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Original Research Article

Assessing knowledge, attitude, and practice of adaptive designs in clinical trials among Indian stakeholders

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ABSTRACT

Background: This study attempted to evaluate the knowledge, attitude and practices of various stakeholders addressing adaptive clinical trials (ACT), as no analogous studies have been published in India.
Methods: Ethics committee (EC) approval was sought before circulating an online pre-validated questionnaire (28 questions in three domains) among 200 stakeholders involving the clinicians, clinical trial unit personnel, and medical advisors from various pharmaceutical industries. The responses collected were analysed using appropriate statistical tests. A p value <0.05 was considered significant.
Results: Out of the 200 participants surveyed, 169 responded, yielding a response rate of 84.5%. When the three distinct stakeholders' median knowledge scores were evaluated, there was no statistically significant difference. The median knowledge score of stakeholders with more than five years of experience did not vary statistically from those with less than five years. In the attitude domain, 21.8% and 17.1% of participants agreed that the validity and integrity of research in ACT are hampered respectively. However, 73.9% felt that ACT has potential benefits while 79.2% believed they were underutilized. In the practice domain, only 4.7% of stakeholders have been a part of adaptive clinical trials.
Conclusions: The study found that fewer stakeholders participated in studies utilizing adaptive designs, which resulted in a decrease in knowledge, perception, and practices among the various stakeholders. This emphasizes the necessity for further educational initiatives in the future, such as planning conferences or training sessions, to raise the understanding of adaptable designs in clinical trials.

Keywords: Adaptive clinical trials, Perspective, Questionnaire, Survey

INTRODUCTION

An adaptive clinical trial (ACT) design is defined as a design that allows modifications to the trial and/or statistical procedures of the trial after its initiation without undermining its validity and integrity.[1] This decreases the time, money, and manpower in doing the same study and allows the trial to be conducted more efficiently and flexibly.[1] The concept was first designed as early as the 1970s. Several types of adaptations have been utilized since then like adaptive randomization, group-sequential designs, sample size re-estimation, drop-the-losers arm, and seamless designs which are regarded as relatively 'modern' and 'novel' methods.

In recent years, the National Institutes of Health (NIH) and the Food and Drug Administration (FDA) have been considering ACT designs to accelerate the bench-to-bedside transition of new scientific discoveries.[2] Adaptive design may offer key advantages over conventional trial designs. Clinical trials incorporating adaptive design can be more efficient, informative, and ethical compared to the trials with conventional fixed design, owing to their requirement of fewer patients and better utilization of money and time.[3,4] The superiority of adaptive designs in

terms of patients, money, and time factors can be attributed to the fluidity of the adaptive trial design.[3] Additionally, it aids the researcher in identifying the errors in the trial at an earlier stage, enabling early determination of futility.[5] Hence, the inclusion of adaptive trial designs is bound to make the drug development process, cheaper and shorter. However, on account of technical issues such as lack of adequate training, insufficient information, and varied perceptions regarding adaptive design trials among the stakeholders, a decline in its use is being observed.[4,6] The major reason why clinical investigators are seldom inclined to adopt adaptive designs is that there is a lack of clarity about the application, uncertainty of accomplishment, practical implications, and interpretations of results and their reporting.[3]

As adequate knowledge and a positive attitude toward the application of adaptive design in clinical trials are necessary for its efficient implementation and accuracy of the trial outcomes, it is important to evaluate what clinical researchers know and think about clinical trials employing adaptive designs. Also, such assessments can decipher the underlying deficiencies, based on which recommendations and policies can be made to satisfactorily address them and thereby enhance patient care and health outcomes. A literature search found that only a few studies from foreign authors were conducted to assess the attitudes and perceptions regarding adaptive designs among clinical researchers.[6-8] These studies revealed a wide gap in the knowledge and utilization of diverse opinions and acceptance of the adaptive trial among the researchers. In India, no such studies have been reported up till now.

Thus, the objective of this study was to assess the knowledge and attitudes toward adaptive designs and practices of adaptive clinical trials among various Indian stakeholders involved in clinical research.

METHODS

After approval from the institutional ethics committee (EC/OA-10/2023), a common online, in-depth survey of key stakeholders of the clinical trials involving the clinicians, clinical trial unit personnel, and medical advisors in protocol development from various pharmaceutical industries was conducted in Seth G. S. Medical College and KEM Hospital, Mumbai, Maharashtra. The responses were recorded for 6 months from March 2023 to September 2023, after which the responses were analyzed.

