D5.6 TB final report on Regulatory and Ethics Consultation

853966 – EU-PEARL

EU Patient-cEntric clinicAl tRial pLatforms

WP5 – Integrated Research Platform for Tuberculosis (TB)

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Definitions

- **Participants** of the EU-PEARL Consortium are referred to herein according to the following codes:

1. VHIR. Fundació Hospital Universitari Vall d´Hebron – Institut de Recerca
2. EATRIS. EATRIS ERIC
3. SYNAPSE. Synapse Research Management Partners S.L. (Termination date: 31/05/2020)
4. MUW. Medizinische Universitaet Wien
5. KU Leuven. Katholieke Universiteit Leuven
6. KCL. King's College London
7. USR. Universita Vita-Salute San Raffaele
8. EMC. Erasmus Universitair Medisch Centrum Rotterdam,
9. LMU. Ludwig-Maximilians-Universitaet Muenchen,
10. Charité. Charité - Universitaetsmedizin Berlin,
11. AP-HP. Assistance Publique - Hôpitaux de Paris
12. CUSTODIX. Custodix NV (Termination date: 08/07/2022)
13. i~HD. The European Institute for Innovation through Health Data
14. BERRY. Berry Consultants LLP
15. ECRIN. ECRIN European Clinical Research Infrastructure Network
16. EPF. Forum Europeen des Patients
17. UNEW. University of Newcastle upon Tyne
18. EUROSCAN. EUROSCAN International Network e.V.
19. PEI. Bundesinstitut für Impfstoffe und biomedizinische Arzneimittel, Paul-Ehrlich-Institut
20. UOXF. The Chancellor, Masters and Scholars of the University of Oxford
21. UMIL. Università degli Studi di Milano
22. DocuMental. DocuMental OU
23. UNIMAN. The University of Manchester
24. Janssen. Janssen Pharmaceutica NV
25. Novartis. Novartis Pharma AG
26. Allergan. Allergan Limited (Termination date: 05/05/2020)
27. AZ. Astra Zeneca AB
28. Novo Nordisk. Novo Nordisk A/S
29. Otsuka. Otsuka Novel Products GmbH
30. Pfizer. Pfizer Limited
31. Sanofi. Sanofi-Aventis Recherche & Developpement
32. Servier. Institut de Recherches Internationales Servier
33. Teva. Teva Pharmaceutical Industries Limited
34. CTF. Children's Tumor Foundation
35. SpringWorks. SpringWorks Therapeutics INC

36. TB Alliance. Global Alliance for TB Drug Development Non-Profit Organisation
37. TEAM-IT. TEAM - IT RESEARCH SL (Start date: 01/05/2020)
38. ITTM. INFORMATION TECHNOLOGY FOR TRANSLATIONAL MEDICINE (ITTM) SA (Start date: 01/02/2022)
39. AbbVie. ABBVIE INC (Start date: 06/05/2020)

- **Grant Agreement**. (Including its annexes and any amendments) The agreement signed between the beneficiaries of the action and the IMI2 JU for the undertaking of the EU-PEARL project (Grant Agreement No. 853966).
- **Project**. The sum of all activities carried out in the framework of the Grant Agreement.
- **Work plan**. Schedule of tasks, deliverables, efforts, dates and responsibilities corresponding to the work to be carried out, as specified in Part B; 3.1 to the Grant Agreement.
- **Consortium**. The EU-PEARL Consortium, comprising the above-mentioned legal entities.
- **Consortium Agreement**. Agreement concluded amongst EU-PEARL participants for the implementation of the Grant Agreement. The agreement shall not affect the parties' obligations to the Community and/or to one another arising from the Grant Agreement.

Abbreviations

Acronym/ Abbreviation	Meaning
ACTG	AIDS Clinical Trials Group
AMR	Antimicrobial resistance
APT	Adaptive platform trial
CAB	Community Advisory Board
CDA	Confidential Disclosure Agreement
CIOMS	Council for International Organizations of Medical Sciences
COVID-19	Coronavirus disease 2019
CPIM	Critical path innovation meeting
CTA	Clinical trial approval
DR-TB	Drug resistant Tuberculosis
DS-TB	Drug susceptible Tuberculosis
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European medicine agency
EU	European Union
EU-M4all	European medicines for all (https://www.ema.europa.eu/en/partners-networks/international-activities/medicines-assessed-under-eu-m4all-procedure)
EU-PEARL	EU Patient-cEntric clinicAl tRial pLatforms
FDA	Food and Drug Administration (US)
GCP	Good clinical practice
GRADE	Grades of Recommendation Assessment, Development and Evaluation (https://www.gradeworkinggroup.org)
IMI	Innovative Medicines Initiative
IMP	Investigational Medicinal Product (FDA)
IND	Investigational New Drug Application (FDA)
ISA	Intervention Specific Appendix
IRP	Integrated Research Platform
ITF	Innovation task force (EMA)

J&J	Johnson and Johnson
LMIC(s)	Low- and middle-income countries
MDD	Major depressive disorder
MDR	Multi-Drug-Resistant
MIC	Minimum Inhibitory Concentration
MP	Master Protocol
MSF	Médecins Sans Frontières
NASH	Non-Alcoholic Steatohepatitis
NF	Neurofibromatosis
NIH	The National Institutes of Health (US)
OFLOTUB	Gatifloxacin for TB
PAN-TB	https://fnih.org/our-programs/project-accelerate-new-treatments-tuberculosis-pan-tb
PK/PD	Pharmacokinetics/Pharmacodynamics
PMDA	Pharmaceuticals and Medical Devices Agency (Japan),
RCT	Randomized controlled trial
REMoXTB	Rapid Evaluation of Moxifloxacin in the treatment of sputum smear positive tuberculosis
SAP	Statistical analysis plan
SoC	Standard of care
SWS	Stakeholder workshop
TB	Tuberculosis
UNAIDS	The Joint United Nations Programme on HIV/AIDS
UNITE4TB	https://www.unite4tb.org
US	United States of America
WHO	World Health Organization
WP	Work package
XDR	Extremely Drug Resistant

