Mumbai Case Studies Meeting

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Project full title:	Creating and enhancing **TRUST**worthy, responsible and equitable partnerships in international research
Project acronym:	TRUST
Type of funding scheme:	Coordination and support action
Work programme topics addressed:	Reducing the risk of exporting non ethical practices to third countries, GARRI-6-2014
Project web-site:	www.trust-project.eu/
GRANT AGREEMENT No:	664771
Name of the Coordinator:	Prof. Doris Schroeder (dschroeder@uclan.ac.uk)

Citing suggestion: Chatfield, K., Schroeder, D. and Muthuswamy, V. (2016) Mumbai Meeting Report, TRUST Project, www.trust-project.eu

Thanks to Julie Cook Lucas for editorial support and to Dr Urmila Thatte and Dr Nandini Kumar for input into the report.

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Background

This workshop forms part of the fact finding activity in the early stages of the TRUST project, gathering information about cases of exploitation and good practice in research involving low and middle income countries (LMICs) from around the world.

With the specific intention of examining cases in India, the Forum for Ethics Review Committees in India (FERCI) hosted a two-day workshop in Mumbai on 11-12 March 2016. Approximately thirty leading bioethicists from India came together with a small number of guests from Europe to discuss cases of exploitation and good practice in research that had been previously identified by the participants.

This report summarises the event and discussions from the workshop.

Meeting delegates, Mumbai, 11-12 March 2016

Front row from left to right: Vasantha Muthuswamy, Sandhya Kamat
Second row from left to right: Swarnalakshmi, Sudha Ramalingam, Roli Mathur, Nandini Kumar, Rema Mathew, Urmila Thatte
Third and fourth row from left to right: Francois Hirsch, Solveig Fenet, Rasheeda Rajamohanan, Sunitha Bandewar, Joyita Sarkar, Lalitha Sawardekar, Kate Chatfield, Durga Gadgil, Sneha Limaye, Doris Schroeder
Fifth row from left to right: Sandeep Bavadekar, Santhanu Tripathi, Francois Bompart, Lalit Vaya, Pradeep Kumar.
Sixth row from left to right: Manoj Das, Sanjay Mehendale, Klaus Leisinger, Raman Gangakhedkar, Mohanan Nair
Last row from left to right, Anshudeep Dodake, Sanish Davis, Kritarth Singh

Introduction and Approach

Prof. Doris Schroeder, Dr Vasantha Muthuswamy, Dr Urmila Thatte

The first day began with a welcome and introduction to the TRUST project from the project lead, Prof. Doris Schroeder, followed by an introduction to FERCI and an explanation of its role in TRUST from its President, Dr Vasantha Muthuswamy.

Forum for Ethics Review Committees in India (FERCI)

FERCI is a registered society and national forum that aims to improve understanding and implementation of ethical review of biomedical research in India, with relevance to local cultural values.

FERCI are the leaders of work package 1 in the TRUST project and, amongst other things, will be responsible for developing a matrix that maps case studies onto identified ethical risks, and producing a report on the generic risks of exporting non-ethical practices to LMICs. The case studies collected and analysed at the Mumbai meeting will inform both of these activities.

Vasantha Muthuswamy and Doris Schroeder opening workshop

Secretary to FERCI, Dr Urmila Thatte, explained how the workshop was to be organised. Attendees from India, who are all in responsible positions dealing with ethics in health research, submitted case reports of exploitation or good practice, prior to the event. These cases were drawn from their own experience or from information that is in the public domain. More than thirty cases were submitted.

Participants from India had travelled from a variety of different regions. Many were medical doctors or other healthcare practitioners; some were scientists or social scientists and all were involved in biomedical research. Many of the participants were also bioethicists and have extensive experience of working with ethics committees in India.

Urmila Thatte

Workshop participants were divided into five groups and the case studies were shared between them. The first part of the workshop was spent discussing the case studies within the groups to draw out the main concerns for exploitation and the primary examples of good practice. Following group discussions, each group was asked to summarise their main findings through presentation of a small number of selected case studies.

Presentation of Case Studies

Following lively and engaging group discussions, each of the 5 groups presented their selected case studies, as summarised below.

Group work

Feedback Group 1

Group 1 presented 3 cases drawn from pharmaceutical studies.

