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RESEARCH ARTICLE

ETHICAL ISSUES IN CLINICAL TRIALS: A REVIEW OF THE RECENT LITERATURE, AN ETHICAL ARGUMENTATION

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Abstract

Purpose: To identify ethical issues and risks involved in clinical trials and develop a conceptual model of identified issues in patient safety in clinical trials.

Methodology: The review comprises of qualitative meta-analysis of available literature to identify potential ethical issues involved in the field of clinical trials. Findings: Our review identifies gaps in following core areas: 1) Research vs. Practice; 2) Inform Consent; 3) Ethical Oversight. Existing literature shows gaps in the true definition of research and does not clarify points of difference to clinical care. Existing guidelines are still confusing about the requirement of inform consent, in which cases it is mandatory and in which cases it should be waived off. There are indiscripencies, how much information should be provided in the inform consent disclosure. Is ethical oversight required in all research studies and if so at what level. We will build a streamline ethical argumentation to identify gaps in the existing literature, evaluate existing guidelines, analyze the contents to reach a conclusion and put forward recommendations for quality improvement.

Conclusions: For the definition of research and its difference with clinical practice, decision should be taken in the best interest of the patient whether it is patient care or it is research.For ethical overview oversight, we suggest concept of proportionate review. Inform consent should be seeked in all researches but if becomes a barrier in patient care then waiver should be granted for the well-being of the patient. All information should be disclosed to the research participant's so that they make an informed decision for their participation.

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Introduction:-

Ethical Issues in Clinical Trials: A Review of the Recent Literature, an Ethical Argumentation. Clinical trials are the planned clinical research studies involving human subjects in evaluation of new treatment approaches(Sackett & Cook, 1994).Hence for, patient safety is involved in this process. Randomized controlled clinical trial is a scientific approach that provides information on new treatment options launched by the biopharmaceutical company. They serve their purpose only when they are properly designed, conducted according to guidelines, supported by adequate

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statistical data, reported as per regulatory guidelines. The principle of clinical trial is simple but the art is difficult and we as researchers have to learn a lot about the art.
Improved technology has forced sponsors to follow current guidelines, adopt risk assessment and mitigation strategy, develop integrated plan for addressing risks (EMA,2013). Patient safety research helps to identify systemic inefficiencies and help in designing techniques for quality improvement. Key challenges and obstacles to the design and conduct of trials are ethical issues and research regulations.

The purpose of this article is to review ethical challenges in current clinical trials, identify gaps in the current literature, and propose recommendations to bridge the gaps. Many authors have identified ethical issues as key risk to patient safety; however, this review evaluates all aspects of ethical issues and risks in a more comprehensive framework. It organizes all identified gaps in clinical trials to develop a risk management model that would be a valuable tool to support clinical trial safety and would help in improvising ethical culture in the world of clinical trials.

Methods:-

A comprehensive literature review was conducted using meta-analysis to identify ethical issues in clinical trials. A literature search was conducted using Pub-Med and Medical Literature Analysis and Retrieval System Online (MEDLINE).Key search words were: Ethical issues in clinical trials, Good Clinical Practice Training (GCP), Risk mitigations, Risk based quality management, Ethical culture in clinical trials, Regulatory challenges. Current research data published within five years was reviewed that met the initial criteria. For each identified issue we will discuss current trends, controversies, and gaps in the existing literature and finally we will put forward recommendations for improvement in those areas. A descriptive content analysis of the available literature has been made. We will check all alignments in the existing research ethics framework to identify gaps and discordance.

Findings:
We identified a broad range of ethical issues and risks involved in clinical trials. For better understanding, we have classified them in following groups.

1) Research vs. Practice
2) Inform Consent
3) Ethical oversight.

Ethical issues:
Protection of rights of the human subject is fundamental in clinical research. Ethical conduct of clinical research is of top priority. With this guideline, we begin our review.

Research vs. Practice:
Existing literature shows gaps in the definition and scope of research and practice. The demarcation line between two modalities in view of current literature is fine and not distinct. For the protection of research participants, it is important to define two terms research and practice and clearly outline the difference.

Research is a design and protocol followed to test an hypothesis, interpret results, draw conclusion through statistical analysis and contribute new knowledge while practice is implement evidence based interventions for the wellbeing of the patient (Principles & Subjects, n.d.). Research with high quality evidence support clinical decision making and improve the quality of patient care. It bridges the gap and helps to evolve patient care (Sugarman et al., 2014).

Different authors have put forward different theories and reasoning's for clearly defining the difference between research and practice. Kass and colleagues (2013) made risk determination as factor to clarify the difference between the two. The authors state, research carries more risk as compared to practice.Faden's approach has received significant support. He states, low risk trials should be governed by same rules as clinical practice(Faden et al., 2013; Peters et al., 2015; Kalkman, n.d.; Staa et al., 2012).

