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COMMENTARY

Ethical issues in a cluster randomised controlled trial for evaluating effectiveness of screening for breast cancer by clinical breast examination in India

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Abstract

This article discusses issues of ethical concern in the conduct of a prospective, cluster randomised controlled trial for evaluating effectiveness of screening by clinical breast examination for downstaging of breast cancer, and in reducing mortality from the disease, in comparison to no screening. This trial was conducted in Mumbai, India, over 20 years, from May 1998 to March 2019. Trained primary health workers provided health education, visual inspection of cervix and clinical breast examination in the screening arm. Women in the control arm were provided only health education and not provided any intervention, though screening mammography is an established, standard procedure, which is also available in Mumbai; the risks of not having the examination, and the benefits of having the examination (mammography or clinical examination by health worker), in terms of early detection and hence the possibility of starting early treatment, were not explained; furthermore, there were several differences in the English and Marathi informed consent forms.

Keywords: *randomised controlled trial, breast cancer, informed consent*

Introduction

This commentary draws attention to ethical violations in a prospective, Cluster Randomised Controlled Trial (CRCT) for testing the effectiveness of screening by clinical breast examination (CBE) in downstaging[a] breast cancer at diagnosis and in reducing mortality from the disease, in comparison to no screening [1, 2, 3]. In this trial, women in the control arm were not provided any intervention, though screening mammography is an established, standard procedure, which is also available in Mumbai; the risks of not having the examination, and the benefits of having the examination (mammography or clinical), in terms of early detection and hence the possibility of starting early treatment, were not explained to the participants; furthermore, there were several differences in the English and Marathi Informed Consent (IC) forms.

The study

In May 1998, the Tata Memorial Hospital (TMH), also described as Tata Memorial Centre (TMC), Mumbai, India, initiated a 20-year prospective, CRCT for cervix and breast cancer screening in a "low socioeconomic, previously unscreened population, in Mumbai, India". The objective was to determine "the efficacy and cost-effectiveness of well-planned health education programmes, along with screening for cervix and breast cancers" using visual inspection of cervix with acetic acid (VIA) and CBE, respectively, in reducing the incidence of and mortality from these diseases. These procedures were to be provided in the trial by trained primary health workers. The trial was funded by the National Institutes of Health, USA, and also supported by the Sir Dorabji Tata Trust, MK Tata Trusts, and the Department of Atomic Energy, Government of India [1, 2, 3].

The randomisation was by cluster, in which groups rather than individuals were chosen as units of randomisation. Twenty independent clusters were numbered 1–20 and randomly allocated to screening or control groups by a draw of lots. Ten clusters were assigned to the screening arm and 10 to the control arm. The study recruited 1,51,538 women aged 35–64 years from these 20 clusters. Of these women, less than 5% were literate and 35% were illiterate, around 55% had school level education, while around 5% had studied above high school level. Around 55% women were Marathi-speaking, while 20% were Hindi-speaking and around 25% spoke other languages (not specified in the paper). Less than 7% reported an income of over INR 1,000 a month (at the time of entry in 1998) [3]. Health education, VIA, and CBE were provided in the screening arm, and only health education in the control arm [3]. This paper discusses one part of the study — the evaluation of CBE for breast cancer.

The report of the study on CBE, published in 2021, stated that the study protocol was amended several times during its long course, particularly in the initial years [1]; however, no details regarding the reason for and nature of these amendments are provided. Women in the screening arm (n = 75,360) received four rounds of CBE conducted by trained female primary health workers, along with information on cancer awareness, every two years. The four rounds of CBE were followed by five rounds of active surveillance every two years via home visits. Those in the control arm (n = 76,178) received one round of cancer awareness followed by eight rounds of active surveillance every two years. Participants in both arms were eligible for free diagnostic evaluation and treatment at the TMH. For this purpose, women from both groups were provided with similar identity cards. Four

rounds of CBE were concluded in December 2007 and follow-up continued until May 2018.

The study was approved by the institutional ethics committees of the TMC. In addition to review by the internal data safety and monitoring committee of the TMC, the trial was annually reviewed by an independent data safety and monitoring board comprising international experts [1].

