Reviewer 1 comments

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| Sr. no | Comments | Reply | Page and line modified |
| 1 | A very similar publication has been written earlier by the author and is stated in this work | It was first IEC monitoring study published in India so that reference was quoted (ref 5 ) |  |
| 2 | The issue has not even been discussed with references from other parts of India or south east Asia or LMICs from other continents. Despite lot of literature being available, the author references just one previous publication of his/her own. | The recent most review article actually gives the real issues with site monitoring and the real scenario also that IECs are only doing passive monitoring and not active monitoring . This article is included in the discussion and the ref no is 3 and 8 |  |
| 3 | The strength of evidence for recommendations is not adequate; the actual recommendations are neither right nor sustainable. | One of our recommendations are routine monitoring and creating an internal DSMB –which is based on the study finding. There are institutes in India where all intramural funded studies are monitored by internal DSMB (Tata Memorial Hospital ) |  |
| 4 | There are loose generalisations, I feel. They are below. At a time when the IEC is facing challenges (resource constraints - human, time and money)to even regularly conduct meetings, it sounds simplistic to state that IEC can take on the responsibility of active monitoring of study sites!   * Use of Clinical trial and clinical studies interchangeably; not all clinical studies are clinical trials and may not require the rigor of a clinical trial. * Data and Safety Monitoring Board (DSMB) is a very different concept whose purpose, scope and conduct are clearly stated in international guidelines. To consider this as an aspect of ‘regular monitoring’ and suggest as a recommendation is inappropriate. * Terms like ‘audit’ and ‘supervision’have been loosely / interchangeably used. What actually the author means is subjective and open to interpretation. It is better to use terms consistently as defined in international guidelines or perhaps define in a glossary | We accept this comment , but once IEC is stabilized with its routine duties , they can try and monitor the sites “for cause ” which is enhancing its own standards and protecting the rights of the participant as required by ICMR 2017 guidelines  a. We agree with the reviewer that Clinical trial and clinical studies were used interchangeably at some sites – on page 9/10 and 10/10  b. We agree with the reviewers that DSMB are created with different scope in it . Here we are referring to a internal monitoring board as regards to Ethics committee which will review protocols of more than minimal risk  c. The reviewers have taken the literal meaning of audit , but here in the study context ,we thought of monitoring finding which is mentioned on page 6/10 and audit report mentioned on 8/10 is regarding regulatory audit report . The supervision term has been used in terms of investigator supervision on the trial site | a. It has been changed from clinical studies to clinical trial on page 9/10 and 10/10  b. We have changed the term DSMB to internal monitoring board on page 10/10  c. the term audit has been changed to monitoring on page 6/10 |
| 5 | . Important omissions;   * In the ICH GCP, ‘monitoring’ is a responsibility of the sponsor of the trial; there is no reference to such regular monitoring visits and how the IEC monitoring related to it * In order to make optimum use of resources, ICH GCP in its latest version suggests ‘risk-based monitoring’ versus regular monitoring of clinical trials. There is no reference to this concept. | We agree with this comment ,that monitoring is solely responsibility of the sponsor , but there are few conditions where IEC has to monitor sites (for cause – if there are repeated violations at some site, too fast or early recruitment ,in annual reporting if IEC find some strange finding) and in this context the monitoring is done and the study is its retrospective analysis . we are at a very primitive level of site monitoring and we will try to inculcate this thought in the study , but again this is responsibility of the sponsor to do RBM | We have included risk based monitoring in page 10/10 and included a new reference 9 |