Selection criteria

The key stakeholders involved in the conduct of clinical trials like clinicians, clinical trial unit personnel (clinical research associates) and medical advisors in pharmaceutical industries were included in the study. The participants unwilling to give consent were excluded.

A sample of 200 stakeholders was targeted by the investigators and the method of convenient sampling was followed. The stakeholders from each of the institution's departments were chosen after accessing the annual report. The email addresses and phone numbers of the relevant stakeholders were obtained from the same source. Email addresses obtained from industry websites and social media platforms like WhatsApp were used to get in touch with the medical advisors from the different pharmaceutical firms.

A Google form questionnaire, pre-validated by 10 experts from different clinical fields with a content validity index (CVI) of 0.96, was sent to the participants meeting the selection criteria through various social networking sites. All the consents were taken in the form of e-consent via the Google form, where the stakeholders not giving the consent were accounted as refusal to participate.

The study questionnaire was divided into two sections in total. Questions about the participants' demographic information made up the questionnaire's first section (Table 1). The second section comprised a total of 28 questions in three domains- A, B, and C for assessing the stakeholders' knowledge, attitude, and practice (KAP). Domain A had 7 multiple-choice questions (MCQs) pertaining to the knowledge component of adaptive designs. A scoring system was used to evaluate the study participants' knowledge, awarding a score of "1" for each accurate response and a score of "0" for each erroneous response. The total knowledge score was 7 where any stakeholder scoring above 5 was considered to have "good knowledge", a score between 3 and 5 meant "intermediate knowledge" and any score below 3 was taken as "poor knowledge" in the context of adaptive designs. Domain B comprised 17 questions about participants' attitudes and perceptions toward adaptive study designs that included a 5-point Likert scale with the options "strongly agree", "agree", "neutral", "disagree", and "strongly disagree". Domain C contained 4 partially closed-ended questions based on the practices and challenges the participants faced during an adaptive clinical trial.

Statistical analysis

Data collected was entered in Microsoft Excel 365 and statistical analysis was carried out using Graph Prism software version 10.2.0. The Kruskal-Wallis test was employed to compare knowledge scores among three types of stakeholders, whereas the Mann-Whitney U test was used to compare knowledge score differences between stakeholders based on years of experience. A p value <0.05 was considered statistically significant.

RESULTS

The questionnaire was sent out to 200 participants in all, and 169 of them responded it with all of their responses, highlighting an 84.5% response rate. Out of 169 responses, 79.88% (135) of the respondents were clinicians, 15.97%

(27) were from pharmaceutical industries and 4.14% (7) were clinical research associates (Figure 1).

Assessment of knowledge

Domain A of the study questionnaire consisted of a total of 7 questions (Table 2) to assess the knowledge profile of the study participants about the adaptive designs. Out of 169 participants, 73.3% (124) correctly responded to the questions on study design modifications in adaptive clinical trials, and 37.2% (63) could identify the types of adaptive designs correctly. 39.6% (67) of participants could answer the most common therapy areas using adaptive designs in clinical trials while only 20.7% (35) were aware of the characteristics of an adaptive design. Only 28.4% (48) and 10.6% (18) of the respondents could correctly answer the case scenarios based on response adaptive and dose escalation designs respectively. The median value of the knowledge-based question scores was 2 with an interquartile range (IQR) of 2-1 for the clinicians, medical advisors from different pharmaceutical industries, and clinical trial unit personnel.

Table 1: Demographic characteristics of the participants (n=169).

