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REVIEW ARTICLE

A Review Assessing Participants' Understanding of Informed Consent for Clinical Trials in Africa

Dorothy Maxwell Kazembe[1,2]*, Tigist Mesfin[1,3], Abigiya Abebe[1,4], Saba Mehari Embaye[1], Esther Nthenya Muthoka[1,5], Kedir Usmael[1,6], Mediha Ahmedin[1], Tsegahun Manyazewal[1]

[1]Center for Innovative Drug Development and Therapeutic Trials for Africa (CDT-Africa)
College of Health Sciences, Addis Ababa University, P.O. Box 9086, Addis Ababa, Ethiopia
[2] Malawi-Liverpool-Wellcome Trust Clinical Research Programme, P.O. Box 30096, Blantyre, Malawi
[3]St.Peter Specialized Hospital, Addis Ababa, Ethiopia.
[4]Department of medicine, St. Paul's hospital, P.O. Box 1271, Addis Ababa, Ethiopia
[5]Tororo General Hospital, Tororo Uganda
[6]Department Of Medicine, College of Medicine and Health Sciences, Dire Dawa University, P.O Box 1362, Dire Dawa, Ethiopia

*kazembedorothymax@gmail.com

ABSTRACT

Background: Informed consent provides detailed information to the participants to make informed voluntary and rational decision to participate in a study. It is a communication tool between investigator and the subject to ensure that high research ethical standards are followed. This review paper assessed the level of participants' understanding of the information given to them by researchers during the clinical research.

Methods: A review approach was used to achieve the study objective.

Results: The findings showed that the level of comprehension varied from study to study. There was a good comprehension in four domains; purpose, voluntariness, benefits and right to withdraw. Poor comprehensions were mostly in risks, side effects, and blinding. Higher level of education, repeated assessments of comprehension, time spent by the researcher explaining and clarifying the information influenced the comprehension.

Conclusion: The study findings point out that comprehension to informed consent is still a challenge that needs to be addressed during the field study. Once the consent is given it becomes a distant memory for most of the participants. This implies that proper tools and cut off points to determine participants' comprehension need to be developed for standard assessment of such.

Key words; Participant; Comprehension; Informed consent; Africa

INTRODUCTION

Informed consent is a process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after being informed of all aspects of the trial that are relevant to the subject's decision to participate [1]. Informed consent is an evolving process which indicates that medicine has encountered widespread changes under the influence of legal and moral requirements. It roots back to 1947 in the Nuremberg and 1964 declaration of Helsinki and now is the guiding principle for conduct in human research [2,3]. Informed consent serves two specific goals; respecting and promoting participant's autonomy and protecting participants from harm [4]. There are three elements that needs to be considered during the process of informed consent: information, comprehension and voluntariness. Information includes the aims, methods, sources of funding, possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-trial access and any other relevant aspects of the study [5]. Comprehension means the ability of the potential participant to understand the information which among other things depends on the individual's maturity, educational level and belief system [5]. On the other hand, the researcher's ability and willingness to communicate with patience and sensitivity, as well as the atmosphere, situation and location where the informed consent process takes place influence participant's understanding. Voluntariness means that an individual's decision to participate is made without coercion or persuasion [6]. The quality of informed consent in clinical research is determined by the degree to which participants understand the process of informed consent. Understanding plays a crucial role in clinical trials because it directly affects how ethical principles are applied in practice [6].

In the African context, comprehension to consent has been an issue of great concern [6]. The challenges with consent comprehension are further amplified by the fact that a considerable proportion of the potential research participants only have basic education, live in rural areas, have limited access to healthcare and are poor [6]. Mostly, the decision to participate is either targeted on getting better care through the trials or receiving the incentives that comes along with participating other than the understanding of the research concept itself [6]. In one review done in the sub-Saharan Africa, the results showed that informed consent is not always truly informed or truly voluntary [7]. Guidelines for obtaining informed consent are difficult to implement due to low literacy levels, socio-economic and cultural factors, on the other hand the local ethics committees are weak or non-existence in some countries [7]. A systematic review of 21 studies on how informed consent was defined and measured in African settings reported poor comprehension among study participants this means that there is a need to come up with a definition that can be applied better in such low literacy settings in Africa [8]. The process of obtaining informed consent may sound simple, unfortunately, things are not always easy and straightforward. There are some challenges that come along with this process, one of it is the issue of comprehension. Comprehension to informed consent is mostly related to the ambiguity of the information, participants' perception, language barriers and predetermination. So, this review is aimed at addressing such issues by assessing the level of participants understanding of the informed consent. Previous reviews assessed how the informed consent is defined and the proportion of participants in clinical trials who understand different components of informed consent in developed countries.