Lay Summary

The EU Patient-cEntric clinicAl tRial pLatforms (EU-PEARL) project is a strategic partnership of 36 entities split between the public and private sectors, designed to shape the future of clinical trials. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and European Federation of Pharmaceutical Industries and Associations (EFPIA). The project uses 4 diseases as case studies, including Tuberculosis (TB) and due to the peculiarity of the disease, and the fact that it is endemic in countries with limited resources for clinical trials, there are challenges for working with TB. These challenges are tackled here where regulatory, ethical and community aspects are examined in detail.

This consensus document is the result of two very productive meetings held in 2022, which brought together researchers, academics, technical partners, TB drugs and regimens developers, trialists, regulators, guideline developers, programme managers, community representatives and nongovernmental organizations

The consultations were held at:

- The Union World Conference on lung health 2022, WORKSHOP "Tools to build TB IRP trials: the EU-PEARL approach"

- TB satellite session, EU-PEARL 2nd Stakeholder Workshop

Acknowledgements

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1. Introduction to EU-PEARL and the Tuberculosis (TB) Work Package (WP)

1.1. What is EU-PEARL?

EU-PEARL has received funding from the Innovative Medicines Initiative (IMI) 2 Joint Undertaking under grant agreement No 853966-2. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA. It is a strategic partnership of 36 entities split between the public and private sectors, designed to shape the future of clinical trials as there is an undeniable need to speed up clinical trials and make them more efficient.

This innovative consortium aims to create a framework for affected communities and professionals and an Integrated Research Platform (IRP) in which novel techniques and treatments developed by companies and organisations can be tested. It is supported by a management structure which has been set up to meet the complex regulatory, ethical, legal, statistical and data requirements.

1.2. What does EU-PEARL hope to achieve?

The main aim is to create a set of tools and a framework ready to setup and coordinate IRPs for any disease. The project uses 4 diseases as case studies, including TB. Due to the peculiarity of the disease and the fact that it is endemic in countries where there are limited resources for clinical trials, there are many challenges for working with TB.

1.3. What is the structure of EU-PEARL?

There are 4 disease-agnostic Work Packages (WPs) that aim to build the tools and framework that could be adopted by any platform and across any kind of disease. These WPs include:

- **WP1**, to focus on governance, quality and sustainability and also covers scale up, coordinates the patients and the community activities.

- **WP2**, to cover scientific, regulatory and operational methodology and aims to develop the Master Protocol (MP) template, that has been reviewed by the community and patients. WP2 also coordinates the statistical design activities and the regulatory and ethic interactions
- **WP3**, to build the clinical network and the patients' data network
- **WP8**, to manage alliances with other initiatives

The other WPs are disease-specific, where four very different diseases are addressed. In each case, a disease-specific MP will be designed based on the MP template developed by WP2, and the key operational requirements established for the implementation of the specific IRPs. Feedback is being gathered from regulatory and ethics experts for endorsement and affected communities and clinical networks are being built.

- **WP4**, Major depressive disorder (MDD)
- **WP5**, Tuberculosis (TB)
- **WP6**, Non-Alcoholic Steatohepatitis (NASH)
- **WP7**, Neurofibromatosis (NF).

The tools and framework created can be used in forthcoming trials and will be made publicly available at the end of the project.

TB is dealt with in WP5, and the main objective is to collaboratively develop all the tools needed and create optimal conditions for the implementation of platform clinical trials. This includes the ethical and regulatory pathway of a platform study design to accelerate progression of combinations of novel TB compounds through phase II and considerations for phase III studies.

1.4. Where are we? Overview of the first three years' progress

After decades without any improvement in TB field, now there are more than 15 new compounds approaching phase I and II. The question being looked at is if platform trials are the correct answer in terms of efficiency, and if they could accelerate the pathway of access for people with TB. In the past few years, due to Ebola, and later COVID-19, this innovative technology has been successfully adapted to the field of infectious diseases.

WP5 has advanced greatly in terms of addressing the gaps in the implementation of platform trials in TB. A TB-adapted master protocol has been finalized, along with an operational platform trial

handbook, a feasibility assessment tool, a capacity building site assessment manual and a community advisory guideline, which includes language-adapted recommendations. Additionally, a biomarker review has been carried out as there is a current lack of biomarkers to assess drug efficacy.

Tasks outstanding include the development of the high-level document on regulatory and ethics recommendations, the aim of the current document.

1.5. Sustainability of EU-PEARL

Sustainability of the EU-PEARL as a whole is one of the main aims of the consortium and of WP5 as well. TB consortia that could put into practice the EU-PEARL concept and theoretical tools have been identified and, among those, the National Institutes of Health (NIH) US project PAN-TB and the IMI project UNITE4TB cover most of the TB new drug pipeline. Indeed, EU-PEARL now holds a Confidential Disclosure Agreement (CDA) with UNITE4TB, and they have adopted some tools such as the biomarker review, capacity building site assessment manual as well as the site readiness score. UNITE4B partners also reviewed the MP interim report to verify its applicability. Many EU-PEARL community advisors are currently engaged by the UNITE4B consortium.