| 6 | The Methods section is not clear to the reader/ reviewer. Use of quantitative analysis is inappropriate. If the author would like to show changes over time, then it is preferable to state in the methods section, what were the actions taken after the first paper; how did this impact / bring about changes subsequently. It is not clear if the study sites in the first and the current papers are the same or different.  It is not a research article in the strictest sense; just an analysis of the reports and would therefore be better to describe the results in text and substantiate with literature evidence in the discussion section. | The method section is clearly mentioning the procedure as in how the study was done and why χ2 test/Fischer Test was used . The actions taken are been mentioned in the prior paper of *shetty etal*.The study sites are different in both the papers , The intention of the author was to see if the research environment has changed over the period of time . Many of the investigators and the sites were the same, but the studies monitored were different. We felt that figures make the presentation attractive and enhances the understanding ,so we would like to retain the figure. We have added few references and expanded the discussion. | We have added discussion on page 10/11 and references added are 3,8,9 |
| 7 | Summary:  Substance   * Provide a clear background and rationale * Rewrite the Methods section clearly * Ensure the contents fit in the heading; do not mix up contents * Avoid repetition and redundancy of contents between text and table and between the different sections * Discuss using references from India, SE Asia, Africa … Are other country IECs adopting similar practices? * Conclusions and recommendations to be drawn considering the comments in 4 and 5 | Majority of the comments have been accepted and changes have been incorporated . Scenario of USA, Australia and New Zealand along with India has been compared and we have added the conclusion section as mentioned | We have added conclusion on page 10/11 |
| 8 | M1 -Of what entities??  M2 - Please say which site  M3- By whom  M4- Did you inform / take consent of authors of previous study?  M5- Reference??  M6 - Of what nature??  M7- How has DCGI monitored IECs?? Detail the process  M8- References?? What is said in the updated guidelines??  M9- Why? Why not? Is it supported with references?  M10 - What does it entail? Provide details to substantiate  M11- When was it given?  M12 - Are they clinical trials? If yes, what phase? If no, what is the nature of clinical study?  M13- Where were the studies done? In KEM or elsewhere?? Details of the study sites?  M14- When exactly was the IEC monitoring carried out? Was it during the ongoing phase of the study? Or in 2018, as the SOP in the reference is dated 2018?? It is not clear how many times a study site was monitored, only once or many times?  M15-What is the nature of the documents reviewed? Why were the site documents brought to the office of the IEC?  M16- This sentence is complex and unclear. Is it referring to the regular monitoring? Or to the IEC monitoring??  M17- If the identity was not noted, how did EC decide on corrective actions for a particular site?  M18 - How was this assessed?  M19- Why EC was not aware of this non-reporting?  M20-By whom is the supervision to be done? Not sure how this was assessed  M21- How was this assessed?  M22- What does this refer to?? As an abbreviation, ICD refers to international classification of diseases  M23 - Auditors prepare an audit report. These terms are confusing and not appropriate terms.  M24 - There is no rationale for use of this test. Apparently, the unit used in this analysis is a study site; one site may have just a random protocol violation / non-compliant informed consent form versus another having systematic issues. They are apples and oranges and not comparable.  M25- Were there no regular monitoring visits conducted by the company?  M26-‘some’ is vague. Please specify  M27- What is the evidence? How many members of the team were interviewed?  M28- Please specify how many  M29- This has already been discussed in the previous heading on informed consent process. Looks repetitive  M30- Was this part of any monitoring by EC? Or EC approval?  M31- Assuming this finding was picked up early on, what action was taken by the IEC?  M32-This should be in discussion. This could also mean that the site is not afraid of EC as there was no effective EC oversight / monitoring. Is this study on 60 patients published? If yes, has EC informed the journal about this ethical deviation  M33- How many sites?  M34- How many trials/ sites were seen in 2008 – 2010?? As stated earlier this method of comparison is not valid.  M35- Avoid use of percentage with a small no – 12 sites?  M36- Not true. At one site the PI had retired!  M37-Avoid use of percentage with a small no  M38-Avoid use of percentage with a small no  M39 - These numbers are shown in the figure.  M40- Was it ongoing during 2011 – 2017 or was it in 2018? Details should have been furnished in the methods section, rather than as a separate section.  M41- Instruction?  M42- What period exactly?  