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Perspective

Community engagement in tuberculosis research: the EU-Patient-cEntric clinicAl tRial pLatforms (EU-PEARL) experience

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ABSTRACT

Objectives: Community representatives are key to ensuring that tuberculosis (TB) research is relevant, culturally sensitive, and appropriate. For all trials (new drugs or treatment regimens, diagnostics, or vaccines) this can result in improvement of recruitment, retention, and adherence to the trial schedule. The early engagement of the community will, later in time, support the process of implementation of new policies designed for successful products. We aim at developing a structured protocol for the early engagement of TB community representatives developed in the context of the EU-Patient-cEntric clinicAl tRial pLatforms (EU-PEARL) project.

Design: The EU-PEARL Innovative Medicine Initiative 2 (IMI2) project TB work package has developed a community engagement (CE) framework to ensure fair and efficient participation of the community in the design and implementation of TB clinical platform trials.

Results: We showed that early engagement of the EU-PEARL community advisory board highly contributes to the process of development of a community-acceptable Master Protocol Trial and Intervention-Specific Appendixes. We identified capacity building and training as major gaps in advancing CE in the TB field.

Conclusion: Developing strategies to address these needs can contribute to preventing tokenism and increase the acceptability and appropriateness of TB research.

Introduction

It is an exciting moment to conduct research in the tuberculosis (TB) field. More than 15 new compounds are currently in different phases of development [1] and new strategies, such as adaptive trial designs and trustworthy longitudinal biomarkers, are now needed to prioritize the different possible regimens [2].

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Even if we have witnessed incredible advances in TB clinical trial design and implementation in the last couple of years, the need remains to provide people-centered interventions, that are not only effective but also acceptable and endorsed by the affected population and appropriate for the local context [3]. The World Health Organization has defined community engagement (CE) as "a cost-effective intervention to improve health service coverage and deliver accessible and people-centered integrated care" [4].

Community representatives can be strong advocates for TB research, contributing to ensuring that research procedures are relevant, culturally sensitive, and appropriate. This can result in improvement of recruitment, retention, and adherence to the trial schedule, finally affecting trial quality and helping to build a supportive environment for research. Moreover, the in-depth understanding of local cultures, priorities, and languages provided by community representatives can be pivotal in helping to close the gaps in the TB care cascade [3].

According to several sources and studies [4,5], CE promotes local ownership of the study(ies) and provides valuable input throughout study planning and implementation finally favoring more effective and transparent dissemination of the main results. Moreover, CE creates a trustworthy environment in which the researchers can communicate with affected communities, finally creating a path of critical information exchange between community members, civil society organizations, and academic and governmental institutions. Ultimately, CE can strongly contribute to the implementation of new technologies and/or treatment strategies.

If tokenism is to be avoided and true partnership between communities and researchers is sought, a structured approach to CE is needed. Here, we report the steps taken and lessons learned in the engagement and active participation of community representatives during all activities of EU-Patient-cEntric clinicAl tRial pLatforms (EU-PEARL) TB work package, including the elaboration of the TB Master Protocol (MP) for platform trials.

Material and methods

The EU-PEARL project

The EU-PEARL (EU Patient-cEntric clinicAl tRial pLatforms) innovative medicine initiative 2 (IMI2) project aims to develop new methods, tools, and frameworks to create a novel enabling infrastructure for conducting people-centered platform trials through an integrated system where pharmaceutical companies, non-profit product developers, academic institutions, and healthcare providers work together, in the context of an integrated research platform (IRP). The intent is to shape future clinical trials that will be more people-friendly by design and people-focused by outcomes. The project is designing platform studies for four different diseases: major depressive disorder (MDD), TB, non-alcoholic steatohepatitis (NASH), and neurofibromatosis (NF). Moreover, general frameworks and tools for designing and executing IRPs in any other disease area are under development.

In this context, the EU-PEARL IMI2 project TB work package has developed a CE framework to ensure fair and efficient participation of the community in the design and implementation of TB clinical platform trials.

Platform trials allow for testing simultaneously and seamlessly several interventions under an overarching MP. The development of MP templates (MPTs) and intervention-specific appendixes (ISA) templates can allow trialists and consortia who are developing their own MPs to have a base to start from with guidance on how to populate the different sections and subsections of the protocol.