Largent and colleagues (2013) came up with the concept of moral distinction between research and clinical practice. In clinical practice, every step is taken to minimize risks and maximize benefits and in research, risks are justified by claiming potential benefits to future patients (Largent et al., 2013).

Most of the authors reject the distinction between practice and research. Firm reasons and criteria's are still missing. Based on the level of risk, difference between research and practice is required. There are certain clinical trials like pragmatic randomized controlled trials where the principles of practice and research both are used. Reasons to keep research and practice as separate domains are still missing. The authors do not accept the concept that based on more risk in research and to protect research participants a clear distinction is important. Based on level of risk these two modalities cannot be separated. This not a correct reason.

Rather the difference can be outlined by using the type of relationship as a reason. Type of relationship between a clinician and a patient and type of relationship between researcher and participant. In Clinical practice the doctor offers the best care for the best interest of the patient. While in research competing interest like financial compensation, career advancement undermines the trustworthy relationship between physician and the patient. When the clinician combines patient care with research the patient is assured that research will certainly offer him care and is a part of the management regimen.

Our article puts forward a different approach, decision should be taken in the best interest of the patient whether it is patient care or it is research. Patient's best interest should be safe guarded in every way. Where research laws and regulations become a barrier in care they should be sublimed and where they prove to be beneficial to protect the rights of the human participant they should be strictly followed and adhered. Procedures like ICF and ethical oversight to protect research participants when used sometimes prove as barriers in offering quick care. Therefore, the defining point should be the best interest of the patient and judgmental decisions should be taken on case-to-case basis.

Ethical Oversight:

Traditional ethical principles that govern clinical trials are: respect for person and communities, beneficence and justice. For the thorough execution of these principles, ethical oversight of clinical research studies is mandatory. In support of this view, International ethical guidelines for research, stresses on supervision of research by an ethics review committee (REC).It also outlines the principles and conducts that should be implemented as part of the ethical conduct of human research.

As per the guidance of the Office for Human Research Protections (OHRP), if the project has the scientific rigor to generate knowledge and data is collected systematically to improve care of patients in future and contributes to the field, then it is considered research and requires ethical review.

Criteria's considered for involvement of REC review are: Purpose of the project, the design of the project, source of funding, data dissemination. These criteria's help to determine whether a project is research and requires a REC overview.

Studies where patient role is beyond patient care and is rather they are participating to improve patient care, role of ethical committee is essential to ensure patient safety. Ethical committee review is warranted in all researches involving human subjects and sponsors who design the research project should not decide the ethical acceptance due to conflict of interest.

Scholars are of opinion; ethical oversight is required in research and not in clinical practice. If a project involves research, ethical committee review is mandatory for patient safety. They rely on the measurement of potential harm .If the harm is minimum, ethical sight is not required whereas the risk of harm is more than minimum, ethical oversight is required(Whicher et al., 2014).

Scholars' have argued, review of patient safety research projects involving data collection by the ethical committee weakens the approach of research personnel's to collect data and questions centered around patient safety. Scholars argue against ethical oversight(Whicher et al., 2014).

Our article proposes, any clinical research that involves human participants, ethical review is warranted for the protection of human participants. Integrity of the human participant is more important than any research.

Several authors also suggest if ethical oversight has to be improved, composition of the REC bodies has to be changed and customized. Qualification, Experience and training of the board members should be evaluated since

clinical research is much different from clinical practice. Based on the protocol of the trial, review should be diverted to those members who have the expertise appropriate to the protocol. Also burden of work on REC boards also affects the quality outcome .Hence for, quality functioning is required by REC boards to improve patient safety. Members should have expertise in both quality improvement methods and research. RECs play vital role in quality improvement (Baily et al.,2006).

There are discrepancies in the current ethical overview system .The system is impediment to research ,some authors have the consensus to streamline the system, while some want a completely new system should be evolved (Faden et al., 2013).

Ethical oversight poses a significant barrier in the smooth running of the clinical trials. Multiple committees pose a significant barrier to researchers. There is lack of standardization among review committees. Rourke and colleagues state lack of standardization leads to different review outcomes of the same protocol that lead to system delays(Rourke et al., 2015).

Some author's want changes in the review process(Faden et al., 2013).Some focus on changes in the steps in the review process. Some suggest case-by-case approach. (Kim & Miller, 2015) . Faden and colleagues call for new system for low risk trials .They also proposed oversight committees instead of RECs for determining the requirement of consent (Faden et al., 2013).

Based on the discrepancies in the current ethical overview system and lack of standardization, reform in ethical committee composition, structure and functioning are warranted. There is a great need to evolve a more efficient ethical overview system keeping in view the issues with the current system. Customized approach of ethical overview will help to resolve problems faced by highly scientific protocols. Board members qualifications and trainings should be continuously updated based on current norms. Different committees should be formed based on different serving goals. Generalized approach leads to system delays.