M43- The para looks like a review. There are no results in terms of number and type of actions vis-à-vis monitoring findings.  M44- If the site is unaware of protocol, it should be trained in the protocol not gCP.  M45- Who was asked to pay – PI or sponsor? Was there an order from DCGI re: compensation amount?  M46- How many? Which?  M47- Avoid redundancy of contents in text and table.  M48- The discussion is short sighted as it is only comparing with the previous study. There is no literature support, despite availability of publications  M49- With small no of sites, such adjectives may look like over-interpretation. Instead of focusing on statistics, it would be better to focus on the nature of deviations and their impact on human protection and data integrity.  M50- Over simplified; as the other issues are still persisting!  M51- Not proved as small numbers  M52- Monitoring is after approval not before approval.  M53- No data in your study to conclude that clinical work overload causes consent deviations  M54- Do ethics committees have the resources required – human, time and money?  M55- Training of EC members in monitoring  M56- Not all clinical trials require a data and safety monitoring board? The need for and the functions is clearly specified in ICH GCP and may be beyond the capacity of the IEC to perform this role  M57- Even if there is external monitoring, the ECs have to monitor studies as per regulations and guidelines  M58- What specific training is required by EC members? What about effective Corrective actions?  M59- Please mention the limitations of the current study.  M60- Is that the only solution? How about research capacity development initiatives to prevent these deficiencies? | M1-The entity is protocol awareness by PI  M2- PI of multiple violation site  M3-by Ethics committee  M4- Dr Thatte was no more interested in the study and Dr Sandhya Kamat was no more working for KEM Ethics committee . they both have been consulted and taken permission before start of the study  M5- reference 3 included  M6- added interventional in nature  M7- many of the sites have been inspected by competent inspectors from DCGI office and new GSR in re-registration of ethics committee with CDSCO site there is column included regarding monitoring of site by Ethics committee  M8- ref no 4 has been added , in NABH accreditation of ethics committee , monitoring of sites is mandatory  M9- there are studies by Pickworth and Shetty et al ,which mentions that passive monitoring can miss many things which active monitoring can find  M10 – SOP 5 contains in detail the monitoring –scope, procedural details and form and punishments  M11-as per KEM ethics committee SOP , retrospective analysis of data can be exempted from review . It is usually done by chairperson who is not part of the study  M12- there were 12 studies , in which 7 were regulatory studies (5 phase 3 and two were phase 2)and 5 were academic interventional studies  M13 – all study monitoring report which was analysed were from KEM site  M14- the studies were monitored once only in the period 2011-2017 , the retrospective analysis of the monitoring report was done in 2017  M15- There is a checklist by which the EC members monitor the site , ICD process, source documents , CRF entry , site facility , documentation between the investigator –sponsor and investigator –EC and regulator is also checked . These all events have already happened , the study is only retrospectively analysis of the monitoring report with the actions taken by EC  M16- it refers to IEC monitoring  M17- The actions have already been taken by IEC , we are analyzing the monitoring report with the findings and the action taken by the IEC , where confidentiality was maintained  M18- IEC has to be updated annually by the PI , if after 2 reminders the PI does not report , EC monitors and this is how it is derived  M19- one of the sites had a close out report send by the sponsor , the investigator forgot to send to IEC . There are many such lapses from the investigators  M20- PI is supposed to supervise the study site and the coordinators  M21- in the report it was written , when the site was monitored and the PI was asked about the inclusion criteria which was violated by him . It was found the PI did not knew the protocol  M22- ICD refers to Informed consent Document  M23- the sites were auditors have audited, such reports have to be submitted to IEC , which was not done by the PI  M24- The themes we found in violations were similar to prior study ,as the data is categorical hence the test. The comparison here was apples with apples only , but if read through the article the actions taken were different in these timespan  M25- out of 7 sites , 5 were monitored by sponsors but there monitoring report was not submitted to EC and 2 were not monitored yet .  