The EU-PEARL TB work package has developed MPT and ISA templates in collaboration with the established EU-PEARL community advisory board (CAB). The CE process has been carefully planned and structured throughout this process to allow the community representatives full participation in the different stages of the process.

EU-PEARL community advisory board

At the beginning of the project, a general EU-PEARL patient and community advisory group has been created including 1-2 representatives from each disease area (MDD, NASH, NF, and TB), in accordance with the available resources. To select the two persons who would participate in the EU-PEARL patient and community advisory group and become the main members of the EU-PEARL TB CAB, TB work package members have performed a search of relevant community advisers with personal experience of TB contacting different CABs and organizations. Thus, candidates from Latin America, Africa, and Asia, as well as some candidates from Europe have been identified. Because of the nature of the project, extended previous experience in TB and the research environment as well as good knowledge of the English language have been pivotal parameters in the selection of the candidates. Moreover, as EU-PEARL is an EU-focused project, but most TB burden lies outside the EU, one person from an EU country and one from a TB high-burden country have finally been selected. Compensation has been foreseen for the participants to warrant significant participation.

The specific training that the TB CAB has received to support the TB work package activities is described in detail in the results section. General training on the main aims and methods of EU-PEARL has been provided at the initiation of the activities.

Results

CAB participation algorithm

In Figure 1 we summarized the established process of CE for a TB IRP.

Immediately after the project began the EU-PEARL CAB has been established and a training program has been developed by the ad hoc created Expert Advisory Group (EAG) including academic and industry representatives with experience in CE in TB clinical trials. The EAG had the role of providing training and guidance to the community representative regarding the main characteristics of platform trials in general and the EU-PEARL TB design, in particular. The training consisted of a first introductory online meeting to present the aim and challenges of TB platform trials and to introduce the CAB to the trial design. Then the CAB has been introduced to the MP task force and included first in the review activities of the EU-PEARL General MP and the TB MPT.

CAB and tuberculosis master protocol template

Clearly structured CAB roles and objectives for MP review were agreed upon using the relevant MP sections as guidance to facilitate community inputs in trial design and procedures (Table 1).

CAB structure and role description have been included in the relevant MPT section and defined as follows:

CAB: An independent group composed of community representatives (from community-based organizations, non-profit civil society organizations, representatives of networks of people affected by the study diseases, or similar entities). The group members should be interested in providing input in the overall clinical trial process and in reviewing scientific works. This can happen by means of capacity building and empowering community representatives in treatment and research literacy activities. The CAB is expected to include people affected by TB or by vulnerable groups such