Criteria's for regular and expedite review-type of participants, vulnerable population, grade of risk, type of study methodology. If vulnerable population is not involved, pose low risk and has a scientifically sound methodology deserve expedite review. In existing literature there are views if the clinical trial is socially important, employs usual care of interventions, research topic is is of real world relevance ,trial will generate high quality of evidence and will directly impact current care practices should receive waiver from consent and deserve expedite review.

There are trials that involve interventions with no evidence of efficacy deserve careful review and consent is mandatory. This category also includes Post marketing trials that serve the interest of pharmaceutical companies. There is no discussion in the existing literature about risks posed by commercial clinical trials and how these risks should be minimized. We suggest,concept of proportionate review based on the study design, methodology, type of patient population involved, type of risk involved.

Design of the project should not rely on strict protocol rather protocol should be subject to change based on the feedback of the project results. Scholars do not agree on implementation of fixed protocol for years, since lot of factors change with time hence for quality improvement, repeated modifications in the protocol is required. Several scholars are of the opinion for patient safety and quality improvement continuous changes should be made in the protocol based on the feedbacks provided by the clinicians and research personnel's and changes should be communicated back to the team in timely manner for patient safety. In such trials where there is need to change the protocol based on feedbacks expedite and high priority review is deeply warranted to avoid administrative delays. Efficient ethical oversight leads quality improvement in clinical trial operation (Whicher et al., 2014).

Research contributes to the generation of new knowledge and human participants are the study subjects on whom new interventions are tried and evaluated. From ethical point of view, any research that involves human participants is governed by regulatory guidelines and requires ethical oversight. Prospective research participants should be treated respectfully. Since in research, participants are exposed to risk for the benefit of others hence for, their protection is the aim of all regulatory bodies.

Informed Consent:
Informed consent stands as the primary ethical issue in clinical research. Inform consent process, itself is the best example of patient safety practice. Inform consent is not merely a form; it is a complete thought process.

In view of scholars, the true purpose of inform consent is to inform the potential risks and benefits to the research participants and provide them an opportunity to take informed decision, thereby protecting their rights(Sugarman et al., 2014; Largent et al.,2013).

The ethical principle of consent revolves around the concept of respect and autonomy. Common consensus is consent is essential in clinical research because of higher risk: benefit ratio in research as compared to the clinical practice. Inform consent form should be clear, simple and easily understandable .It should not be a complex form.

Key information is presented in concise and focused way. This helps in addressing ethical issues that require careful thought and consideration. Documentation of Inform consent using standard operating procedure (SOP) helps in resolving legal issues involved in patient care. Inform consent process helps the human subjects in taking informed decisions for their health. This process protects patient's safety and rights.

Parental consent in perinatal context: In neonatal and/or perinatal clinical trials informed consent is seeked from the parents. Parents should be informed about the purpose of the research, study procedures, and alternative options of treatment while seeking consent for participation in the clinical trial. Valid consent is vital in the neonatal trials. There is still no proprer method of obtaining consent in neonatal trials. Parents should take best decision in the interest of the infant. The parents should assess the risk: benefit of participating in the research. Parents should be well informed about refusal and withdrawal process during the consent process(Duley et al., 2016).

To simplify the inform consent process, different authors came up with different models. Standard informed consent model ;written disclosure of all information is provided and written consent is obtained(Anderson, Ad-, Schreiner, &Schonfeld, 2014).Targeted consent model; information is disclosed verbally and consent is obtained in writing (Wendler, 2014). Integrated consent model information is disclosed verbally, no written document is signed, and consent is documented by the physician in electronic records (Hamel, Kim, & Miller, 2014). In streamlined consent, no consent is sought (Faden et al., 2013). Anderson and Schonfeld (2014) believe written document of the consent is essential and irrespective of the risk levels correct standard procedure should be opted(Anderson et al., 2014). Elsayyad (2012) states inform consent protects patient's dignity.

Our view is: Human participants are active partners in research and their rights are protected by inform consent form. The concept of consent is highly important in the ethics of research. Low risk trials do not need consent shows disrespect to the human participants. If the research is socially important, poses minimal risk, and inform consent will make is infeasible, in this scenario, waiver to consent can be granted. Criteria's for waiver-infeasibility and complexity, time and resources.