The first case concerned the widely publicised demonstration project of the human papillomavirus (HPV) vaccine in 2009. Before initiating the project, formative research was undertaken to study the feasibility of vaccine delivery, as well as aspects of communication and advocacy strategy. Participants in this large project in two states were teenage girls from urban, semi-rural and rural backgrounds. In one state many of the rural participants were tribal girls living in hostels.

A major concern with this study was that informed consent was provided by school heads and hostel wardens in place of assent from the girls and consent from their parents or legally authorized representatives. Parents of non-resident students could not understand the contents of the brochures and assumed the project was a governmental initiative. Other concerns included:

- The failure to report the deaths of four of the tribal girls in one state and two in the other state although these were not related to the study.
- The literacy status of the parents in tribal communities.
- The medical knowledge that the HPV vaccine does not address all strains that can lead to cervical cancer (this information was neither shared with the ethics committee nor with participants).
- The question whether this demonstration project, which looked like a Phase IV clinical trial, could be treated as such by Indian researchers and regulators.
- The question of where the final accountability lies when so many research groups are involved in a study.
- The lack of awareness about whose laws are applicable for a multi-national study in an LMIC.

The second case concerned a phase III drug trial with a large number of participants that was already underway in India when it was discovered that the drug induced bladder tumours in mice and rats. Indian law requires that carcinogenicity studies need to be completed before phase III studies, whereas European laws state that carcinogenicity studies can run parallel to clinical trials and can still be ongoing at the time of phase III. There is therefore, a clear conflict between the two legal domains.

Whilst the study was welcomed because it addressed an unmet medical need, concerns were raised about the management of patients in such a study. If there were a risk of cancer development in the future, this would – due to the time delays – not be picked up as part of this study. Therefore the data would be missed and no compensation or support would be available.

The third case presented by Group 1 concerned post-trial access to treatments. The case described a patient who had been taking a low cost standard treatment for a chronic condition before being enrolled in a study. He was informed that there would be three possibilities for treatment in the study, to be decided at random:

1. You receive a new drug which might be superior to all existing treatments
2. You obtain another drug which is standard care
3. You receive a placebo

At the end of the study, the subject felt better but as soon as the study ended the participant was taken off the study drug. The participant came from a low socio-economic background. Because he was feeling better he requested that he be kept on the study drug for a longer period of time but the investigator told him that this was not possible. The patient died shortly afterwards.

The main concern arising from this study was about post-study access to treatments and whether the participants should have long-term access to the study drug when the drug is not yet licensed and has not passed all safety tests for long-term use. Alternatively, should such patients be provided with a given standard of care for a specified period of time? Should that be a standard part of a study protocol?

Group 1

Other concerns included:

- When patients are taken off existing treatment for a study there is a need for a 'wash out' period prior to the start of the study and clear monitoring is needed during this wash out phase.

- More precise guidance is required on what kind of patients can be taken off their drugs for participation in a study.
- Interim analysis is not always shared with the participants in pharmaceutical studies. If the interim analysis shows that the new drug is superior, should the placebo arm be stopped? However, the pharmaceutical investigators may object to this on the grounds that unblinding of the participants can affect the reliability of results.
- Another concern was whether there is a need for a placebo arm in such studies. Should a placebo be used in such studies when an existing standard treatment is available?

Feedback Group 2

Group 2 presented two case studies, one of exploitation and the other of good practice.

Group 2

The first case concerned a well-known study about the inclusion of Bhopal Gas tragedy survivors in clinical trials. During this infamous chemical disaster in 1984, methyl isocyanate, (a poisonous gas) was released from the Union Carbide factory. The survivors suffered from a range of chronic conditions and the government established a special hospital offering medical care and long term follow up. Ten clinical trials were subsequently conducted with the survivors as participants. Many of these patients were not aware that they were participating in a clinical/ drug trial and at least ten serious adverse events (SAEs) were noted. No informed consent was sought.

There were many identified concerns, including:

- Why were trials that could have been conducted on another population imposed on those who had already suffered significantly?
- Better processes were needed for seeking informed consent when the patients were recruited for trials.
- Patients seemed to be under a therapeutic misconception that they received standard treatments for their symptoms.
- The reporting of adverse events (AEs) and SAEs were inadequate.
- The provision of compensation for harm incurred during a trial were not considered.