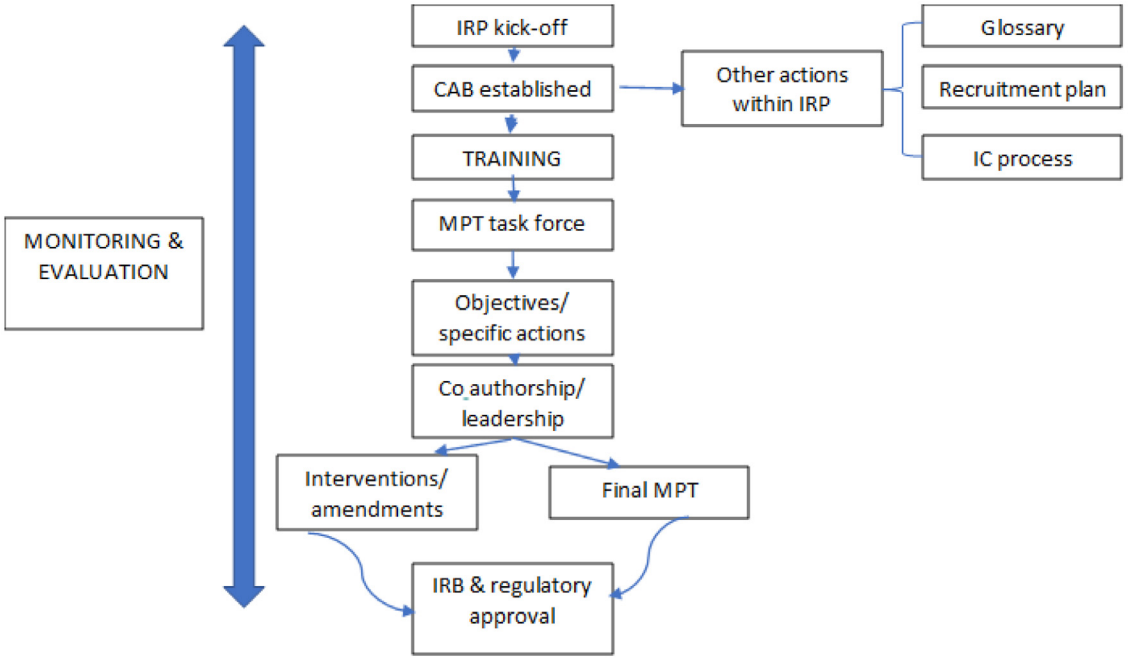

Figure 1. CAB participation algorithm. CAB, community advisory board; IC, informed consent; IRB, institutional review board; IRP, integrated research platform; MPT, master protocol template.

Table 1
CAB Role in MP drafting.

Section	CAB Role and Contribution
Introduction	Provide evaluation of overall risk/benefit balance.
Endpoints & outcomes	Review and select relevant endpoints, including the identification of relevant participant reported outcome measures and participant-reported experience measures.
Design	To be informed of the rationale for the design and ensure the adequacy, consistency, and proportionality of the study procedure to the objective of the study and participants' expectations.
Population	To be involved in the evaluation of inclusion/exclusion criteria and in the development of outreach strategies. Provide feedback on other Challenges and Barriers to Eligibility and Enrollment Outside of Inclusion and Exclusion Criteria. Assessment of the feasibility and capability of the inclusion of vulnerable population.
Study intervention(s) and concomitant therapy:	To contribute to the subsections "Continued access to intervention", "Concomitant therapies/ disallowed medications" and "Rescue strategies after treatment failure or arm is stopped for futility", providing feedback on the adequacy and proportionality of the intervention to the condition to treat.
Study assessments and procedures	To help select and adapt the tools used to assess personal outcomes such as quality of life and Health Economics. To appraise study procedures and adequacy with the objective of the study. To adapt procedures to the cultural background of the community. To help define possible compensation of study participants.
Statistical considerations	To provide feedback regarding the relevant analysis sets of population and subgroups analysis.
Supporting documentation and operational considerations	To be actively involved in the definition of the informed consent process and to provide feedback on amendments and re-consent. Ensure that all documents are available in plain language and accessible format. Assess complements to the written information for participants (e.g., video, graphics) to favor inclusion of illiterate population.

as people living with HIV/AIDS (PLWHA), and represent the main regions included in the study. The CAB should be appointed before the approval of the protocol, and be involved in the concept and development, as well as in the review of its instruments. The Sponsor must provide CAB members training in platform trials in general, and this study in particular. The MPT should support the CAB's regular follow-up of the study, by means of meetings and training and encourage strong and regular interaction with the study team.

Moreover, besides discussing the entire concept of the protocol, consultation with CAB has been planned for each of the areas where the community input is more relevant, providing input on the overall risk/benefit balance and support in the review and selecting relevant endpoints, including participant reported outcomes measures and participant reported experience measures. Furthermore, important feedback has been gathered regarding the study design as the CAB ensured the adequacy and proportionality of the study procedure to the objective of the study and participants' expectations.

The CAB also supported the finalization of the inclusion/exclusion criteria and the development of outreach strategies. Community representatives have underlined that beyond eligibility criteria, other several challenges and barriers that may prevent people from enrolling in clinical trials should be taken into consideration and that CE may provide strategies to overcome these challenges/barriers.