The results from this review will help researchers, policy makers and other health stakeholders in decision making and coming up with standards and tools that can be used in assessing participant comprehension, hence ensuring that study participants enroll to clinical trials whilst fully aware of what the study is all about and what is expected of them. Since informed consent is one of the important aspects of research ethics, this review will help to promote the protection of human subjects by ensuring that their autonomy is safeguarded, which states that welfare and interests of a subject participating into clinical research are always above the society's interests and welfare. In addition, it will help improve other ethical important concepts, such as transparency, trust, satisfying regulatory requirements and promoting integrity in research.

OBJECTIVES

- To assess the level of participants understanding of the informed consent components and concepts given to them by researchers.
- To investigate how the researchers assess participant's understanding of the informed consent.

MATERIALS AND METHODS

Systematic search of literature

This review was performed based on the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA 2015) guidelines. The electronic databases of PubMed, Cochrane Central Register of Controlled Trials and google scholar were searched to select important studies. In order to make the search as comprehensive as possible there was no restriction to years. Key terms used: participant; comprehension; informed consent; Africa.

Eligibility criteria

Studies were included if they were conducted in Africa, assessed participants' or guardian comprehension of informed consent information (understanding the nature or purpose of the study; the risks and side-effects; benefits; the voluntary nature of participation; freedom to withdraw from the study at any time; confidentiality) assessed how researchers assess participants' comprehension and involved participants who were in clinical trials. Studies were excluded if they used an intervention to improve participant comprehension, evaluated methods of informed consent, involve participants with cognitive impairment.

Study selection

Firstly, the titles and abstracts of all searched studies were read just to have an overview of what the studies were. From the title and abstract of all studies identified by the data base search, duplicated studies and those that did not clearly satisfy the inclusion criteria were excluded. Full texts of the remaining studies were reviewed to identify studies which were suitable for inclusion criteria and data extraction.

Data extraction

Data was extracted by two review authors independently: the country where the study was conducted, the year of publication, the phase of the study, the baseline characteristics of the study population: (the source of the population, the number of participants and their age and sex), the medical specialty of the clinical research, seriousness of the disease studied, the type of questions participants had to answer and the domains of informed consent assessed: understanding of the nature and purpose of the study, risks, side-effects, benefits, voluntariness, freedom to withdraw at any time, confidentiality, compensation and the availability of alternative treatment.

RESULTS

A total of 25,263 studies were found in the electronic data base of PubMed, Cochrane central registry of controlled trials and google scholar. A total of 1005 duplicated studies were removed. 24,258 studies were screened by the titles and abstracts, 24,231 were excluded, since they did not meet inclusion criteria (e.g., They were not clinical trials). The remaining
27 studies full texts were thoroughly read and 19 were excluded as they did not have relevant information. Eight studies were eligible for this review. The eight studies were from South Africa, Nigeria, Ghana, Mali, Botswana, Malawi and two from Kenya. See figure I.