Inform consent waiver:
According to international guidelines, a research ethics committee may grant a consent waiver on basis of three criteria's: minimal risk, social value and if consent process adds infeasibility to the research. As per current ethic guidelines, inform consent is not required in research activities with minimal risk. But, it fails to exactly define the type of studies that are classified under minimal risk class (Faden et al., 2013). Authors have come up with the view, researches that are directed to system and use data to improve current strategies do not require inform consent, while studies that require interventional and experimental procedures definitely stress on the need for written inform consent. Miller and Emanuel (2008) suggest if the interventional procedures are based on evidence-based standards and do not pose any harm, then in these cases also inform consent is not required and human rights of the subject are neither violated. Certainly, inform consent is required in researches in which patient is put in study arm, since more risk is involved hence for inform consent is required in these cases(Miller et al.,2008).

Consent should not be required for both patients and health care providers to participate in routine minimal risk qualitative improvement projects. Faden and collegues(2013) consider the criteria of waive and based on Rawlsian notion of common purpose proposed, pragmatic randomized clinical trials RCT with minimal risk and approved by REC committee can proceed without consent (Faden et al., 2013).Mc Kinney and colleagues (2016), argue for a waiver may be granted by REC, if the risk is minimum and with inform consent the study is unworkable and

infeasible (Hallian et al., 2016). Kupersmith et al. (2013) also believe inform consent is not desirable in low-risk situations.

Our article proposes, waivers should be granted on case-to-case basis based on best interest of the patient. Inform consent should be seeked in all researches but if becomes a barrier in patient care, then waiver should be granted for the well-being of the patient. Judgment about requirement should be an individualized approach rather than generalized approach.

Disclosure of Information in Inform Consent:
There is also some disagreement what information should be disclosed while seeking informs consent. As per current regulations the potential research participants should receive comprehensive information about every element of the study .Subjects should be informed about the purpose, goals and objectives, methodology, steps, procedures, alternative treatments, risk and benefits ,compensation for injuries and about their rights. Whicher and colleagues (2014) state that purpose of the study should be disclosed. Wendler (2014) used the term added risks to define incremental risks. Wendler (2014) says, participation is voluntary and participants can withdraw anytime. Kim and Miller (2015) added voluntary participation should be a part of conversation about the trial. Authors also emphasize about detail disclosure of the trial if there are incremental risks involved in research participation (Hamel et al., 2014).

There is a conflict about disclosure of randomization information during inform consent. Some authors disagree ion disclosure information about randomization(Hamel et al., 2014; Wendler, 2014). Since studies are blinded disclosure of randomization should not pose any risk (Wendler, 2014).Feudtner and colleagues (2013) agree disclosure of randomization is not required since it doesn't adds any risk. Kim and Miller (2015)view is to not conceal any information including randomization.Neil (2014) states randomization should be disclosed to avoid false hopes and beliefs for a given treatment.

Our review proposes, ethical principle of respect underlines the foundation of disclosure of information in research(Principles & Subjects, n.d.). In existing literature, there is a misconception that risk is the underlying phenomenon for disclosure of information. Instead of risk, it is the principle of respect that drives the concept of disclosure. All information should be disclosed to the research participant's so that they make an informed decision for their participation.

Conclusion:-

For the definition of research and its difference with clinical practice, decision should be taken in the best interest of the patient whether it is patient care or it is research. Where research laws and regulations become a barrier in care they should be sublimed and where they prove to be beneficial to protect the rights of the human participant they should be strictly followed and adhered. Therefore, the defining point should be the best interest of the patient and judgmental decisions should be taken on case-to-case basis.

For ethical overview oversight, we suggest concept of proportionate review based on the study design, methodology, type of patient population involved, type of risk involved. From ethical point of view, any research that involves human participants is governed by regulatory guidelines and requires ethical oversight and the level of involvement of ethical committees should be based on the concept of proportionate review.

Inform consent should be seeked in all researches but if becomes a barrier in patient care then waiver should be granted for the well-being of the patient. Judgment about requirement should be an individualized approach rather than generalized approach.Ethical principle of respect underlines the foundation of disclosure of information in research. All information should be disclosed to the research participant's so that they make an informed decision for their participation.

New drug molecule discovered in the laboratory finds its way to the market after critical research(Pfizer,2009). Human subject protection is the aim of every clinical trial and all procedures should be designed to overcome the risks (FDA, 2011). Emphasis on discovery and profits rather than patient safety reflects lack of ethical culture (CCR 2ed.indd, 2010).This issue carries international relevance, hence for a global conversation is required to build firm international ethical guidelines for the protection of human participants. Collaborative approach to the problem at global level will help to develop international ethical standards for the design and conduct of clinical trials.

Strong scientific and organizational support, vigilance is essential for continuous improvement in trial conduct. The trial should be scientifically and ethically sound. Early risk assessment and mitigation ensures ethical outcome of the clinical trial.

Prevention of risk is a better choice compared to reactive management.

Policy Implications:
Health policy makers should link regulatory goals to patient safety indicators and support education and research. Clinical trials open new doors and address questions in an innovative way, bring new approaches in practical applications, hence for ethical conduct of the trial for quality assurance is essential.

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