References:

EU-PEARL: https://eu-pearl.eu

PanTB: https://fnih.org/our-programs/project-accelerate-new-treatments-tuberculosis-pan-tb

UNITE4TB: https://www.unite4tb.org/

2. Consensus on Regulatory Considerations for TB Platform Trials

2.1. Master protocols: Definition and Concepts

2.1.1. Integrated Research Platform (IRP) and Master Protocol (MP)

An IRP is a novel clinical development concept which centres around a Master Protocol (MP). It can accommodate multi-sourced interventions using the existing infrastructure and operational procedures. Moreover, it is built with an existing infrastructure that remains stable over time and benefits from an optimized, defined and smooth regulatory pathway. A MP can be described as a single overarching protocol with multiple sub protocols, allowing for the simultaneous / continuous evaluation of one or more investigational drug under the same protocol. There are different platform trial designs, i.e.: basket trials, umbrella trials and then platform trials.

Basket trials are to evaluate a single drug/drug combination across multiple target populations. Participants may share a single marker or specific mutation or have an overarching condition seen in various diseases/organs and each study has a specific objective, scientific rationale and detailed statistical analysis plan (SAP). A positive response in a single sub-study can allow for expansion of that sub-study.

Umbrella trials evaluate multiple drugs, administered singly or in combinations, in a single disease population. Participants can be randomized to available arms.

Platform trials contain design elements common to both basket and umbrella trials as multiple investigational drugs/drug combinations are used across one target population in a simultaneous, sequential and adaptive design. They can use different strategies to allocate participants and specific tools to analyse results.

In a standard clinical trial, there can be multiple treatment arms and a final analysis where treatment arms are compared with a control arm. Platform trial, interim analyses can be carried out to influence certain early decisions and participant allocation, for example, if are there any treatment arms that need to be stopped due to safety or efficacy reasons or if the allocation needs to be modified. Also,

in a platform trial, additional arms could be added sequentially and incorporated to the trial. In this way, trials are conducted in a perpetual and open-ended manner; whereby current treatments can be stopped at any time and/or new treatments added when they become available, and the control intervention can even be adapted along the life of the project if there is enough evidence to proceed. For example, while other regimens are already ongoing, a new regimen with favourable early safety and efficacy data can be added to the platform trial, using the same trial infrastructure and main master protocol. There are costs in term of protocol development, operational procedures, site readiness and ethical and regulatory clearance so it optimises the resources. To have this all combined into one trial is actually the definition of a platform trial and that is the thinking that EU-PEARL has for TB.

2.1.2. Main recommendations for developing a Master Protocol (MP):

- Clearly describe and justify the design
- Maintain scientific integrity
- Ensure quality of trial conduct and optimise clinical feasibility
- Ensure safety of trial subjects
- Maintain data completeness, accuracy, consistency, validity, uniqueness and integrity
- Reassess benefit-risk balance at critical steps throughout clinical trial (*program interim analysis*)
- Validate companion diagnostics

2.1.3. Advantages and challenges of MPs

MPs have very clear advantages as they provide a common framework which regulates the trial and allows for the inclusion of individual intervention specific appendices. Therefore, multiple treatment options can be assessed simultaneously using the same protocol and adding new arms whenever a drug is mature. They could offer increased efficiency in drug development, minimising operational requirements, and potentially leading to faster drug development. They also have increased flexibility and reduce the time for access to new medicines.

The initial operational complexity could be a challenge in MP development. There are potential concerns with scientific value and justification, data integrity and ownership and there is also a need

to ensure adequate oversight together with early detection and immediate communication of safety signals as it is crucial to protect the safety of the trial subjects. There could also be challenges in controlling Type I error for false positive results or in managing within the MP the impact of emerging data providing new insights and the rapid evolution of standard of care (SoC). For example, if some results are unexpectedly positive, that should be managed within the MPs as well and the SoC may need to change. Data access, data protection and intellectual property rights remain issues to be discussed. Finally, face to face direct comparison between investigational arms could be seen as a threat from the private sector.

In conclusion there is a lot to gain from MPs but there is also a lot of challenges that need to be addressed.

2.1.4. Why an MP for TB?

MPs are a good option for TB drug development for many reasons. Firstly, TB drugs are urgently needed to offer personalized medicine and overcome resistance amplification. In addition, clinical research is time consuming, there are limited funding opportunities and limited TB trial capacities; indeed, there are many trial-naive clinical sites. The TB community is also usually very collaborative, offering a non-competitive space and is willing to share expertise and insights as well as challenges. This also creates an excellent environment in which an MP may work.

Platform trials offer an opportunity to focus efforts and collaborate towards the common goal of progressing the best new drug(s) and best regimen(s). In the landscape of TB drug and regimen development, the main objectives are typically the development of one or more new drugs as a single agent or as part of a regimen, shortening treatment duration, development of safer/better to adhere regimens or the development of creation of a PAN-TB regimen which may be applicable to the entire TB range of susceptibility.

The TB community is looking for new regimens which can be shortened compared with what is currently available. Additionally, a panTB regimen that can be used across the spectrum of the disease, independently of the resistance testing. The field is also looking for biomarkers and to establish biomarkers to use as surrogate endpoints to finally accelerate the development of new drugs and regimens.

2.2. Regulatory process for MPs and Platform trials in EU and US

2.2.1. Submission models EU

MPs in Europe can be submitted as one trial with the posterior addition of sub protocols (also called Intervention specific appendices (ISA)s). In this case the sub protocols must be linked by an overarching scientific justification, adhere to the common outline of the MP. If you open or close a certain sub protocol, then a substantial amendment to the MP will be required. It could be summarised as one big trial.