Recruitment commenced in May 1998, was completed in April 2002, and was done in the following manner: After completing community rapport building, a baseline household survey for the enlistment and a brief sensitisation of eligible women, group health education programmes were conducted in both the screening and control arms [3]. In the screening arm the women were invited to participate in the cervical cancer screening (VIA) and breast cancer screening (CBE) programme. Informed consent was taken after counselling by a medical social worker and a signature (or left-hand thumb impression for non-literate women) was obtained on the consent letter that was printed in the local language (which in this case would be Marathi, although the paper does not specify this). This procedure of obtaining consent was witnessed by another woman from the same community; this woman then signed on the consent form as a witness. All participating women received identity cards. Women in the screening arm received four screening rounds of CBE (conducted by trained female primary health workers) and cancer awareness sessions every two years. This was followed by five rounds of active surveillance every two years [1,3]. The eligible women from the control arm, however, were not invited for screening; they received one round of cancer awareness followed by eight rounds of active surveillance every two years and were provided an identity card and information about the availability of screening and treatment services for cervix and breast cancers at the TMH [3]. The paper does not provide information on how many women in all were contacted and how many refused, whether anyone wished to withdraw at any stage, and whether women actually withdrew, and if so, why. Details of the group health education programme have not been described in the paper.

The design and conduct of this trial raise multiple ethical concerns, as discussed in the following sections. This discussion draws upon responses provided by the TMH to an application filed under the Right to Information Act (RTI) in 2015 by Adv Veena Johari, Mumbai. These responses, which include the IC forms, are provided as supplementary material with this commentary [available online only, link provided at the end of the text].

Ethics in framing the research question

For more than 50 years, mammography (X-ray of breast), CBE by a doctor, a nurse, or by other trained health workers, and breast self-examination by the individual, have been promoted for screening to diagnose breast cancer at an early stage, in order to decrease morbidity and mortality from this disease [4, 5].

In a comparison of mammography and physical examination in 1994, the lead author of the study under discussion [1] had concluded, "Current evidence suggests that screening by PE [physical examination] is as effective as screening mammography in reducing mortality from breast cancer" [6]. In another paper in 2000, the same author had noted that, "there is sufficient circumstantial evidence to suggest that clinical breast examination is as effective as mammography in reducing mortality from breast cancer and that *the time has come to compare these two screening methods directly in a randomised trial"* [7, emphasis added by author]. Later in 2021, while writing about the study in question here — the Mumbai trial — this author goes on to write,

> *Clinical breast examination was the obvious choice at that time [early 1990s]. But there was little information available on its effectiveness, so this could not be applied for population screening. Encouraging results were, however, emerging from the Canadian National Breast Screening Study (CNBSS). Early results of the study published in 1992 revealed that, in women aged 50–59 years, mammography provided little added benefit over clinical breast examination in terms of mortality reduction* [2].

And yet he goes on to say that "These results made it imperative that a randomised trial of clinical breast examination versus no screening was conducted" [2].

When the effectiveness of screening in general and that of CBE in particular was established, what were the imperatives that led to designing a study in which the control group was denied an intervention that was known to be effective?

Ethics begins at the stage of formulation of the research question. Was there genuine clinical equipoise in this case? Was there any uncertainty about the effectiveness of CBE that this trial set out to address? The researchers neither provide adequate rationale nor attempt to explain why established screening interventions — mammography and CBE — were not compared for effectiveness, and why the control arm consisted of no screening[b]. Indeed, in view of the problems associated with mammography and its limited efficacy in women below 50 years of age, there was a need for comparative effectiveness research[c] comparing mammography with other screening options such as physical examination [4].

Ethics of withholding an available intervention

It is unethical to withhold an established, available intervention that is known to be beneficial, even if it be mammography in this case, with its limitations, complexity and high cost. Mammography may be a complex technology, and screening is not offered in India as part of a public health programme. However, mammography could have been offered in the trial. In Mumbai, where the trial was conducted, there is an abundance of tertiary hospitals with

the requisite X-ray equipment and trained radiologists, and mammography is also available at TMH, which conducted the study. In fact, the English version of the IC form prepared for this trial states that mammography is a standard procedure and is available in India: *"The standard screening procedures for cervix and breast cancers are Pap smear and Mammography in developed countries. Such facilities are also available in some centres in India and you may choose to undergo these tests on your own, if you do not wish to participate in this study".*

The context of this trial needs to be borne in mind while assessing the value of providing information about breast cancer and the option for women to undergo these tests on their own. While some education and awareness of breast cancer may have been given, critical information pertaining to the benefits of screening was not provided to women in the control arm while seeking their informed consent, and they were exposed to the risks of not getting early diagnosis, as discussed later. Such education cannot be treated as a substitute or compensation for not actually providing available screening procedures during a trial, as ethical guidelines demand [8].