Demographic characteristics	Categories	% (N)
Age distribution (years)	≤30	49.1 (83)
	31-40	37.8 (64)
	41-50	7.1 (12)
	51-60	4.7 (8)
	≥61	1.1 (2)
Qualification	MD/ MS or equivalent	80.4 (136)
	DM/ MCh or equivalent	7.6 (13)
	MBBS	7.1 (12)
	MSc/ PhD or equivalent	3.5 (6)
	BAMS	0.5 (1)
	M.Pharm	0.5 (1)
Subject specialty	Pharmacology	64.4 (109)
	Anesthesia	5.9 (10)
	Clinical pharmacology	3.5 (6)
	Community medicine	3.5 (6)
	Pediatrics	2.9 (5)
	Obstetrics and gynecology	2.3 (4)
	Neurology	1.7 (3)
	Oncology	1.7 (3)
	Microbiology	1.1 (2)
	Radiology	1.1 (2)
	Pathology	1.1 (2)
	General medicine	1.1 (2)
	Life sciences and clinical research	1.1 (2)
	Psychiatry	1.1 (2)
	Internal medicine	0.5 (1)
	Cardiology	0.5 (1)
	Conservative dentistry and endodontics	0.5 (1)
	Surgery	0.5 (1)
	Orthopedics	0.5 (1)
	Urology	0.5 (1)
	Ayurveda	0.5 (1)
	Dermatology	0.5 (1)
	Physiology	0.5 (1)
	ENT, head and neck	0.5 (1)
	Surgical gastroenterology	0.5 (1)
Years of experience in clinical trials	<5	83.4 (141)
	>5	16.6 (28)
Current employment	Institution	79.8 (135)
	Pharmaceutical industry	16.1 (27)
	Clinical research organization	2.3 (4)
	Clinical trial unit	1.8 (3)

Table 2: Knowledge of the study participants about adaptive designs (n=169).

Questions to assess knowledge	Correct responses, % (N)
Adaptive study design modifications	73.3 (124)
Adaptive trial designs are a design that allows modifications of?	49.7 (84)
Adaptive trial designs allow modifications in methodology that include?	23.6 (40)
Types of adaptive clinical trial design	37.2 (63)
Therapy areas where the adaptive designs are applied most in a clinical trial	39.6 (67)
Characteristics of adaptive clinical trials	20.7 (35)
Case scenario on response adaptive design	28.4 (48)
Case scenario on dose escalation design	10.6 (18)

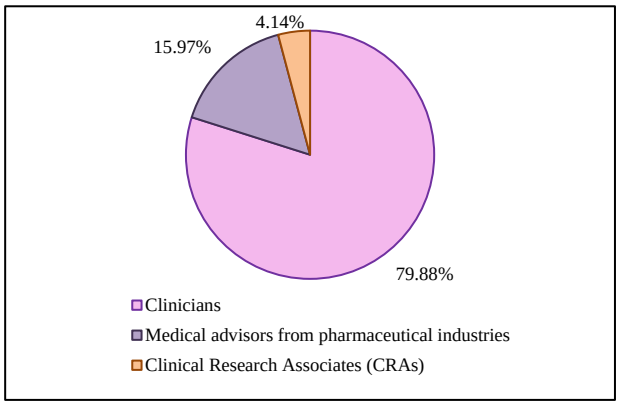

Figure 1: Types of stakeholders.

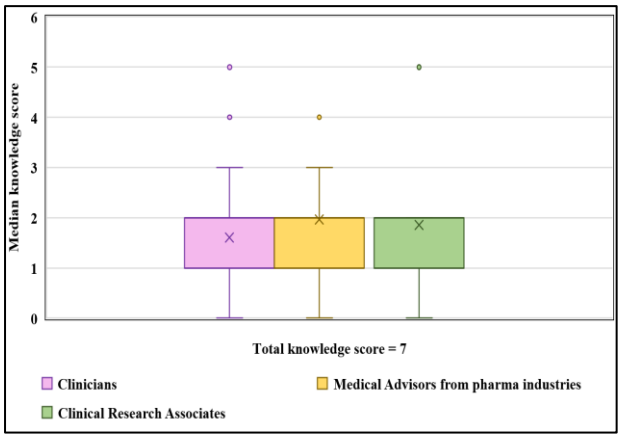

Figure 2: Comparison of median knowledge scores among the different stakeholders.

Statistical significance test for comparison was done by the Kruskal-Wallis test; data were expressed as median and IQR. P value =0.19 (*p<0.05 considered statistically significant).

The median knowledge scores among these stakeholders were compared using the Kruskal-Wallis test and were statistically insignificant based on the p-value of 0.19 (Figure 2). There was also no statistical difference in median knowledge scores [2 (2-1)] between stakeholders with <5 years and >5 years of experience respectively, based on the p-value of 0.94 using the Mann-Whitney U test (Figure 3).