On the other hand, if the different sub protocols (or ISAs) are not linked to the same research question and can be seen as independent trials, then they can be submitted as separate clinical trials. The MP does not constitute a trial on its own and there always needs to be interventions and regimens to be attached to it. So, when a new or amended sub protocol is submitted, the MP always needs to be part of this submission. . When there is a shared control arm in the MP, the MP and its subprotocols always need to be submitted as “one” trial.

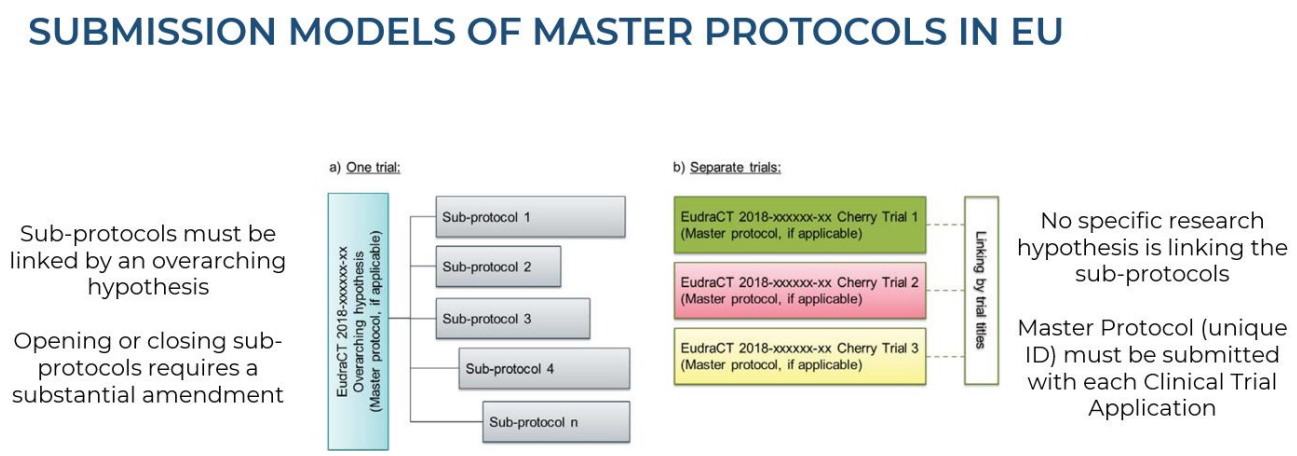

Figure 1 *Submission models od Platform trials in EU. From: Regulatory Considerations for TB Platform Trials, Karin Rombouts, EU-PEARL Workshop Tools to build TB IRP trials: the EU-PEARL approach - November 3rd 2022*

2.2.2. How to interact with the EU regulatory bodies

The European medicine agency (EMA) has a specific Innovation Task Force (ITF) and sponsors can directly request a meeting with them to have an early dialogue on the innovations to cover regulatory,

technical and scientific issues. These meetings facilitate an informal two-way information exchange where the sponsor can check concepts with EMA, and EMA can learn about recent developments in innovate medicine and align themselves accordingly. Informal advice can be given to further develop the strategy or MP. If a concept is too vague, the ITF can refuse a meeting and if it is too specific already, then other formal procedures may be more appropriate.

As the MP advances, and at any stage of an investigational medicinal product (IMP) development, EMA is open for scientific advice, for example discussing best methods and study designs to generate the required data to support registration .

2.2.3. Submission models US

In the US, the Food and Drug Administration (FDA) recommends opening an Investigational new drug application (IND) specific for MPs or for platform trials to reduce complexity and increase transparency. This is in line with FDA recommendations for oncology products and COVID therapeutics and prevention products. Their advice is for the MP to be the single trial that is conducted under such an IND and the sponsor of the MP trial would be the holder of the MP IND and will be responsible for the proper monitoring and the conduct of the MP. The sponsor of such a MP IND is responsible for the trial and should ensure the proper monitoring and adherence to the MP. The sponsor is also responsible for the rapid communication of any serious safety issues to all participating clinical investigators, the FDA and the sponsors of all investigational products related to the MP. In addition, they are responsible for rapid implementation of protocol amendments to address serious safety issues to the MP and submission of letters of authorisations of the IND holders.

At the other hand, the holder(s) of the investigational product IND(s) monitors the safety of the specific investigational drug and evaluates all the accumulating safety data from all the trials including the investigational product, including those that they are conducting themselves as well as those that are being conducted by others. The various INDs can refer to each other.

2.2.4. How to interact with the US regulatory bodies

In the U.S.A., a critical path innovation meeting (CPIM) provides an opportunity for FDA and stakeholders to discuss potential scientific advancements in drug development. The CPIM does not

substitute the formal regulatory meetings, nor is it a venue to market product or a chance to seek endorsement and there is no in-depth data review by the FDA. A potential topic for a CPIM could be innovative conceptual approaches to clinical trial design and analysis. It provides a way to get informal advice and align with the FDA. Of course, there are also the FDA formal meetings.

2.2.5. Sponsorship in platform clinical trials

In the EU, the sponsor should be the entity that oversees the platform trial from an investigative perspective. Of course, there will be individual conversations with each company with respect to their own regimen or products and any deviations from the master protocol will be specified in the ISA, including clinical trial procedures, inclusion or exclusion criteria, any safety issues requiring special attention and so on. This will all need to be discussed on an individual basis amongst partners, but overall, it seems to be much more efficient if there is a single body that acts as the sponsor of the platform trial. Usually, it is an academic group that acts as sponsor for complex clinical trials. For example, in the US, the NIH has taken on this role across all the different ACTIV (Accelerating COVID-19 Ttherapeutic Internventions and Vaccines) studies.