M26- the correction is done  M27- Evidence is the monitoring form and the report present in EC office given by the members. Atleast one member preferably the PI is interviewed  M28- ICD related 4 issues , already mentioned in the text  M29- Under protocol deviations , every aspect of protocol is included even ICD issues ,so has to be included. But we accept it can be repetitive  M30- it was part of IEC approval , not followed by the PI  M31- IEC would not have allowed to include that data in analysis , so the entire effort of the PI would have been wasted  M32- This was an academic study , the student was asked to repeat the study as that data was not be used .And his 6 month term was extended for completion of the study  M33- at 3 study sites  M34 – the trial site numbers are different in both the studies ,but the comparison is between the similar themes .  M35 – we will include number with %  M36- After study recruitment was over ,he retired but that information was not intimated to IEC …  M37 – same question as M35  M38- We will include numbers as well  M39- the numbers represent the theme  M40- it was ongoing in 2011-2017 ,has been clarified in methodology  M41- included the word instruction  M42- period included  M43-the corrective action table mentions specific action for each theme  M44- we appreciate the comments and suggestions included  M45- PI was asked to pay as he is the caretaker of patients  M46- all the lapses have been enumerated  M47 – Some text data deleted from page 6, which were being repeated in Figure.  M48- the discussion has been enhanced by including with other studies  M49 – all these deviations have some impact on human protection and data integrity and has been incorporated. Also, the data is represented in percentage in figure 1 as the number of sites monitored were varying in the previous study and this current study (7 in previous study vs 12 in current study). Percentage data will give a better perception of finding.  M50- some scenario may exist, but few issues had shown good hopes  M51- we accept the comment , but same site monitored had shown improvement  M52- site feasibility approval , investigator approval is done based on our knowledge about the site  M53- one sentence included  M54 – that are quoted as biggest hurdles  M55- already mentioned in the text , if monitoring of site has to be done , prior training is a must    M56- ICH –GCP requirement is very specific and has been included in the text , but now ICMR guidelines 2017 and currently CDSCO NABH accreditation of ECs – one of the criterias are does EC monitor s the site  M57- same answer as M56  M58- specific training is given by industry working in DSMB boards . the corrective actions are taken as per the SOPs of KEM EC  M59- The limitations of the current study are it is a retrospective analysis of monitoring reports and corrective actions taken by specific EC . These data cannot be generalized to other setups . As routine monitoring is not a norm for EC , the sites selected for monitoring were majority times for cause .  M60- This is one of the solutions recommended , even if the research capacity development initiatives are taken , protocol deviations, AEs, site errors , AV consent issues can only be tackled by site monitoring . | M1-Changed on page 2/11  M2- changed on page 2/11  M3- changed on page 2/11  M5 – on page 3/11 , ref 3 added  M6- included on page 3/11  M7- included on page 3/11  M8 – section added on page 3/11 and ref 4 added on page 10/11  M9- ref 3, 5included on page 3/11  M10- ref 7 included  M20- on page 4/11 , included investigator  M22- included Informed Consent Document on page 4/11  M26- Included 2 on page 5/11  M33- included on page 6/11  M35- Included on page 6/11  M41- included in Page 8/11  M42- included in Page 8/11  M44- included in Page 8/11  M46- - included in Page 8/11  M48- Included on page 9/11  M49- - Included on page 9/11  M52- Included on page 9/11  M53- Included on page 9/11  M54- Included on page 9/11  M55- Included on page 10/11  M56- - Included on page 10/11  M57- same as above    M59- Included in text on page 10/11 |

Reviewer 2

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| Sr. no | Comments | Reply | Page and line modified |
| 1 | The paper does discuss issues relevant to the fields of bioethics and medical ethics in the developing countries. It could influence policy and practice if revised | We have revised the discussion and conclusion part | Included in Page 10/11 |
| 2 | There are important omissions and loose generalizations which have been indicated where they occur in the text of the paper. These need to be modified. | All the comments are accepted and accordingly the article has been modified |  |