Similar serious violations have been pointed out also in the other arm of this trial — screening for cervix cancer [9], which was declared to be unethical as discussed later in this commentary. Both the arms — screening for cervix and for breast cancer — tested the efficacy of an intervention by withholding effective and available care from the control group. This is in violation of existing guidelines that specify that a new intervention must be tested against the best current proven intervention, except in certain circumstances.

A related issue here is that of confusion over the use of the term "standard care". The IC form mentions that mammography is a standard screening procedure and is available in India. However, the study also describes the absence of care as constituting "usual care" or "standard care", with that then serving as an explanation for not offering any intervention in the control arm. This cannot justify causing harm to participants in a trial.

Ethics of cluster randomised controlled trials

CRCTs, used to evaluate complex or multifaceted interventions, randomise intact social groups, or clusters of individuals, rather than individuals. CRCTs are known to pose distinct methodological and ethical challenges when compared to individual randomised trials. The value, contribution, appropriate use, ethics, and limitations of CRCTs, and the difficulties of carrying them out, have been discussed. CRCTs are not the only tool available to clinical researchers and epidemiologists [10, 11, 12, 13]. Among the 15 recommendations set by the Ottawa Statement on the ethical design and conduct of cluster randomised trials, a key one is that researchers *explicitly justify* the choice of a cluster-randomised design rather than an individual randomised one [14, 15].

Researchers are expected to always explain the rationale for the choice of their trial design, as to why it is the best available option, both scientifically and ethically. In this trial, it was not a totally new/untested drug or procedure being studied, but an intervention of known effectiveness. In addition, the design required an extremely large number of participants and had to be carried out over a very long time period (over two decades). Given all this, one would have expected the researchers to provide a strong ethical rationale for their choice of the experimental method such as CRCT, and explain why no other method was suitable for their objective. The authors do not explain why the conventional RCT, where individuals are randomised, was not suitable for the trial, why cluster randomised design was more appropriate. It needs re-iteration here that the screening intervention as well as data collection in this case were to be at the individual level, and not at a cluster/group level.

Irrespective of the fact that the Ottawa guidelines for ethical design and conduct of CRCTs emerged around 2013, after this trial had begun, it is expected that while initiating the trial the options for design and methodology would have been discussed before deciding upon the CRCT. The rationale for the choices, as also other methodological details, should have been given in the present publication reporting the trial results [1].

Even if CRCTs were to be used, they do not necessarily have to use a placebo or no-intervention control. In this case, the argument for a no-screening control was that screening was not offered in India and hence that constituted "usual care". As explained earlier at length, this argument ignores the availability of mammography; and not providing it to more than 75,000 women required extremely high levels of ethical justification, considering that it deprived the affected women of an accepted intervention that could have slowed disease progression or prevented irreversible damage, or even death. At the end of active screening, there were 198 cases of diagnoses or deaths in the screening arm and 151 cases of diagnoses or deaths in the control arm [1: see Table 3]. Could some of the suffering and deaths in the control arm have been reduced or prevented if the women had been provided mammography screening?

Informed consent in CRCTs

The informed consent (IC) process has been the subject of much discussion and debate in the discourse on the CRCT design. It is an evolving field, where based upon a review of reporting of CRCTs, researchers have made suggestions on how existing guidelines need to be modified or refined [16,17]. In CRCTs, obtaining IC from participants is seen to raise logistical and methodological concerns, one of which is obtaining IC from a very large number of participants [18]. As mentioned earlier, the study opted for cluster randomisation for such a trial, where individual informed consent would have to be obtained from over 1,53,500

women spread over twenty clusters, randomised into screening and control arms.