Platform trials are complex to develop and implement. There is a need for solid co-participation of investigators, sponsors and companies to construct a robust network that could start and maintain a platform trial. Every actor has specific knowledge that is key for the success of the project. Unfortunately, standalone initiatives are hard to set up and are usually doomed to failure.

However, there are some key aspects to consider in platform trials, for example, each investigational product owner will need to submit the drug information folder to the regulatory agencies and undergo an independent review, independently of their participation in a platform trial. Therefore, you have to consider the advantages and disadvantages of going in this direction.

Nonetheless, platform trial regulation is still in the first steps of discussion and there are open brainstorming forums that will outline the future regulatory pathway regarding platform trials.

2.3. The role of WHO, as a supranational expert body

World Health Organization (WHO) is not a regulatory agency, but they do play a role. WHO

endorsement of new innovations is key for the adoption and implementation by TB programs. They become important at a later stage by assessing the evidence that is produced for a new drug, a new regimen or new vaccine, a new diagnostic and make recommendations. They try to evaluate not only the efficacy and the safety of this new product is, but also what the final outcome and impact are anticipated to be when implemented under field conditions. This health technology assessment will help in the final adoption of new innovation by health providers.

2.3.1. Regulatory authorities assess the efficacy, safety and quality of a new TB drug and/or regimen.

However, WHO tries to look beyond the safety and efficacy, to what would make them recommend the use of drug X or regimen X, Y, Z from a programmatic point of view. WHO has issued a Target Regimen Profiles document (World Health organization, 2016) to facilitate drug developers to identify important features and align with community and programmatic needs at country level. This document prioritized the needs of end-users, care providers and policymakers to have shorter, safer and easy to operationalize regimens.

Therefore, WHO develops consolidated guidelines to provide policy-makers and implementing partners with evidence-based recommendations on the management of people with TB. The guidelines are elaborated using a systematic methodology for evaluating the evidence, ranking it in terms of certainty, whether it can be trusted and making it generally visible to finally provide unbiased recommendations.

In terms of evidence, the WHO grade evaluation system places randomized control trials at the top in terms of quality of the evidence, followed by prospective studies, retrospective cohorts and other case series. Studies can be upgraded or downgraded according to the study design or the presence of biases. The final decision of the quality of the evidence is thoroughly discussed and agreed between the task force group and external contributors.

2.3.2. Regulators and Public Health Guideline Makers

There is a new trend which is gaining importance, whereby regulators and supranational coordinating health agencies, like WHO, are increasingly collaborating with each other. For example, EMA governs

the approval of products for the EU and, can provide scientific opinion according to Article 58 of the EU legislation, which states they can evaluate products which are not intended to be used in the EU but to be used in low-income countries like, for instance TB products. Article 58 has now been reworked and rebranded to European medicines for all (EU-M4all) framework. The EMA will provide a scientific opinion, although the product EU authorization will follow the approved pathway. WHO, through the WHO prequalification team, can collaborate with EMA in the elaboration of the advice regarding new products adjusted to be closer to LMICs regulatory agencies and the WHO experience gained so far. Sponsors can seek scientific advice from EMA regarding the adequacy of the studies they would like to carry out with the product(s), including the design and validity of platform trials. Scientific advice under EU-M4all will include a coordinating response were WHO is involved.

So, request for scientific advice are submitted first to the EMA, which then involves WHO and finally the regulatory authorities from the countries which are also observing and/or commenting during the procedure.

Seeking input into development plans from the EMA in collaboration with the WHO and national authorities from low-income countries is powerful as it assembles the sensitivities and viewpoints from all relevant stakeholders. This type of approach is extremely cohesive, coherent and federal, in the sense that it assembles people with different points of view. This means that the regulatory authorities are looking at concrete evidence, the guideline makers are looking at concrete evidence plus accessibility evidence. This approach provides a broad consensus about new innovations and creates a multilateral flow of knowledge exchange that helps to increase the formal capacities of all the participating entities.

In addition, WHO is assigning a type of ranking to the regulatory bodies in terms of their capacity (“maturity level”) to assess innovative health products, which goes from one to four(World Health Organization, 2022). When an entity is at three and above, then it is considered to be more stringent and their capacity to evaluate a product is considered as extremely valid and can be taken as a reference in other countries and for WHO prequalification..

The federation approach by multiple regulatory and supranational bodies allows for the rapid approval and implementation of new innovations around the world, which helps to bring better treatments to people in low-income countries, usually the last ones in benefit from breakthrough advances.

2.4. TB platform trials and regulatory approval

In principle, using platform trials as basis for registration should not be an issue. Indeed, seamless Platform Trials for COVID-19 have been used to support registration for new treatment for COVID-19. Specifically in the field of TB, however, the following major regulatory concerns need to be addressed:

- Criteria to proceed to phase III
- Phase IIB data might support registration, through conditional authorization, in DR-TB population; registration in DS-TB population requires phase III data
- Use of concurrent controls
- Extrapolate data from Drug Susceptible (DS-TB) and Drug Resistant (DR-TB) populations.

Other topics of importance that have not been treated in detail during the discussion are the use and number of interim analyses, the justification of non-inferiority margin and the amount of safety data needed.

Moreover, TB regimens are composed of many drugs and each drug has its own challenges and needs. There is a need to discuss with regulators whether the new drug should be approved as a TB drug for use with any other active TB drugs, or only as part as the regimen in which it was investigated, limiting the final deployment of the drug.