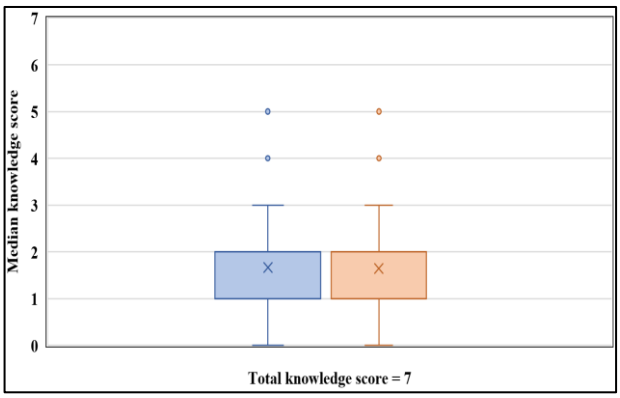

Figure 3: Comparison of median knowledge scores based on years of experience.

Statistical significance test for comparison was done by the Mann-Whitney U test; data were expressed as median and IQR. P value =0.94 (*p<0.05 considered statistically significant).

Assessment of attitude

The domain B of the questionnaire included a total of 17 questions to assess the attitude of the study participants toward the adaptive trial designs. Out of 169 respondents, 21.8% (37) and 17.1% (29) agree that the validity and integrity of research in ACT are hampered respectively. 79.2% (134) of the participants believe that there is underutilization of ACT designs in India while 73.9% (125) feel that the potential benefits outweigh the additional efforts required to implement an adaptive design. Also, 66.2% (112) of the respondents think that the incorporation of adaptive clinical trials has an impact on drug approval (Table 3). Concerning the attitude toward the barriers in the conduct of ACT in India (Figure 4), 86.9% (147) believe that it is because of a lack of understanding of the adaptive design, 85.7% (145) agree that lack of expertise among stakeholders, 60.3% (102) thought due to lack of funding by the investors, 74.5% (126) due to lack of efficiency in protocol development, and 72.7% (123) agree that there is a lack of statistical knowledge. 73.9% (125) think that there is a preference for traditional clinical trials over ACTs while 56.8% (96) believe that ACTs are underreported. In addition to this, 66.8% (113), 64.4% (109), and 75.1% (127) of respondents believe that fear to cost, the time required, and rejection by the regulatory authorities respectively can act

as barriers in the conduct of ACTs. 63.9% (108) and 61.5% (104) also concur that the availability of data infrastructure and data management respectively can be a challenge in the execution of ACTs in India.

Table 3: Attitude of the study participants toward adaptive designs (n=169).

Attitude based questions	Responses	% (N)
Do you think the validity of research gets hampered with adaptive clinical trials?	Strongly agree	3.5 (6)
	Agree	18.3 (31)
	Neutral	28.4 (48)
	Disagree	42.6 (72)
	Strongly disagree	7.1 (12)
Do you think the integrity of research gets hampered with adaptive clinical trials?	Strongly agree	1.1 (2)
	Agree	16 (27)
	Neutral	30.1 (51)
	Disagree	45.5 (77)
	Strongly disagree	5.9 (10)
Do you think there is underutilization of adaptive clinical trial designs in India?	Strongly agree	24.8 (42)
	Agree	54.4 (92)
	Neutral	17.7 (30)
	Disagree	2.9 (5)
	Strongly disagree	0
Do you think the potential benefits outweigh the additional efforts required to implement the design?	Strongly agree	16.5 (28)
	Agree	57.3 (97)
	Neutral	20.1 (34)
	Disagree	5.3 (9)
	Strongly disagree	0.5 (1)
Do you think that the incorporation of adaptive clinical trials has an impact on drug approval?	Strongly agree	14.2 (24)
	Agree	52 (88)
	Neutral	30.7 (52)
	Disagree	2.9 (5)
	Strongly disagree	0

Table 4: Practice-based questions for the stakeholders who were part of adaptive designs in clinical trials (n=8).