Consent in CRCTs is taken at two levels: (i) Consent *from the clusters* to participating in the trial and to randomisation of particular clusters/units; and (ii) Consent from individuals to receiving an intervention within the trial. For the first, CRCT researchers would have to approach a "gatekeeper" or local community representative to provide consent or permission for the trial and for randomisation; a step which would involve identifying such gatekeepers, meeting them along with community members, maintaining records of this process and of the subsequent meetings recording consent, etc. There is lack of clarity in the CRCT discourse on these and other important ethical questions, such as who can act as gatekeeper, who may speak on behalf of a particular group, who can give meaningful informed consent, and how to identify such gatekeepers (or "guardians") [19, 10, 11, 12, 13]. The study under discussion reports that "involvement of local community leaders was sought during recruitment of participants and implementation" [1]. No further details have been provided of the demographic characteristics of these local community leaders, how they were identified, what kind of information was provided to them and by whom, how their involvement was sought, and the nature of their involvement in the recruitment process and afterwards through the trial.

Individual informed consent

Only English and Marathi versions of the IC form were provided in response to the request in the RTI application for copies in English and various languages; copies in Hindi or other languages were not provided in response to the RTI. It is not specified, either in the reply to the RTI or in the publication, whether the IC form was translated into languages other than Marathi, namely Hindi or other languages. The paper reports that around 20% of the study population were Hindi speaking, while 25% spoke languages other than Marathi or Hindi [3]. There is no mention of how informed consent and signatures were taken from over 60,000 non-Marathi speaking women, if the forms were not translated into those languages.

The English and Marathi versions of the IC form for the two parallel studies — screening for cervix and breast cancer, respectively — were the same; the form mentions that a study was being done "to find out whether these cancers can be detected early by doing simple tests". Both versions contain technical terms such as "randomly allocated", "intervention" and "control arms", without explaining what exactly they mean, what the implications and consequences would be for the women in the respective groups. In keeping with the principles of respect for the autonomy and dignity of individuals and communities, which form the essence of IC [19], in CRCTs, prospective participants approached for consent should be given full information, including facts such as that clusters have already been randomised, and their cluster has already been allocated to one of the study arms. This is to enable the participants to make an informed choice based upon an informed understanding of what her participation involves for her in the short-term and in future. The informed consent process should be tailored to the study arm to which the cluster has been allocated. For instance, in the study under discussion, there should have been two different individual informed consent forms — for the control and the intervention arm, respectively; while the information about the objectives and method of the study would be common to both the groups, the informed consent section should have specified which arm the participating woman would belong to, whether control or intervention. Each IC form should explain clearly in which arm the participant is placed, the procedure(s) the participant will or will not undergo, the information collected from them, the duration of the trial, the benefits of the procedure, the risks of not having it, and how the findings will be used. A study of the IC forms received in reply to the RTI application indicates that such requirements were not rigorously followed during the trial. After a short paragraph about the study, the English version of the IC has separate sections for the Intervention Group and Control Group, with provision for signatures at the end of the information. The Control Group document mentions that if they notice some of the symptoms of cancer of breast (or of cervix) that are explained during health education, then they can approach TMH. It does not mention anything about the advantages of screening and the risks of not screening. The Marathi version contains no such section; there is only one document for IC, in which it is stated, "if you consent to be a participant then you will be asked some questions, besides some examinations will also be done on you. If your division (*vibhag* used in Marathi) is in the control group, then you will have to only answer some questions. But if you live in the division which is in the study group, then you will have to come for examinations". The information about the study is then followed by one proforma entitled "Consent of participant", which states that "I have read/I have been fully explained about the study and understand its implications and my rights as a participant. I agree to take part in the study and if required allow myself to be examined by trained female health workers and if necessary undergo further investigations and treatment at Tata Memorial Hospital"; followed by space for the signatures of the participant and the witness. This means that while signing the form in Marathi, the women were not aware of the arm they were in — control or intervention. They were not aware of the difference between getting and not getting screened, or the benefits of early diagnosis. The wording would indicate to the women that some of them will have to simply answer some questions, while others would have to answer some questions as well as go for simple examinations of cervix and breast. Clearly, those in the control arm were not told about what standard care consists of, the risks of not having the examinations in terms of delayed detection, or the benefits of having any examination (whether mammography or clinical examination) in terms of

early detection and hence the possibility of starting early treatment. In other words, the risks of not being given the examinations if one is in the control group were not explained in the IC form — neither in the English version for the control group nor in the Marathi version for both groups.

If the women in the control arm were given adequate explanation about the trial and its length, about availability of standard care and its benefits and risks, it is possible that many women may not have agreed to participate, since not only was it not beneficial for their health, they were also exposed to risks, mentioned above in the preceding paragraph.