2.4.1. Criteria to proceed to phase III: using phase IIc to facilitate the transition from phase II to phase III

The transition from phase II to phase III in the Gatifloxacin for Tuberculosis (OFLOTUB) project and in the Rapid Evaluation of Moxifloxacin in the treatment of sputum smear positive tuberculosis (REMoxTB) study resulted in an unsuccessful phase III study. It was not the only unsuccessful phase III study and the discussion at the time was centred around the hazard ratio for the endpoint that was used, which was the time on treatment to reach culture conversion. This endpoint in the phase II trial could not adequately predict the result in the phase III trial. Discussion about whether a stricter criteria for the hazard ratio of time to culture conversion could predict better the outcome of the phase III clinical trial is still a matter of discussion. Phase II studies usually have a small sample size and the

likelihood to predict the real effect of the intervention is not clear. A trade-off between type I and II error and available resources should be carefully assessed. Phase IIc, as a prolongation of Phase IIb, will help to fill this gap and also better inform the plan to move on to a successful phase III study.

2.4.2. Use of concurrent control

“Non-concurrent” control in a platform trial is the “new external” control in the more standard trials. The use of non-concurrent control should be justified and described upfront. Sponsors should explain why it is not feasible to use concurrent control, what the intended amount of non-current control is that will be used, what the justification is for using that set of non-current control data and, in addition sensitivity analyses will need to be performed.

In terms of regulatory preferences, FDA, especially in the oncology field, requires the primary analysis to be performed using “concurrent” control data and the WHO grading evaluation system places randomized concurrent control trials at the top in terms of validity of the evidence. If you are presenting the results of a study where you have a cohort study with some historical controls, then the value is expected to be downgraded in the WHO grading evaluation system.

2.4.3. DS-TB versus DR-TB populations

The use of data obtained from DS-TB cohorts to support registration of the same drug or the same regimen in DR-TB different regulatory pathways can be considered:

- Comparative trial in DS-TB + single arm study in DR-TB + appropriate PK/PD package, indicating that the regimen retian activity in DR-TB population could support the registration in both populations
- Conduct 2 comparative studies in a platform trial, i.e., one in DS-TB and one in DR-TB populations
- From a data analysis perspective, information regarding minimum inhibitory concentration (MIC) or a biomarker that covers or predicts drug susceptibility and prognosis could be used as a covariant in earlier trials to investigate the impact on efficacy in DR-TB. The PK/PD package could be strengthened with that information. Then it could be learned how much different is the efficacy depending on the drug susceptibility testing and could subsequently inform the design of the confirmatory trials.

In the case of new drug entities that have new mechanisms of action and have not been previously used in the field, there is likely to be a low chance of resistance in the community. If sponsors are

able to demonstrate high efficacy with this new drug or a combination of new drugs, the results from the DS cohorts' data can probably be extrapolated to DR ones, given the unmet medical need and with a full justification. PK/PD packages and MIC information will help with extrapolating the results to other TB population.

Now there is bedaquiline resistance, and there is a new definition of extremely drug resistant (XDR) TB, if you look at it from the perspective of a drug developer who would want to develop a drug for that indication, the unmet medical need in this population becomes very important.

Nonetheless, if the new product is authorized for treatment of TB based on DS and/or MDR TB clinical trials, there is no regulatory need to also get an indication for XDR TB as this would be covered as long as susceptibility to the new product has been demonstrated.

Therefore, if there is a chance to extrapolate data as suggested, it would be of great benefit for all Multi-Drug-Resistant (MDR)TB and XDR TB population. It is probably possible, but the regulators opinion should always be sought to confirm the assumption. Ensuring a strong PK/PD analysis and generating the appropriate MIC information could help to bring the required information together to support registration. This approach could be further investigated in the future.

2.4.3.1. Can the stage of the disease also differentiate populations?

The difference between the DS-TB and DR-TB populations is merely the fact that the bacterium has a major resistance to 2 major components of the six months DS-TB regimen, which is rifampicin resistance plus resistance to isoniazid. DR-TB usually has the same disease natural history as DS-TB. However, people with DR-TB are usually diagnosed in a later / more severe stage of the disease as they spend a lot of time being offered a non-effective treatment, and diagnosis of DR-TB is only made after a lack of response to the standard DS-TB treatment. Adjusting by disease severity will make the DS-TB and DR-TB final outcome more comparable if they are exposed to the same investigational drugs.

If a trial is carried out with a new regimen, defined as a regimen including new or repurposed drug(s), the possibility of cross resistance, if the molecules have a new mode of action if compared to previous drugs, is less likely. Then, if the trial is carried out in DS-TB cohorts, it would be reasonable to assume that adding a DR arm would give experience and the preliminary results will encourage including the DR-TB population in the scope the new regimen. It is also important to provide evidence on MICs

during the trials to try to gather up strong evidence to support a registration in a population underrepresented or not included in the trial. The principle would be that the disease is the same in the DS- and DR-TB population, there only is a difference in the resistance profile of the mycobacterium, ie resistance to drugs which are not part of the new regimen tested.

2.4.3.2. Important elements for regulators concerning DS and DR-TB

First there is the bacterium, and it is important that the bacterium is sensitive to all the drugs in the regimen. They need to be sensitive, not only to the new chemical entities, but to all the drugs in the regimen.

Secondly, the disease stage of the participants is important. People affected by DR-TB are probably sicker and have more comorbidities, making the disease more difficult to treat. Therefore, stratified randomization by disease severity to prevent disease stage imbalance is needed.

Moreover, the comparator arm used for the trial has to retain susceptibility, so it would be challenging to have a single comparator combination for both DS and DR TB.