The second case from Group 2 was presented as an example of good practice. This case concerned the conduct of the first ever phase I HIV vaccine trial in India and was a joint initiative between an overseas partner, a sponsor and an Indian partner. For this trial, national review mechanisms were put in place, the local communities were involved at every stage of planning and implementation, and social and cultural values were respected and given due consideration.

Activities at different levels contributed to the good practice. At the national level, steps were taken to manage the agreement between funders and other partners, and to ensure the protection of national and participants' interests (Central ethics committee approval, IPR issues, data sharing, samples transfer, post-trial access, publication policies, media sensitisation etc.).

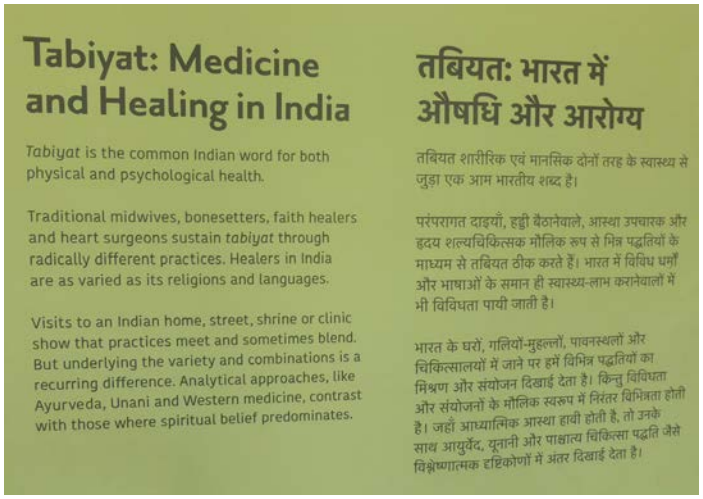


Exhibit from the Medicine and Healing in India Exhibition, Mumbai Museum, co-sponsored by the Wellcome Trust

Steps taken at the institutional level included:

- Protocol development team: Involvement of local investigators
- Scientific and ethics review
- Risk mitigation policy
- Discussions with media and parliamentarians
- Data and safety monitoring board (DSMB)
- Training of site investigators and teams: Good clinical practice (GCP), Good laboratory practice (GLP), Human Participant Protection etc.
- Engagement of all local stakeholders
- Adverse and serious adverse events reporting
- Quality assurance at all levels
- Proper communication between all units

Steps taken at the local level included:

- Identification of all key stakeholders
- Community sensitization, education and awareness
- Development of Community Advisory Board (CAB)
- Involvement of community members in:
    - Protocol development,
    - Informed consent processes and
    - Development of educational material in local languages

In addition, steps were taken to protect the safety and welfare of participants including:

- A two-step informed consent process for screening and enrolment; a consent comprehension test was employed to help ensure adequate understanding
- There was a long observation period following administration of study product
- Systems for grievance redressal were introduced
- Insurance was provided for both trial related and unrelated harm.
- Post-trial care and support was available

Feedback Group 3

Group 3 presented three cases that incorporated both good practice and the potential for exploitation.

They began with a presentation of various community based studies that generated overlapping concerns about sponsor responsibilities, consent/assent, post-trial coverage and access to care. The most contentious of these community studies concerned an NGO initiative to reduce neonatal mortality through home-based neonatal care from 'trained health workers'. Impacts of the introduction of trained health workers in one village were compared with 'standard care' in another. Findings showed that neonatal mortality and fatality rates due to neonatal sepsis could be reduced considerably through trained health workers. The contentious nature of this case stemmed from the following concerns:

Group 3

- The results could have been predicted from similar studies that had previously been conducted in similar environments and hence the 'control' village were knowingly denied access to care
- There was no institutional ethics committee involvement as the NGO did not fall under any ethics committee jurisdiction
- No assent or consent was sought
- A question was raised about what 'standard care' entailed? When this does not meet basic standards of neo-natal care should it be declared as a baseline?
- Finally, when funders provide money for NGO activity, what is their degree of accountability?

