence of absence.
3. Using convoluted statistics with new-fangled statistical contortions in alliance with a permissive bio-statistician to put a positive spin on a negative result is best avoided.
4. Non pre-specified (not mentioned in initial study protocol) post hoc data dredging is a red flag for many reviewers and editors.
5. Not doing any tests for determining the normality of data distribution is a common fallacy.
6. Using parametric tests for non-parametric or small data sets is another pitfall in analysis.
7. Multiplicity of analysis without a correction can lead to one comparison which delivers false positive significance. Multiplicity of analysis involves comparing results at multiple time points, comparing results in multiple groups and comparing multiple parameters between study groups. Correction is necessary to avoid multiplicity induced spurious conclusions based on significance achieved by happenstance.
8. When there are multiple confounding variables in an observational analytical study, the same has to be factored into the analysis. At times univariate analysis leads to significant results, but once multivariate analysis factoring in the confounding variables is done, results prove to be non-significant. Adequate adjustment at inclusion/exclusion criteria level or statistical analytical level is a must to account for confounding of the results.
9. Incorporation of a biostatistician to evolve a statistical plan ab initio at the protocol along with sample size calculation based on outcome variables is essential. Grounds up statistical inputs will help us flesh out a cogent protocol which is the most important stage of any research.
10. Uncritical acceptance of statistical outcomes without introspection of clinical value is a pitfall best avoided.
11. Both Intention to treat (ITT) and per protocol analysis may be done ideally. Not doing ITT analysis where there are many patient dropouts in either study arms is fallacious.

Pitfalls in Discussion (Pitfalls in Interpretation of Results)

Discussion involves an interpretation of results derived from the study. Here a comprehensive literature review is a must.

1. Repeating results again in toto in discussion section is a common error which is counterproductive and unnecessarily increases word count.
2. Springing results not stated in "results section" on the unsuspecting reviewer/reader in discussion is also to be avoided.
3. Discussion is about interpreting your results in light of pre-existing literature involving similar research efforts. Tabulation of results of comparable studies helps to contextualize your results.
4. Discussion of previous literature while omitting to

contrast with your results is a common pitfall made by many authors.
5. Including own previous studies and articles irrelevant to the present research effort to increase self-citation is a practice frowned upon by many editors.
6. Forgetting to reassess hypothesis in light of results obtained is a common omission.
7. Restricting discussion on only variables which deliver significant results at the cost of variables not achieving statistical significance is a common pitfall.
8. **Limitations.** Often authors are reluctant to discuss limitations of the study. Limitations must include inadequacy of sample size, deficiencies in methods detected mid-stream by the authors (which can be avoided by other researchers doing research on similar lines in future), confounding variables omitted erroneously which were detected later, any other issues detected by authors which can affect both internal validity and generalisabililty of results. It is also an appreciable endeavor to suggest the ways to eliminate such pitfalls in any future research endeavors in that subject. A well-fleshed-out limitation section is a boon for any future researchers.
9. Selective inclusion of studies that support your hypothesis and omitting contrary results from some studies to bolster your hypothesis will be detected at some stage and must be strictly avoided.
10. Inflation of the importance of one's findings in a study is easily detected and discouraged by reviewers and reflects intellectual bias.
11. **Conclusion**. Conclusion must reflect what the results of the study are and cannot include things which have not been proven or disproven by the study in question. It is better to overreach on conclusion. Future research directions can be suggested in conclusions.
12. The popular refrain "Further larger studies are required in this area" without a proposed route map for further research on similar lines is a cliché best avoided.

Miscellaneous Pitfalls

Certain other seemingly minor pitfalls can cause much heartache due to article rejections. Same are mentioned in Table 1. The deadly sins which definitely end in rejection are also mentioned in Table 2.

Pitfalls in Journal Selection

Selection of the right journal after the research project/thesis on completion is very important. The aim of every researcher is to submit in an internationally reputed high-impact journal but it may not always be feasible. Certain appreciated pitfalls in journal selection is as follows.

(a) Not exploring into previous issues of journal to understand the ethos and the areas of interest of a journal is a common pitfall.
(b) Not reading author instructions in detail of the candidate journal is a common mistake.
(c) Not scanning previous issues for the journal for similar articles is a common pitfall. This particularly applies to case reports/case series. If a similar case has been published in the journal in recent times, it would be better to avoid submitting your similar case however rare it might be to that journal.
(d) Submitting basic research to a clinical journal without any translational message and vice versa is sure shot recipe for rejection.
(e) Understanding the nature of the readership prior to submission is essential.

Table 2: The cardinal sins of article submission (These result in rejections and might eventuate in banning of authors by particular journals from submitting future research articles)

Plagiarism from previous studies
Duplicate publication submission in multiple journals and salami slicing
Using the wrong study design to answer the wrong research question
Ad hominem attacks on editorial team and reviewers, and also on previous efforts by other researchers
Fudging of data and establishment of "dry labs"
Non-adherence to instructions to authors
Unclear clinical and histological pictures with prominent distractors or image manipulation and image plagiarism

Conclusion

The aim of this article is not to cover each and every possible pitfalls in article submission, but to evolve a kind of checklist which includes the most common reasons for rejection, which can be avoided by following this list. The author expects this article to provide a route map to both inexperienced and seasoned researchers to guide their research effort into tangible publications in respected journals.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

Suggested Reading

Katz, M. J. 2006. From Research to Manuscript. A Guide to Scientific Writing. Dordrecht, The Netherlands: Springer, pp. 152.