Practice-based questions	Response	% (N)
Capacity of work in ACT	Protocol development	50 (4)
	Study coordinator	25 (2)
	Principal investigator	25 (2)
Preference over conventional clinical trial design	Yes	75 (6)
Prior training in ACT	No	87.5 (7)
Interest in training	Yes	100 (8)
Topic preference for training in ACT	Statistical application and interim analysis	50 (4)
	Trial conduct and methodology	25 (2)
	Ethical aspects	12.5 (1)
	Regulatory aspects	12.5 (1)
Challenges faced during the conduct of ACTs	Lack of applied training	25 (2)
	Statistical complexity	25 (2)
	Fear of bias during interim analysis	12.5 (1)
	Ethical aspects	12.5 (1)
	Regulatory challenges	12.5 (1)
	Operational/feasibility challenges	12.5 (1)

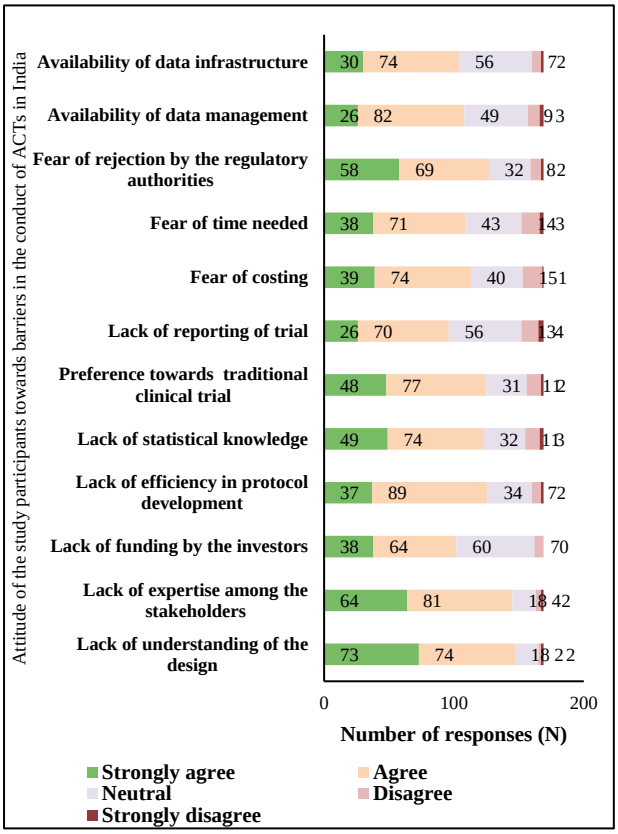

Figure 4: Attitude of the study participants toward barriers in the conduct of ACTs in India.

Assessment of practice

Domain C of the questionnaire constituted the practice-based questions which revealed that only 4.73% (8) of 169 participants were part of adaptive designs in clinical trials (Table 4). Out of the 8 stakeholders who employed adaptive designs, only 25% (2) of them were involved in more than 3 ACTs while 50% (4) of them worked at the capacity of protocol development. When asked about their preference for ACTs over conventional clinical trial designs, 6 out 8 responded "yes" while the majority couldn't specify the reason for preference. 7 out of the 8 did not have any prior training in ACTs. All of them responded "yes" to interest in training with the majority preferring topics like statistical application and interim analysis followed by trial conduct and methodology. The major challenges faced by the stakeholders during the practice of ACTs are lack of applied training, statistical complexity, fear of bias during interim analysis, ethical, regulatory, and operational challenges of an adaptive design as highlighted in Table 4.

DISCUSSION

The Indian healthcare system has historically relied on traditional clinical trial designs, and there may be a cultural preference for familiar methodologies. This has led to a reluctance to explore or adopt new approaches, including adaptive designs.[9] There is a dearth of awareness studies especially in India that can help pinpoint areas where knowledge of adaptive study designs is lacking among different stakeholder groups, including researchers, clinicians, regulatory authorities, and industry professionals. To address the potential barriers to adoption of ACT, understanding the attitudes and perceptions of stakeholders toward adaptive study designs is crucial and therefore, the present study was undertaken.

It was seen from the demographic profile of the study that the majority of the respondents were less than 30 years old and with equivalent MD/MS qualifications which indicates that a higher number of young doctors with less clinical experience have taken an interest in participating in the study. As seniors are busy with many other responsibilities, usually clinical trials are done by junior doctors to gain experience and as a part of their specialty or super specialty training. Participants with pharmacology as a specialty branch have responded more which can be due to the access and also, they are primarily dealing with drug development and can recognize the value of adaptive designs more compared to other medical branches.[10]

When the study participants' knowledge was assessed, the majority could answer the question about how the adaptive designs allow modifications in methodology and statistical analysis. However, very few could answer correctly regarding the specific modifications in the methodology allowed in adaptive designs. In other knowledge-based questions pertaining to study types, therapy areas, characteristics, and case-based scenarios, less than half of the participants could answer correctly indicating a vivid knowledge gap. Also, there was no statistical difference in median knowledge scores among the different stakeholders or with the years of clinical trial experience.