Among those,

1. Geographical: Isolated or nomad communities with a high TB burden are often difficult to reach and retain in treatment. Innovative solutions like technology-assisted follow-up applications may be of use to include this population in clinical trials.
2. Financial: Trials can require a substantial time commitment for treatment or travel. Absence from work and transportation expenses can represent barriers to enrollment. According to the United States Food and Drug Administration (FDA) guidance, reimbursement for travel expenses to and from the clinical trial site and associated costs such as airfare, parking, food, and

lodging do not raise issues of undue influence and are generally considered acceptable practice.
3. Transportation: In some areas, even with a budget dedicated to coping with participants' expenses, travel may be a relevant challenge because of a lack of infrastructure or public transport both for participants traveling to trial sites and the logistics for implementing the trial.
4. Lack of available caregivers for those who are dependent on the trial candidate. In most settings, women are more affected than men in this sense. For example, the lack of childcare facilities may discourage young women from enrolling in a trial or adhering to the trial schedule of visits.
5. Cultural: Some communities pay a historical mistrust toward 'western' medicine in general, and clinical trials in particular.
6. Literacy: TB disproportionally affects communities with significant levels of illiterate individuals. As trials grow in complexity, the informed consent process becomes harder to be truly informed for participants.

To overcome these barriers and challenges mitigation strategies and trial dimensions should be discussed with CAB in order to allow efficient participant enrollment and finally improve the trial recruitment rate.

Finally, the CAB provided input on the informed consent process and was included in the revision of the instruments (e.g., questionnaires and other data collection instruments) to be used in the trial to establish a clear and understandable language for any participant.

CAB and language

The active participation of community experts in MP drafting and in the other transversal activities of the consortium led to identifying language as a transversal element in which community advice is of utmost importance.

In particular, several documents refer to 'patient representative', 'patient engagement,' or 'patient representation'. The precise definition of 'patient' remains unclear, and there exists no generally accepted definition of 'patient'.

In the context of TB, the description of someone as 'patient' may be misleading: is a patient someone with an undiagnosed TB infection? Is this person a patient when latent TB infection is diagnosed? Is a person with active TB but not in medical care a patient? Is a person who denies treatment a patient? Is a person who had a successful TB therapy a patient because there might be a risk of relapse? Is a person cured a patient?

What do all these people have in common? They have a health issue in common: the risk of being harmed by TB if not even the risk of being killed by TB.

In this understanding, these people belong to an informal group or 'community'. TB organizations and programs acknowledge this fact by referring to "TB people", "People with TB" or "TB survivors" (used by several organizations, including TB Alliance, World Health Organization, and others). This terminology is now widely accepted by the TB research community even if the term 'patient' can be still found, mostly in medical publications.

Clinical trials and studies in the TB field are often multifaceted: while testing a new (experimental) combination treatment, surrogate markers for treatment success or diagnostic interventions may be evaluated in the same study. The term "patient" is therefore not only rather unclear but does not even adequately describe study participants.

Another term that sounds rather inadequate is "subject". There is a strong trend to avoid any term that may objectify the individual participating in a trial and "Trial participant" represents the most correct term to replace it. Consequently, the TB CAB had proposed to replace the term "patient representative" with the term "community representative" throughout all EU-PEARL documents.

The EU-PEARL CAB aimed to ensure that the research conducted is relevant to the diverse community needs and advocated for the well-being of study participants. This resulted in the elaboration of a glossary of terms to use in trial documents that take the community's views into consideration.

The EU-PEARL glossary for tuberculosis platform trials

Community: No generally accepted definition exists; here used as a description of formal associations, groups, and networks or informal groups of people with common (health) issues, or most affected or vulnerable to a disease (TB in this case).

Community engagement: Involvement of communities in research activities with the aim to improve their health; CE happens through a process of consultation and feedback with community representatives.

Community representatives: Persons who represent the interest and/or needs of groups of people with common issues. They have to ensure that the research is relevant to community needs and does not answer scientific questions only. Community representatives should advocate for the well-being of study participants, ensure appropriate informed consent, and secure access to research benefits.

Patient engagement: Used if a patient participates in a CE process; it does not confound with recruitment.

Patient representatives: (i) Sometimes used for community representative; (ii) in the legal context used to describe someone empowered to make or communicate health care decisions on behalf of an incompetent patient; (iii) someone who will assist patients in obtaining services.

Study participant: Any person who is participating in a study. The use of this term should not be limited to participation in clinical trials which investigate new treatments but should also be used in the context of studies that investigate diagnostic or other (e.g., preventive) interventions.