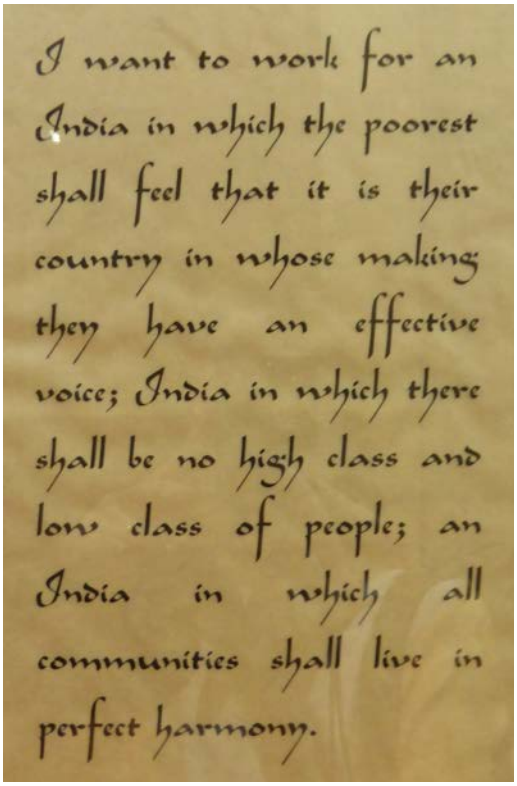
The second case presented by Group 3 concerned the recording, monitoring & reporting of adverse events (AEs) during a clinical trial. They began with an example of good practice whereby AE recording was segregated from the rest of the medical records using a simple colour coding method for the forms, which meant they could be easily identified at a later date. It was proposed that the possibility of under-reporting of adverse events could be minimized using this colour-coding method and that it was easy to implement even in remote/rural areas.

The group further stressed the importance of a local site Data and Safety Monitoring Board (DSMB) in multicentre, multinational trials involving human participants. Whilst there can be ethnic and regional differences in occurrence and severity of AEs and SAEs among populations, there is normally no local DSMB to monitor such trials. Ultimately, the pooling of data from different regions could result in masking the severity of some AEs and SAEs that may tend to occur more frequently in certain populations.

The third case presented by Group 3 concerned good practice in seeking consent for secondary use of samples. A situation was described where it became clear that left-over blood samples from one study could be put to further use through gene testing which might enhance understanding of the disease in question and avoid the need (and expense) of establishing a new population study. The problem was that consent had only been sought for the primary use of the samples.

In this case the ethics committee decided that:

- Approval of the sponsor was needed
- A separate 'link study' could be set up
- The link study was approved on the condition that further consent would be sought from the study participants from whom the blood had been collected.
- A clause for further contacting the study participants was included so that they could be provided with the gene tests results and optional counselling at the discretion of the study participants.
- Participants who declined to consent would have their blood sample discarded and
- Under no condition should the samples be sent abroad.



from Gandhi's office in Mumbai

Feedback Group 4

Group 4 presented three case studies, two with evidence of exploitation and one of good practice.

The first case concerned exploitation in a genomic study conducted in a tribal population. Researchers from five foreign universities and one Indian University designed a genetics study involving tribal populations in multiple Indian states. The study population (1000) included families and individuals, both adults and children. Participants were paid for blood samples and DNA was extracted, half was stored for future research in India and the rest was transported to overseas laboratories for genetic analysis. Participants were given a further payment if they agreed to have their photo taken.

Ethics approval was sought from the five foreign universities but not from the Indian partner. The study results were published in high impact journals including one with photos of the participants. The remaining blood samples, along with the demographic data, were sold to a multinational corporation. Royalties were shared between the collaborating universities and used for future research. The Indian collaborator was thanked in the acknowledgement for helping with the samples.

Ethical concerns raised by this study concerned:

- Lack of communication of research results to participants.
- Lack of permission from local ethics committees
- Lack of community consultations (tribal heads, gatekeepers, local representatives)
- Lack of strategies for return of results/feedback
- Lack of local benefit of the research
- Lack of plan for genetic counselling

In addition concerns were raised about publication ethics, commercial benefits from sample resale, and benefit sharing, as well as reuse of samples and data.

Selfie Group 4

The second case presented by Group 4 was about the need for cultural sensitivity in research involving children/ pre-teens. In this particular case some of the questions and statements on an information sheet were deemed inappropriate for the participants.

The need for additional protection of a paediatric study population was emphasized and the problems with automatic import of documents from the Western context were highlighted. It was suggested that it may be necessary to formulate two different consent/assent forms for age groups 10-14 and 15-18 years.