Grindstaff TL, Saliba SA. Avoiding manuscript mistakes. Int J Sports Phy Therapy 2012;7:524-30.

Senturia SD. How to avoid the reviewer's axe: One editor's view. *IEEE Trans Ultrason Ferroelectr Freq Control*. 2004;51:127-130.

Yan F, Robert M, Li Y. Statistical methods and common problems in medical or biomedical science research. *Int J Physiol Pathophysiol Pharmacol*. 2017;9:157-163.

Porcino A, Moraska A. Avoiding Common Writing Mistakes That Make Your Editors and Reviewers Cringe. *Int J Ther Massage Bodywork*. 2015;8:1-3.

Azer SA, Dupras DM, Azer S. Writing for publication in medical education in high impact journals. *Eur Rev Med Pharmacol Sci*. 2014;18:2966-2981.

Shakiba B, Salmasian H, Yousefi-Nooraie R, Rohanizadegan M. Factors influencing editors' decision on acceptance or rejection of manuscripts: The authors' perspective. *Arch Iran Med*. 2008;11:257-262.

Turcotte C, Drolet P, Girard M. Study design, originality, and overall consistency influence acceptance or rejection of manuscripts submitted to the journal. *Can J Anaesth*. 2004;**51:**549-556.

Lee KP, Boyd EA, Holroyd-Leduc JM, Bacchetti P, Bero LA. Predictors of publication: Characteristics of submitted manuscripts associated with acceptance at major biomedical journals. *Med J Aust*. 2006;**184:**621-626.

Radford DR, Smillie L, Wilson RF, Grace AM. The criteria used by editors of scientific dental journals in the assessment of manuscripts submitted for publication. *BrDent J*. 1999;**187:**376-379.

Clark GT, Mulligan R. Fifteen common mistakes encountered in clinical research. *J Prosthodont Res*. 2011;55:1-6.

Knight KL, Ingersoll CD. Structure of a scholarly manuscript: 66 tips for what goes where. *J Athl Train.* 1996;33:201-206.

Button, K.S., Ioannidis, J.P.A., Mokrysz, C., Nosek, B.A., Flint, J., Robinson, E. S.J., *et al*. Powerfailure: Why small sample size undermines the reliability of neuroscience. *Nat. Rev. Neurosci 2013;*14,365-376.

Cumming, G. The new statistics: Why and how. *Psychol. Sci. 2014;*25,7-29.

Kirk, R.E. Practical significance: A concept whose time has come. 1996; *Educ. Psychol. Meas.* 56,746-759.

Altman DG, Schulz KF, Moher D, Egger M, Davidoff F, Elbourne D, et al. CONSORT GROUP (Consolidated Standards of Reporting Trials). The revised CONSORT statement for reporting randomized trials: explanation and elaboration. Ann Intern Med. 2001 ;134:663-94.

Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al. Standards for Reporting of Diagnostic Accuracy. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. BMJ. 2003;326:41-4.

Strange K. Authorship: Why not just toss a coin? *Am J Physiol Cell Physiol.* 2008;295:C567-C575.

Fontanarosa PB, Flanagin A, DeAngelis CD. Reporting conflicts of interest, financial aspects of research, and role of sponsors in funded studies. Journal of American Medical Association 2005;294:110-111.

Leppink J, O'Sullivan P, Winston K. The bridge between design and analysis. Perspect Med Educ. 2017;6:265-269.

Leppink J, Kok EM, Bergman EM, Van Loon MH, De Bruin ABH. Four common pitfalls of quantitative analysis in experimental research. Acad Med. 2016;91:891.

Leppink J, Kulasegaram KM. Avoiding common data analysis pitfalls in health professions education research. Acad Med. 2016;91:11.

Pierson DJ. The Top 10 Reasons Why Manuscripts Are Not Accepted for Publication. Respir Care 2004;1246-52.

Kallet RH. How to write the methods section of a research paper. Respir Care 2004;49:1229-1232.

Bordage G. Reasons reviewers reject and accept manuscripts: The strengths and weaknesses in medical education reports. Acad Med 2001;76:889-896.

Sullivan EJ. Top 10 reasons a manuscript is rejected (editorial). J Prof Nurs 2002;18:1-2.

Ehara S, Takahashi K. Reasons for Rejection of Manuscripts Submitted to AJR by International Authors. AJR 2007;188: W113-W116.

Bordage G. Reasons review ers reject and accept manuscripts: The strengths and weaknesses in medical education reports. Acad. Med. 76:889-896.

Branson RD. Anatomy of a research paper. Respir Care 2004;49:1222-1228.

Rosenbaum, Paul R.; Rubin, Donald B. The Central Role of the Propensity Score in Observational Studies for Causal Effects". Biometrika 1983;**70**:41-55