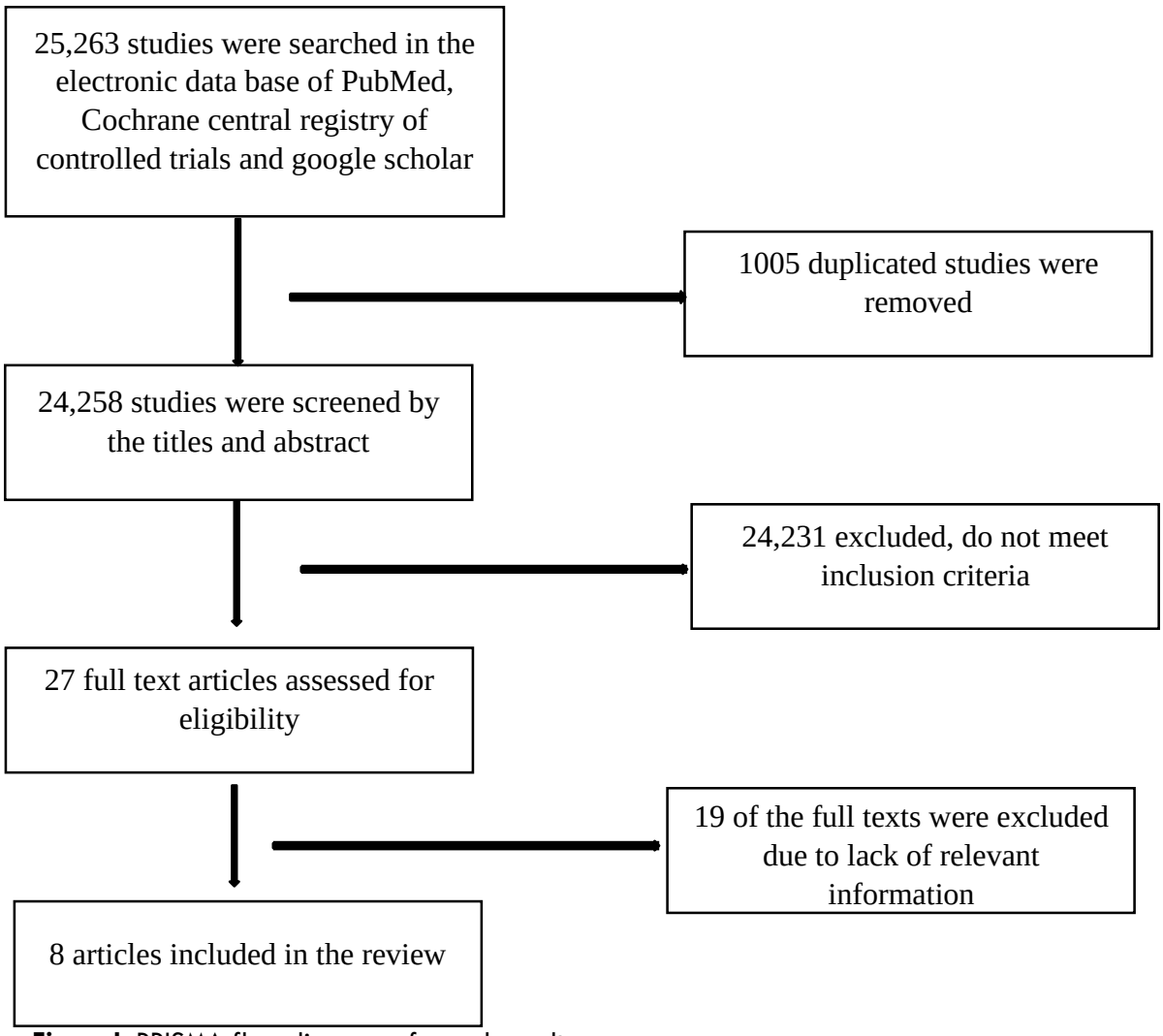

Figure I: PRISMA flow diagram of search results

Study characteristics

Final analysis included 8 studies [9–16], with a total number of 4209 participants. The participants were adults 18 years above. Two studies recruited the guardians/mothers of the participants since the studies were conducted in children [12,14]. One study used either guardians or the participants themselves as some of the participants were seriously sick [9]. Five studies assessed the participants themselves [10,11,13,15,16]. The studies subject of interest was; malaria [11], vaccines [14], oncology [12], cardiovascular disease [10], HIV and AIDS [9,15], maternal health [13] and microbicide [16]. The details are presented in Table 1.