Apart from this failure to communicate adequately all the information and risks in simple language comprehensible to women with limited ability to read or write, in their languages, there are several other discrepancies in the English and Marathi versions of the IC form, which should have been identical in content.

- The following information, about standard care, from the English version is not there in the Marathi version (*Annexure 4 of RTI response in Supplementary Files*):

  > *The standard screening procedures for cervix and breast cancers are Pap smear and Mammography in developed countries. Such facilities are also available in some centres in India and you may choose to undergo these tests on your own, if you do not wish to participate in this study. (Annexure 5 of RTI response in Supplementary Files)*

- About the examination for the intervention group, the Marathi version states, "These examinations will be done once in 18 months for the next 6 years." The English version, however, states, "these examinations will be conducted once every 24 months for 8 years."

- The English version says that the cervix would be painted with 4% acetic acid with a cotton bud before examination, but this is not mentioned in the Marathi version, which only says "mouth of cervix will be examined with speculum" (*done patichya chamcha* used in Marathi).

The presence of such multiple differences in the English and the Marathi version — the Marathi form would have been actually used more widely in the field than the English one, given the inclusion of a large number of Marathi-speaking women — and the absence of documents in Hindi and other languages indicate lack of attention by the researchers to diligently complying with the IC procedure and its intent to respect and protect trial participants, and to ensure that correct and complete information was provided in simple language to all the participants.

The study reports that in addition to the internal data safety and monitoring committee of the TMC, an independent data safety and monitoring board comprising international experts reviewed the trial annually. In response to a query in the RTI application about the visits by the monitoring committees to review the trial, it was stated that no records were available. This could mean that the visits were not conducted — or that they had failed to maintain records, both of which are a violation of regulations. It was also stated that details of the meetings of the ethics committee and safety review committee were exempt from disclosure as they contained patient information. Information could have been shared after redacting names and personal identifying information. In view of this response from TMC, it is not possible to know whether such ethical issues were raised and discussed at the review meetings.

What emerges is that the trial specifically recruited a large number of women from poor socioeconomic backgrounds with very poor literacy levels; but while obtaining consent the researchers did not make adequate efforts and take precautions to communicate to them all the information, including that pertaining to standard care, risks, and which arm they were in, in a simple manner that would have been comprehensible to them.

It is extremely pertinent to point out here that, in 2009 the Tata Memorial Scientific Review Committee expressed concern that this trial was unethical for control arm and the control arm should be stopped; however, it was not stopped [20]. In 2012, the other arm of this trial on screening for cancer of cervix with VIA had been declared unethical by TMH and the US Office for Human Research Protections (OHRP) based upon their investigation, because consent had been improperly obtained from the trial participants [20]. It was found that the women had not been provided with adequate information to understand the differences between the research procedures and Pap smears to screen for cervical cancer. Major discrepancies were found between the IC form submitted to the US National Cancer Institute (NCI) grant applications and the IC form actually used during the Mumbai trial — the former included information that 'Pap smears are standard cervical screening procedures in "developed countries;" that Pap smears are available in India; and that women could obtain Pap smears on their own if they did not wish to participate in the Mumbai RCT' [20:69]. However, such critical information was missing from informed consent forms actually used in the Mumbai trial [20]. The researchers did not adequately inform the women in the control group about alternatives for getting cervical cancer screening and the women did not give adequate informed consent [21].

Similarly, this commentary finds several ethical violations in the breast cancer screening arm of the trial. These violations are extremely serious, particularly given the large number of participants recruited in the control arm and the prolonged period for which it was conducted, in order to achieve mortality reduction dictated by dry statistical requirements, namely, to detect 25% reduction in mortality from breast cancer with 80% power and 5% type I error [1, pp 2-3]. Over

76,000 women were deprived of an effective screening method, and exposed to risk and harm, for no personal advantage, but only to provide information of benefit to the larger community.

Fair participant selection

Participants for clinical trials are identified or recruited based upon the incidence of the disease among them, or some specific feature associated or relevant to the research topic. The risk of breast cancer — the disease being studied in this trial — is seen across all classes and castes in India. Yet, it is seen that only poor, uneducated, women from slums, who lack resources and power to defend their interests, and are vulnerable to being misled or misinformed, were chosen as participant for this screening trial, the benefits of which would accrue to women of all classes in the country. Effectively women in these trials have been simply exploited as the means to an end. Given the socio-economic background of these participants, the health information and awareness provided in the control arm need not necessarily translate into agency and action to access healthcare, due to the constraints imposed by their very same socio-economic conditions [22].