Study subject: The technical term for study participant. The term is currently not endorsed by the TB research community.

Discussion

Structured CE and participation have proved pivotal in the activities performed by our project. Nonetheless, guidance is lacking on this topic in the TB field and the most recent guideline available on Good Participatory Practice in TB drug trials have been published more than 10 years ago [3].

In our experience, with the EU-PEARL CAB, capacity building and training were identified as crucial steps to favor CE. In other studies, the gap in knowledge between the researchers and the CAB members has been identified as a major issue in forming and implementing CABs, leading to miscommunication [6]. Therefore, when planning new TB drugs clinical trials, it emerges the need to include the community from the very first stages of the process. This ensures that the communication pathway between researchers and CAB is well established before the design and implementation of the trial start and the objectives of the CAB participation are clearly stated. Moreover, during this time it is possible to thoroughly train the CAB regarding the characteristics of TB trials. Nevertheless, we are currently not aware of any available CAB training packages on TB clinical trials. The development and continuous update of such documents may facilitate CAB creation and implementation in this renewed TB research scenario and should not be limited to new drug trials. Furthermore, considering the possible different levels of literacy and experience in the TB research field of the CAB members, it is important to evaluate the

development of individualized or ad hoc training, according to the participants' needs.

The inclusion of the community in vaccine studies and new diagnostic trials is pivotal to ensure that innovative, acceptable, and reliable tests and preventive tools are developed, as too often we forget that TB care starts from diagnosis and prevention. In the context of other diseases, the inclusion of the community in preclinical laboratory research has been proved to be an occasion of mutual learning, finally leading to establishing new collaborations and improving the research efficiency [7,8]

Language is also a transversal topic that has been widely discussed in the last years in TB research, prevention, and care. The first language guide for TB communications "Every word counts" [9] has represented an important landmark and now a new updated document "Words Matter" has recently been published [10]. The EU-PEARL CAB in this context advocated once again to replace the word "patient" with "trial participant" and to use a more appropriate and empowering language, producing a positive change, and contributing to ending stigmatization. A small TB trials glossary has been then developed in the context of the project to promote this language shift and once again sensitize trialists on this topic. The glossary has been limited to the main terms used in trial documents and does not include other terms, such as TB survivors, that are accepted and used by the TB research community.

The main limitation of our study is represented by the inadequate geographical, gender, and cultural representativeness of our CAB. The need to ensure that all these elements are properly represented in the study CAB can contribute to improving the obtained outcomes, finding strategies, and defining research tools and frameworks that are acceptable and appropriate for all the trial participants. This can finally ensure that the trials performed are really fair and accessible to the entire TB community.

Conclusion

Engaging the community in TB research, especially in TB clinical trials, from the very beginning is crucial to favor the trial-related process and to design and implement people-centered studies, finally ensuring that the trial design and implementation are relevant to the community needs and promote the well-being of the participants.

The developed EU-PEARL TB CE algorithm and the plan for CE in the MP drafting represent an example of how to proactively involve the community in the conception of TB platform trials from design to implementation.

Nonetheless, these tools represent only a first step, and a long unexplored road is still ahead of us. Considering the rapidly evolving of this renovated TB research scenario, guidance on how to perform effective and meaningful CE is deeply needed not only in clinical trials for new drugs but also to study rapid, reliable, and user-friendly diagnostic tests and innovative and effective TB vaccines.

Declaration of competing interest

The authors have no competing interests to declare.

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Authors' Contributions

The authors confirm contribution to the paper as follows: study conception and design: Francesca Saluzzo, Juan Espinosa Pereiro, Stephanie Seidel, Daniela Maria Cirillo; contributed data: Stephan Dressler, Ezio Tavora dos Santos Filho; analysis and interpretation of results: Juan Espinosa Pereiro, Adrian Sanchez Montalva, Stephan Dressler, Francesca Saluzzo; draft manuscript preparation: Francesca Saluzzo, Juan Espinosa Pereiro; critical revision of the draft: Daniela Maria Cirillo, Adrian Sanchez Montalva, Norbert Heinrich, Jesus Gonzalez Moreno. All authors reviewed the results and approved the final version of the manuscript.

Transparency declaration

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