Finally, the justification of non-inferiority margin is also very relevant. A decision needs to be made to determine a non-inferiority margin that is accepted by all stakeholders working in the fight against TB. A very wide non-inferiority margin could lead to non-efficacious intervention under field conditions, whereas a non-inferiority margin too narrow could limit the number of new interventions that get approved and become ready to improve health.

These three elements will be important for regulators, and this is a topic that may evolve, and more thinking needs to go into, for example, how to maximize the use of the data generation in one population to support use in another population.

2.5. TB Biomarkers: a regulatory perspective

Health authorities are very open for biomarkers to be used as surrogate endpoints, but they need to be comfortable with the biomarker that will be used. It is not clear whether platform trials can establish or validate biomarkers and it is unlikely that the data from a phase II study will be sufficient.

The major problem is that current biomarkers, culture-based biomarkers, only capture what happens

until the culture turns negative, which usually is many weeks after the sample is collected. Additionally, culture-based biomarkers do not have a strong capacity as final outcome surrogate maker, since they do not predict the long-term treatment outcome: cure versus unfavourable outcome, as reported in the results of the REMOX study (Gillespie et al. 2014). The publication found that the markers of time to culture conversion and the rate of decline of bacterial load measured by culture did not qualify as trial level surrogate markers, which was not extremely surprising because they did not consider the overall duration of the treatment. If a person converted to culture negative at two months and got another four months of treatment, versus got another two months of treatment that was of course a factor that a culture-based biomarker could not capture.

2.5.1. How well do culture-based biomarkers predict or not predict the long-term outcome?

Currently there is insufficient information available. There is no validated model that predicts long-term outcome based on culture. A Phase IIc clinical trial approach could potentially cover that deficiency, allowing for the collection of long-term data from a subset of participants. The data could be used to tailor future phase III studies. The approach is that a Bayesian analysis would take a proportion of people having unfavourable outcomes in the phase IIc approach and make a prediction on whether a phase III study will be successful or not. There have been examples where culture was used as a biomarker that then led to unsuccessful phase III studies. Phase IIc study designs have not yet been used for decision making as to what should go into phase III but it is a very promising approach, that actually fills a knowledge gap, about culture and their predictive power.

2.5.2. From the regulatory perspective, which characteristic a predictive treatment response biomarker should have to be used as a decision rule in TB trials?

Endpoints in TB clinical trials to date are related to sputum culture, either as a qualitative (presence or absence) or quantitative data (time to positivity of recurrent sample or time to persistent negativity). One of the most important disadvantages of this is its poor capability to predict the final outcome, in particular to predict occurrence of post-treatment relapses. Neither conversion rates measured at certain time points during treatment, nor time to sustained conversion or any other culture related

measurement assessed during TB treatment can predict potential relapses after end of treatment with sufficient probability. On the other hand, from a regulatory perspective, the evaluation of relapse free survival is key to approve new drugs, and it seems unlikely that current surrogate biomarkers could substitute the currently accepted long-term endpoints, since they encompass an important person-related and programmatic outcome. Long-term regulatory-accepted outcomes, despite having demonstrate to be robust and consistent in supporting effective new drugs, require long and complex trials design, and an ostensible financial expense.

There are also other disadvantages of culture-based outcomes. In platform trials where interim analyses are used for potentially stopping treatment arms early for safety or futility, or also for excellent efficacy, time is important. Current turnaround of culture results is 8 weeks, meaning that lots of the advantages of a Platform trial design fade into waiting

Other limitations of culture-based outcomes are, of course, that they are very labour intensive and only a limited number of labs can currently perform such tasks. There is a risk of contamination and high-quality procedures, and audits need to be in place. There are also collection, transport and processing characteristics that could influence sample results

The liquid culture, usually used in clinical trials, has additional challenges. It is not a direct measurement of bacterial count, but it measures the time until a close signal occurs in an automated system, the so-called BACTEC™ MGIT™ device. Therefore, there is a true need for real-time biomarkers for assessing clinical improvement that can replace culture-based outcomes as a gold standard for efficacy measurement. In an optimal case, these would be biomarkers that can promptly measure early treatment response and simultaneously predict long-term treatment outcome. However, the introduction of such new biomarkers is really challenging and not expected to happen in the upcoming years. The need to fulfil a lot of requirements, analytical validation, clinical validation, clinical utility and treatment development utility and, in the ideal case, being technically undemanding, low cost and a short turnaround time.

Regulatory acceptance and approval are essential for new biomarkers. The EMA and FDA offer procedures for qualification of novel methodologies for drug development and qualification of biomarkers. For example, the EMA qualification process is a scientific pathway leading to either qualification, opinion, or giving a qualification advice on the development and validation of those new

biomarkers. Also, the FDA have an existing similar procedure for classification of new methods as biomarkers that can be used as surrogated endpoints in clinical trials.

2.6. Take home messages:

- **Early Health Authority advice is highly recommended** as MP clinical trial designs can be quite complex. It is strongly advised to have early interactions with health authorities to agree and align up front with health authorities on design and methodological aspects, affected populations, endpoints, randomisation, blinding strategies, statistical adaptations, submission strategies and other topics.
- **Find ways to seek inputs on platform trial designs in a collaborative manner**. Although this is a new concept, reach out to relevant health authorities early on and engage with them to collaboratively understand and agree on the design that would be most beneficial. It makes sense to make the most of all the opportunities out there to discuss the concept and **the detailed plans**, for example with EMA, FDA, WHO and other national regulatory authorities.
- **Trying to reach consensus via joint and/or parallel scientific advice between EMA, FDA and other authorities** from the northern hemisphere, together with the countries from the southern hemisphere where the trial will be run, could lead to a more rapid approval of these new regimens. Maybe a sponsor could submit a package for a scientific advice simultaneously to EMA, WHO and some of these countries, plus maybe FDA and then they could have a joint discussion of all the different aspects.
- **For EU approval, there should be one single sponsor of a trial.** This is typically the entity that is in charge of the platform trial or its subprotocols from an investigative perspective, which is usually an academic institution There is an obvious need to hold individual conversations with each company to discuss the gear of their investigational drug within the Master Protocol and the clinical trial as a whole. Contract trial agreement should clearly define the role and responsibilities of each stakeholder in the clinical trial.
- **Keep DS and DR-TB populations separate or discuss a valid approach with health authorities before initiating the trial,** as merging the data to draw conclusions and