Table I: Characteristics of studies included

Author	Country	Number of participants	Age of participants	Type of participants	Subject under study	Critical condition involved	Method of assessment
Naanyu *et al.* (2014)	Kenya	21	18yrs above	Patients/guardians	AIDS Clinical Trials Group	Yes	A qualitative, cross-sectional and descriptive approach- in-depth interviews
Adawale *et al.* (2016)	Nigeria	75	18yrs above	Patients	Malaria clinical trial	No	Cross-sectional survey-questionnaires and a forced-choice checklist
Burgess *et al.* (2019)	South Africa	46	18yrs above	Patients	Cardiovascular risk clinical trials	No	Close-ended (self-report) and an open-ended (descriptive narrative) assessment
Jepkemei *et al.* (2018)	Kenya	187	18yrs above	Guardians	AMPATH Haemato-Oncology study	No	Descriptive cross sectional-Two sets of semi- structured questionnaires
Hill *et al.* (2006)	Ghana	1661	18-45yrs	Patients	Impact of (vitamin A supplement) VAS on maternal mortality	No	Semi-structured interviews and 12 focus groups 2 years after the study
Krosin *et al.* (2006)	Mali	163	18yrs above	Guardians	Malaria vaccine trial	No	Questionnaire
Chaisson *et al.* (2011)	Botswana	1835	18yrs above	Patients	Placebo-controlled, randomized trial for the prevention of tuberculosis among HIV-infected	No	20-question true/false quiz
Ndebele *et al.* (2014)	Malawi	225	18yrs above	Patients	Microbicide trial	No	Structured questionnaire interviews with a random sample of 203 participants Four in-depth interviews with research nurses Two focus group discussions with 18 study participants

Assessment tools

Naanyu et al used in-depth interview. Burgess *et al*. used both close-ended (self-report) and an open-ended method (descriptive narrative). Adawale *et al*. used questionnaires and a forced-choice checklist. Japkemei *et al*. used semi-structured questionnaires. Hill et al. used semi-structured interviews and focus groups. Krosin et al used questionnaires. Chaisson *et al*. administered a quiz of 20 true or false questions. Ndebele *et al*. utilized three ways: structured questionnaires, in-depth interviews and focused group discussions. The tools varied significantly in the number of items assessed. Participants were assessed on several domains of informed consent, thus: nature and purpose of the study, risks, benefits, voluntariness, freedom to withdraw at any time and confidentiality.

Results on comprehension assessment

To assess the comprehension of the informed consent by the study participants, the following domains of the informed consent were analyzed; understanding of the nature/purpose of the study, awareness of potential risks and side-effects, potential benefits, voluntariness, freedom to withdraw at any time, confidentiality, blinding and compensation.

Understanding of the nature/purpose of the study

Four studies out of the eight assessed understanding the purpose of the study. Adawale *et al*. reported the highest level of comprehension, almost all the respondents showed that they comprehend to the information given to them concerning the purpose of the study, 99% of 76

participants, which was good [11]. Chebungei *et al.* reported that 76% out of 187 participants indicated that they understood the purpose of the study, a small number (5%) could not recall the purpose, while the rest stated other reasons other than the main purpose of the study [12]. Hill *et al.* reported 75% out of 1661 participants had an understanding of the nature/ purpose of the study [13], in this study women verbalized that they were taking part in research. The study aimed at assessing the effectiveness of vitamin A, but some women verbalized that the research aimed at assessing if women are taking the capsules and whether it had side effect. With these answers one would tell that the figure 75% is not really a true reflection of the comprehension to the purpose of the study. Chaisson *et al.* reported that 91% out of 1835 understood the purpose of the study, this was associated with higher level of education [15]. There were varying opinions, "from very easy to understand" to "difficult to understand" [9]. Reading the form and further explanation from the researcher several times helped others to understand [9]. Length of the form, complexity and no further explanation made it difficult to understand the purpose of the study for some participants [9]

Awareness of potential risks and side-effects

Three studies assessed participants understanding on the risks involved upon participating in the studies[9,11,15]. One study assessed participants understanding on both the risks and the side effects [8]. One study assessed only the side effects [14]. Burgess *et al.* reported that only 17% of 46 participants understood the risks, 54% of them understood about the side effects, many of the participants could not even recall that there were risks involved, some participants could at least mention one potential benefit [10]. Adawale *et al.* reported that only 13% out 76 participants understood the risks, it is very worrisome that the majority (87%) could not recall being told of any risks involved [11]. In this case it's hard to conclude if risks were really discussed or it is really poor comprehension on the part of the participant since benefits of participating yielded good comprehension of 100%. Chaisson *et al.* reported that 60% of 1385 participants understood the risks [15]. Krosin *et al.* reported a very small percentage; 7% of 163 understood the side effects, the majority 93% failed to identify the existence of side effects of the study drug [14].