The third case from Group 4 addressed a case of good practice about equity and authorship credit in international collaborative research initiatives. It noted that formal Memorandums of Understanding were developed in consultation with local collaborating institutes before the start of the project. Engagement between the overseas partners and local collaborators were undertaken iteratively and regularly during the various stages of the project's life span. And an approach about how decisions on authorship were to be made was agreed early on in the project.

Feedback Group 5

Group 5 presented three case studies, again including one case of good practice and two cases of exploitation.

Group 5

The first case to be presented was an example of good practice. A large vaccine study with more than 11,000 participants, with multiple partners and conducted in multiple sites in multiple countries was undertaken with the following aspects of good practice:

- The high level of communication between ethics committees to ensure uniform ethical standards of conduct
- Dialogue and continued communication with the local community – by research staff, investigators, and fieldworkers
- Seeking of informed consent was an interactive process
- An impartial witness was included in interactive processes of informed consent
- Feedback and recommendations for better practices were discussed based on the study findings
- Site teams used several methods and materials to make the process easily understandable in the local dialects
- The study staff were trained to convey in a consistent manner consent information in the local languages
- Training sessions and transcripts were certified, reviewed, and approved by the local Ethics Committees
- Some sites used assessment of understanding of informed consent documentation tools for assessing comprehension
- Separate approaches for the informed consent process and enrolment for women aged ≥18 years, for women aged 13–17 years, and for girls aged 10–12 years were prepared
- GCP training and capacity building workshops for the investigators were undertaken.
- Sites collected data and submitted this to the coordinating centre following the data confidentiality and consent process
- A midwife counsellor met privately with all women and young girls entering the study
- Sponsors provided treatment to participants even in cases of unrelated issues
- At the end of the study, the sponsors and investigators facilitated adequate referral and long-term support of the research participants
- Post-trial access to the investigational vaccine was given (as documented to be more effective than the comparator vaccine)
- The hard copy data, consent documents and source documents were archived at the coordinating centre
- Sharing of the results on completion of the study

The second case from Group 5 described the unethical conduct of an international researcher who came to India to conduct a phase I/II trial in spite of a pending request from his own local ethics committee for more preclinical data before approval could be granted.

The study was conducted with 25 participants, most of whom were illiterate and some of whom did not speak English or the local regional language. They were not informed that this was the first study to be conducted in humans. Vulnerable participants were included and appropriate procedures for informing patients and obtaining informed consent were not followed. Specific safety precautions that should be taken for first-in-human trials were not implemented. Additionally there was no specific insurance policy and no compensation guidelines were available. Regulatory procedures required for the first in human trials and international collaboration were not properly adhered to.

The third case from Group 5 concerned a herbal product. India is a biodiversity rich country with many resources in the form of medicinal plants. The government of India has recognised six indigenous systems of medicine as official and there are many herbal and herbomineral formulations that are available in the specific pharmacopeias. This has generated a lot of interest from Western researchers. On the other hand, there are numerous unsubstantiated Indian claims for the cure of chronic conditions and diseases like HIV/AIDS, cancer etc.

One such case involved an unqualified practitioner in India who had taken some herbs that are considered to be useful for HIV/AIDS treatments, developed his own combination, and tried it on some patients. He went on to present his observations and findings from use of this specific formulation at an international conference where he sought interest and funding from international researchers for a project on the basis of an unproven claim for the cure of HIV/AIDS. This, in turn would give the foreign researchers access to his formulation and lead to the possible application for a patent, he suggested.

Subsequently a number of renowned foreign researchers submitted a proposal for funding, including him as one of the investigators, and sought approval from the Indian Health Ministry's Screening Committee (HMSC) to cover material transfer and patent issues. There was pressure from the foreign researchers to have the study approved but they were not aware that in India only a formally educated investigator from a recognised traditional medical system can act as the Indian collaborator; investigators must be trained experts in their area of work.

This case is of concern because:

- The international collaborators were interested in funding research without knowledge about the ethical and other regulatory requirements for undertaking such research in India.
- The researchers were willing to act upon information delivered at a conference without any scientific validation.
- The Indian investigator was also not aware of the HMSC requirements or his responsibility as investigator from the GCP, GLP or GMP perspective as he was a traditional healer and had no formal education in any recognised system of medicine.

Plenary Session

The final activity of the workshop was a plenary session where participants were encouraged to discuss issues that had not already been raised, or those that needed further thought. The resulting discussion is summarised below under the main themes that emerged.