The defining characteristic of all adaptive designs is that results from interim data analyses are used to modify the ongoing trial while maintaining its integrity or validity and also, it is designed in such a way that the regulatory requirements or the power bargain is taken care.[1] In the present study, some stakeholders felt that the research integrity and validity in adaptive clinical trials are hampered, showing their ignorance. Although a majority believe ACTs have the potential benefits over additional efforts in implementing adaptive designs and significantly impact the drug approval process, many respondents thought that ACTs are still underutilized in India. Regarding the barriers to the conduct of ACTs, the factors to which the majority of the stakeholders agreed were a lack of understanding of design, lack of expertise, fear of rejection by regulatory authorities, and lack of efficiency in protocol development. This finding might be because out of all the respondents, most of them were clinicians who neither have the expertise nor the acumen to write an efficient protocol for drug development as compared to the clinical research associates or the pharma industry professionals. More than half of the attitude-based responses also favored lack of funding by investors, fear

of cost, and time to be a challenge in the conduct of ACTs. However, in reality, the purpose of using adaptive clinical trials is to have more flexibility in the study design which acts as a gateway to save more time and money and to prevent wastage of resources.[11]

The results of our study support the cross-sectional survey conducted in the UK by Dimairo et al about the lack of expertise and knowledge among the various stakeholders. The perception regarding the barriers to conducting ACT was found to be similar in both studies, especially with respect to inadequate data management infrastructure, fear of regulatory approval, and lack of expertise in protocol planning and implementation.[6,7] While Dimairo et al study focused only on the qualitative assessment of perception and attitude toward ACTs, our study provided a comparative assessment of knowledge based on the type of stakeholders and years of experience in clinical trials which did not differ statistically.[8]

The low practice of adaptive designs was evident from the present study as only 8 out of 169 respondents have been a part of an ACT. This makes it difficult to discuss the practice-related questions as such few responses cannot be generalized. However, it is important to note that the few stakeholders who employed ACTs in our study, faced major challenges like lack of applied training, statistical complexity, fear of bias during interim analysis, ethical, regulatory, and operational challenges of an adaptive design. These findings were similar to the results of a 2016 survey by Hartford et al on the perception and use of adaptive designs that also talked about the requirement of consistent training to choose the right adaptive design, appropriate planning for operational efficiency such as for drug supply management and data management and the concern of regulatory acceptance.[12]

Our study is the first questionnaire survey to report the dearth of knowledge, experience, and practice of adaptive designs among Indian stakeholders. Although the utility of ACTs has been long established, this study has revealed low awareness about ACTs in the context of today's clinical research. This can be a hurdle in the current scenario because a majority of the studies are planned with adaptive designs. So, the earlier authors have also recommended further awareness studies. Another strength of the study would be the comparative assessment of knowledge, the analysis of which revealed that there is poor knowledge among all the clinicians, pharma industry professionals, or clinical research associates irrespective of their years of experience in clinical trials.

The limitations of the study would be a small sample size where the responses could not be generalized to a larger population of stakeholders. As the response rate was very low, the credibility of the responses from the participants cannot be assured. Since adaptive designs are incorporated in oncology protocols, we could not target oncologists as the institution does not cater to oncology services. This can lead to a sampling bias in the study. Stakeholders like ethics committee members and regulatory board members, who are equally significant in the context of clinical trials using adaptive designs, were not included in the study.

Owing to the dearth of knowledge and expertise in ACTs, more educational interventions like training sessions or conferences should be conducted for all to enhance awareness about adaptive designs. Maybe future studies can be conducted targeting other stakeholders like ethics or regulatory board members with a higher sample size to make a more generalizable interpretation of the knowledge, attitude, and practice of using adaptive designs in clinical trials.

CONCLUSION

The study revealed less knowledge, lower perception, and fewer practices among the different stakeholders in India because very few were involved in studies using adaptive designs. This highlights the need for more educational interventions like organizing training sessions or conferences in the future to enhance awareness about adaptive designs in clinical trials.

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