Potential benefits

Three studies out of the eight assessed the potential benefits of participating in the study. According to Burgess *et al.* 52 % of 46 participants understood the potential benefits of participating in the study [10]. Adawale *et al.* reported 100% comprehension (100% of 76) on the benefits of participating in the study [11] which was good, nevertheless, one may turn to think that the potential benefits were over emphasized by researchers hence having a good comprehension by all the participants. Chebungei *et al.* reported a 77% understanding of the potential benefits out of 187 participants [12].

Voluntariness

Four studies assessed the concept of voluntariness. The study by Burgess *et al.* demonstrated that many participants (96% of 46) understood the concept of voluntariness [10]. Adawale *et al.* reported that only 20.3% of 76 understood the concept of voluntariness, and it was expressed by most of the participants (57.7% of 76) that they thought people are chosen because they are seriously ill [11]. Further some participants said they thought participating in the study will help them get diagnosed and receive free treatment. Krosin *et al.* reported that 57% of 163 participants understood the concept of voluntariness [14]. Chaisson *et al.* reported that 78% of 1835 participants understood the concept of voluntariness [17]. Emphasis on comprehensive to voluntariness was noted as quoted from one of the studies, "I was explained to… I got to a point where I was contented and I appended my signature so as to participate in the study…I made the decision alone." [9]

Right to withdraw

Four studies assessed the concept of right to withdraw. 96% of 46 participants understood their right to withdraw at any time, despite the large percentage, Burgesss *et al.* had some participants expressing that they considered withdrawing as being disrespectful and in the long run one would lose some benefits [10]. Adawale *et al.* reported that 100% of 76 participants understood their right to withdraw at any time [11]. Krosin *et al.* reported that only 10% of 163 participants understood their right to withdraw at any time and withdrawing was perceived as loss of self-determination by the participants and some parents had a belief that third party permission is required to withdraw their child from the study which meant the child may be kept in the study despite the wishes of the parents or child [14]. Chaisson *et al.* reported that 75% of 1835 participants understood their right to withdraw at any time [15].

Blinding

Three studies out of eight studies assessed blinding. Burgess *et al*. reported that 20% of 46 participants understood the concept of blinding [10]. Chaisson *et al*. reported that 66% of 1835 participants understood the concept of blinding [15]. Ndebele *et al*. reported that 68% of 226 participants understood the concept of blinding [16].

Compensation

Three studies out of eight studies assessed compensation. Adawale *et al*. reported poor comprehension to the issue of compensation in one of the studies (29% of 76 participants) [11]. Krosin *et al*. reported that almost half (44% of 163) of the participants understood compensation [14]. Chaisson *et al*. reported that 90% of 1835 participants understood the concept of compensation [15]. Despite repeated reading, some participants had difficulty understanding the concept of compensation [9].

DISCUSSION

This review indicates there are still gaps when it comes to comprehension of the informed consent by study participants, with a few domains being comprehended to for instance: understanding of the purpose/nature of the study yielded good results, ranging from 75%-99%. This is in line with one review that was done globally, around 75% of individuals comprehended well to the nature/purpose of the study [18]. There were few percentages of individuals who could not recall at all the information given on this matter and some who were giving explanations a somehow related to what was explained to them.

Awareness of potential risks and side effects had poor results, except for one study which had 54% out of 46 participants who comprehended to the concept of side effects. The majority of participants could not recall that there were told about any risks or side effects. This was also reflected in one study done by Fortune *et al*. only 17% could name three or more potential risks of the medication they might be exposed to, whilst 20% could identify none [19]. This is a bad sign, as it indicates that the majority of the participants' consent without fully understanding what they are volunteering to. Surprisingly, there was a positive response pertaining to the potential benefits, the majority of the participants understood the concept, which leaves a lot to be desired and one may be tempted to think that the researchers might have overemphasized the benefits as one way to influence the potential subject to enroll in the study. Researchers must at all cost refrain from unjustified deception, withholding information and undue influence [20].

Voluntariness and right to withdraw concepts were understood, except for two studies which had 20% and 10% for voluntariness and right to withdraw respectively. Voluntariness of participants is to some extent questionable, mostly it could be associated with the benefits/incentives that come along as one participates in a study for example better access to diagnosis and treatment which is somehow difficult to access outside clinical trials due to the poor health system. The stage of illness drove others to participate, despite the lack of clarity on what the study is all about. To some they thought participants were enrolled because of the seriousness of their condition not necessarily because they willingly accepted to partake in the study. Right to withdraw was associated with lack of self-determination and being disrespectful to the investigators. It must be made clear to participants that it is acceptable to withdraw at any time and it means no offence and no penalties will be given for making such decisions [21].