Brainstorming session

Clinical trials with healthy volunteers.

In India (and some other LMICs) some people take part in multiple clinical trials for financial benefit. The question was raised as to whether we need a national registry for participation in clinical studies. Also, whether there should be a maximum amount of money that someone can earn as a healthy volunteer.

In India some contract research organizations (CROs) use a biometric based volunteer management system with inter-linkages with some other CROs to prevent the participation of healthy volunteers in many trials without a wash-out period in between. However, there is no obligation for trial coordinators to link up with. A recommendation that there should be a national biometric system for clinical trial participation has been discussed for some time, but no further development can be reported. This is an area where action could be taken.

There needs to be much greater transparency. If you explain why you are doing what you are doing you become more transparent and people are less vulnerable. Such transparency should also be evident when discussing compensation for those who take part in trials. Most bioequivalence studies conducted in India are for companies that are not from India (e.g. USA). The studies are openly undertaken for international/multinational companies.

There is a difference in payment to healthy volunteers in government or private medical facilities. People often ask researchers in government facilities: “Is that all you are going to pay us?” A fine balance has to be found reached between undue inducement and fair compensation for the time and effort of the volunteer. Compensation does not need to be in the form of cash. Safety concerns for the individuals as well as the validity of the scientific data generated when volunteers are on simultaneous or frequent trials are the main concerns. Very little has been published on this topic for/ from India.

Instead of focusing on the compensation of individual study participants, the overall principle should be that unless a drug is to be registered in e.g. India the study should not be permitted to be carried out in the country. Under the present system, some ethics committees examine whether a study is useful for local people. They also look for risk versus benefit, and the unmet health needs of the country.

Ethical issues concerning studies of medical devices

Device regulations were introduced in India in 2005 and only for a limited number of devices which are termed 'notified'. As a result, ethics committees are unsure about the testing of non-notified medical devices. Some are controlled for quality but the rest are not governed by any regulations. Market surveys / observation studies / registries are undertaken by companies to follow the usage of these devices, and possibly reduce adverse events and increase acceptance. For example, a company marketing stents used in routine care might like to obtain data without incurring the costs or compensation responsibilities related to a clinical trial. They might claim that this is only for registry purposes, not for a clinical trial, therefore resembling a marketing and not a scientific study given that patients are asked to pay for the treatment.

Recommendation: Registry studies should be in the public domain. Currently the data cannot be accessed by outsiders.

Motivation for participation in trials and post-trial access to treatment

People in lower socio-economic classes are much more likely to participate in studies. What would increase participation amongst those in higher socio-economic groups in LMICs?

Plenary session

In France for example healthcare is free so the motivation to take part in medical studies is mostly altruism. Should pharmaceutical companies only do trials on people who already have access to another treatment (so we know that they do have a meaningful choice)? How can one refuse to participate in a drug study if the alternative is no treatment? In India, for example, free healthcare is available only to a small percentage of population. 80% of the health care costs are paid through out of pocket expenses by the public.

represents undue inducement.

Clinical trials should not be a route to accessing high quality care. If there is a problem with access it should be dealt with elsewhere. If there is truly an access problem then companies should consider lowering the price of drugs to make them more accessible. People could be asked to pay according to their ability to pay. But, differential pricing can also lead to conventional drug trafficking for profit. There are many rich people in India now. Is it fair that they should get medicines at a lower price just because they live in India? In the context of

access to drugs, other unresolved questions are: should people in clinical trials for chronic conditions obtain access to successful drugs for the rest of their lives?

If a strategy for post-trial access were implemented this would be a massive jump forward on access to medicines for some. Post-study obligations are very important. We cannot just avoid the issue by claiming it might form an undue inducement.

Going back to recruitment problems in India across all classes. Maybe educating people will help recruitment. All the benefits we receive from drugs today are because people have taken part in research in the past. This is what we should be telling patients/people. It is a way of giving back to society.

Closing the workshop

Prof. Schroeder thanked FERCI for organising a very productive workshop. Dr Muthuswamy thanked her team as well as all participants for their hard work. The participants thanked the TRUST project and FERCI for giving them this opportunity to discuss all these common issues across India.

Dr Thatte, Dr Muthuswamy and Ujjwala Parulkar, the administrative organiser of the workshop