In general, whether it is trials for cervical cancer screening [3] or for testing injectable contraceptives [23] or the human papilloma virus (HPV) vaccine [24] in India, it is seen that often poor women either from urban slums or rural areas constitute as the participants. Such choices regarding participant selection by socially well-placed, elite groups of researchers from within the country, are similar to the tendencies of multinational pharma companies and/or researchers from developed countries to use populations in less developed countries for their research [25-27]; a case of social-political elites using the socially disadvantaged.

Concluding remarks

Provision of procedures such as mammography for breast cancer screening or Pap smear for cervical cancer screening in India is not limited by the complexity of the technology or lack of resources. In India, the competence, technology, and infrastructure to provide many complex medical procedures exist. In fact, India is an important centre for global medical tourism, catering to international patients for very complex medical treatments such as organ transplantation, hip and knee replacements, etc. Expertise and resources for services more complex than mammography are available in India; but the issue lies in their uneven distribution, which restricts access, or creates barriers to equitable access. Such technologies are available, but inadequate in the public hospitals and not affordable in the private sector; making them inaccessible to the large section of the population using both these sectors. But they remain available and accessible to the affluent sections that can afford to pay. The problem therefore lies in the highly inequitable, fragmented and highly commercialised healthcare system in the country, wherein an inadequately resourced public healthcare infrastructure is unable to provide a comprehensive, universal healthcare service, from primary to tertiary levels, while the private sector provides these services at a price out of reach of most of the population. The stance that no-screening is standard care in India or that complex, expensive technologies cannot be provided in low-resource settings, hence less expensive options are the only way out, is a rather disingenuous argument, and serves to ignore these glaring inequities of the healthcare system in India. It is not the cost or complexity of mammography as a population screening measure for breast cancer, but the fact that there are uncertainties regarding its effectiveness as a public health intervention [28, 29], that should be the decisive factor.

Public health researchers and practitioners need to be aware of (and, as researchers, also examine) the factors giving rise to such scenarios of "low-resource settings" for healthcare, namely the larger context of health policy, planning and financing, and the need therefore to address questions of how healthcare should be organised in a just and equitable manner to ensure universal and comprehensive healthcare to all citizens, irrespective of their socioeconomic status. These constitute macro-ethical concerns of medical ethics and public health ethics [30]. It is beyond the scope of this article to go into the details, but at the minimum, criteria such as efficacy, safety, sensitivity, specificity, and effectiveness, not cost alone, should shape decisions regarding the provision of technologies of proven benefit to all, through a rationally planned public healthcare system that also respects the autonomy and dignity of patients.

Notes: *[a] As per WHO, downstaging or early diagnosis refers to early identification of cancer in patients who have symptoms of the disease; while screening seeks to identify those individuals in an apparently healthy population, who have the disease but do not have the symptoms. Screening and early diagnosis form components of early detection of cancer, which increases chances of successful treatment, as against detection at later stages (Guide to cancer early diagnosis. Geneva: World Health Organization; 2017. Licence: CC BY-NC-SA 3.0 IGO https://creativecommons.org/licenses/by-nc-sa/3.0/igo*

[b] Incidentally, a 1997 paper comparing two-modality screening (mammography and clinical examination) with single modality screening (clinical examination alone) [31] points out that, "Evidence from an RCT in North America comparing screening with clinical breast examination to no screening will never be available. Therefore, evidence on clinical breast examination from existing trials and projects must be examined. In fact, only the CNBSS allows comparative evaluation of clinical breast examination, and the comparison is with two-modality screening, not "no screening." It is worth pondering over the ethical implications underlying this statement and what it means for the Indian study.

[c] Comparative Effectiveness Research refers to studies aimed at generation and synthesis of evidence for comparing the benefits and harms of alternative methods for prevention, diagnosis, treatment of a clinical condition, or to improve the delivery of care [32, 33].

Supplementary files:

1) Response from TMH to RTI questions
2) RTI TMH Annexures 1-3
3) RTI TMH Annexures 4-5, informed consent forms

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