Compensation calls for a lot of ethical concerns, it may have undue influence as participants may be coerced or may alter their decision to make an informed decision to participate in a trial [22]. Compensation yielded poor results in some studies, despite repeated reading and explanation. Compensation to research participants for clinical trial related injury, death or Serious Adverse Effects (SAE) should be thoroughly discussed. This concept is still strange to many people in developing countries. It's been noted that this concept is rarely discussed and if at all discussed, the discussion is shallow and participants mostly lack access to legal recourse and health insurance is neither subscribed to nor available in many rural communities and it leaves many participants hanging without knowing their right to be compensated once faced with unforeseen circumstances whilst participating in a study. In addition, there is little literature on compensation to research participants for clinical trials on trial related injury, death or SAE, further studies need to be done.

Time factor when assessing comprehension is of great concern, once the informed consent form was completed, it became a distant memory for most of the participants; by the time of interviews, they could barely remember its content [9]. Since most of the clinical trials take long to complete for example phase III and IV it would be wise to do repeated assessments of informed consent comprehension. We can borrow a leaf from Chaisson *et al*. they administered comprehension quiz at enrolment and during follow up, and it

demonstrated that participants generally understood key study information. Additionally, it also proved that administration of quiz both at enrolment and follow-up was feasible and is a useful means of determining whether subjects had sufficient information to enroll in the trial. Participants' understanding of information decreased slightly following enrolment, but the rate of passing improved following the first re-assessment, from this we can conclude that providing quizzes over the course of an ongoing clinical trial may reinforce key study information [15].

Time spent by the researcher explaining every detail of the study had a positive outcome to participant comprehension. It is of great concern that only few investigators assess the participants understanding, a lot of questions come to mind: is it that they are scarred of losing a good number of potential subjects if they assess their comprehension and realize that they did not comprehend? Or what steps can be taken to those who still do not comprehend despite using all possible ways of conveying the consent information to them? Unfortunately, there is no guideline or measurement scale to suggest the level of comprehension one is eligible to be enrolled in the study and this need to be looked into. Investigators need to reflect on their practice and the ways in which they give information and interact with participants during a study.

CONCLUSION AND RECOMMENDATIONS

Participant understanding has not really changed over the years. Poor comprehension or no comprehension at all defeats the present practice of providing sound ethical basis experimenting with human participants. The majority of the participants understood the purpose of the study, voluntariness, right to withdraw and benefits. The risks involved and concepts of placebo, blinding and randomization were not clearly understood. Researchers need to put extra efforts in making sure that participants understand the informed consent before enrolling in the study and informed consent should always be a process not a one-time thing, therefore reassessments of the comprehension to informed consent during follow up visits need to be put into consideration. Ethical regulatory bodies should make it a requirement that all clinical trials assess participant comprehension to the informed consent after it has been administered and a grading system and a cut-off point should be put across to act as a guideline in measuring the acceptable level of comprehension for one to proceed to enrolment into the trial.

LIMITATIONS

Two domains were not assessed; confidentiality and availability of alternative treatment because they were not assessed in the chosen studies. We were unable to assess how investigators in the main studies evaluate the participants' comprehension as the studies selected herein did not tackle that and as mentioned above only few studies attempt to do that. There was high level of heterogeneity in the underlying medical condition across studies, this might have an effect on the level of understanding.

ABBREVIATIONS

AIDS - Acquired Immuno-Deficiency Syndrome
HIV - Human Immuno-Deficiency Virus
ICF- Informed Consent Form
ICH-GCP- International Conference of Harmonization-Good Clinical Practice
MRI - Magnetic Resonance Imaging
PRISMA - Preferred Reporting Items for Systematic Review and Meta-Analysis
USA - United States of America
VAS - Vitamin A Supplement

CONFLICT OF INTERESTS

There are no conflicts of interests in this study

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AUTHOR CONTRIBUTIONS

All authors made a significant contribution to the reported, whether that is in conception, study design, execution, acquisition of data, analysis and interpretation, or in all areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. Study design and first draft: DMK, TM. Data check and revision of the draft: TM, AA, SME, ENM, KU, and MA. All authors reviewed and approved the final version for publication.

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