obtaining approval could be problematic if not been previously discussed. Be sure to include a strong PK/PD package and data on MICs and also include appropriate sensitivity analyses to ensure strong support in the registration application to potentially enable extrapolation of the results from the DS cohorts' data to DR ones, given the high unmet medical need.

- **The quality of the data** (Good clinical practice/GCP compliance) remains as important as ever for regulatory purposes, also in platform trials.
- **Use platform trial designs in phase II trials as a learning phase**, then implement it into phase III registrational trials. Outcomes of a phase IIC trial will de-risk the phase III program. A Bayesian analysis would take a proportion of the participants having unfavourable outcomes in the phase IIc trial into account to approach and make a better prediction on the success of the whether a phase III study will be successful or not. Phase IIC study designs are very promising approaches to better inform phase III designs, increasing the likelihood of positive results and regulatory approval; although there could be a delay in the implementation of the phase III clinical trials, since phase IIC relies on long-term follow-up of phase IIB trials
- **Build good relationships with the countries where the TB platform trials will run**, as TB trials are likely to be conducted outside of Europe or the US. Ensuring efficient governance and management is key for a rapid recruitment rate and high-quality data collection.
- **There is a need for real-time biomarkers for assessing TB response** that can replace culture-based outcomes as a gold standard for efficacy measurement in earlyclinical trials. In an optimal case, these would be biomarkers that can promptly measure early treatment response and simultaneously reliably predict relapse free survival outcome.

2.7. References:

EU

European regulator's view on platform trials, lessons recently learned, Hofner and Pétavy, EFSPI Basel 2018

CTFG (2019) Recommendation Paper on the Initiation and Conduct of Complex Clinical Trials

https://www.hma.eu/ctfg.html#c4141

Complex clinical trials – Questions and answers, version 23May2022

https://health.ec.europa.eu/system/files/2022-06/medicinal_qa_complex_clinical-trials_en.pdf

USA

FDA Complex Innovative Trial Design (CID) Pilot Meeting Program to support the goal of facilitating and advancing the use of complex adaptive, Bayesian, and other novel clinical trial designs.

Master protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics, FDA guidance for Industry:

https://www.fda.gov/media/120721/download -

COVID-19: Master Protocols Evaluating Drugs and Biological Products for Treatment or Prevention, FDA guidance for Industry:

https://www.fda.gov/media/148739/download

GENERAL:

Tools to build TB IRP trials: the EU-PEARL approach –The Union World Conference on Lung Health - Workshop November 3rd 2022

Accelerating the Development of New TB Drugs –The Union World Conference on Lung Health – Satellite Session by PAN-TB and UNITE4TB, November 8th 2022

WHO handbook for guideline development

https://www.who.int/groups/guidelines-review-committee

Nix-TB trial by the TB Alliance

https://www.tballiance.org/portfolio/trial/5089

Gillespie, Stephen H et al. “Four-month moxifloxacin-based regimens for drug-sensitive tuberculosis.” The New England journal of medicine vol. 371,17 (2014): 1577-87. doi:10.1056/NEJMoa1407426

World Health Organization. (2022). WHO Global model regulatory framework for medical devices

including in vitro diagnostic medical devices.

World Health Organization. (2016). Target regimen profiles for TB treatment.

3. Consensus on Ethics Considerations for TB Platform Trials

3.1. Adaptive platform trials: definition and ethical considerations

Ending the TB epidemic by 2030 is one of the United Nations Sustainable Development goals and WHO, as part of their End TB strategy, underlines that new tools are required to sustain and accelerate progress. In particular, a new vaccine that is effective pre- and post-exposure, better diagnostics, shorter drug regimens, and more effective targeted treatment for latent TB infection is required. WHO also says it is not merely to stop TB, but also to end the TB epidemic and therefore a broad package is needed, including the underlying factors that need attention. There were 10,6 million new TB cases in 2021, including DS and MDR TB and WHO recognizes that as a public health crisis. In addition, trial costs and funding for TB falls far short of what is needed. Therefore, we should consider new approaches to conventional clinical trials.

The Adaptive Platform Trial (APT) Coalition provides interesting considerations on APT definition, design and implementation (APT Coalition, 2019). The coalition endorsed the term APT because it conveyed three crucial elements (see figure). First, an APT is a prospective experiment — *a trial* — of alternative care strategies. Second, it is *a platform*, with a master (or core) protocol, upon which multiple questions can be asked about the effectiveness of interventions for a particular disease or condition. In this way, the design is similar to basket or umbrella trials. However, the third element, '*adaptive*', distinguishes this class because, like other adaptive trials, it uses information generated during trial conduct to alter subsequent operations in a pre-specified way. In other words, APTs differ from traditional trials in that they use a master, rather than a stand-alone, protocol and they use adaptive, rather than fixed, design features. Both elements (master protocol and adaptive design features) add complexity, but with the intent of improving the efficiency of knowledge generation.

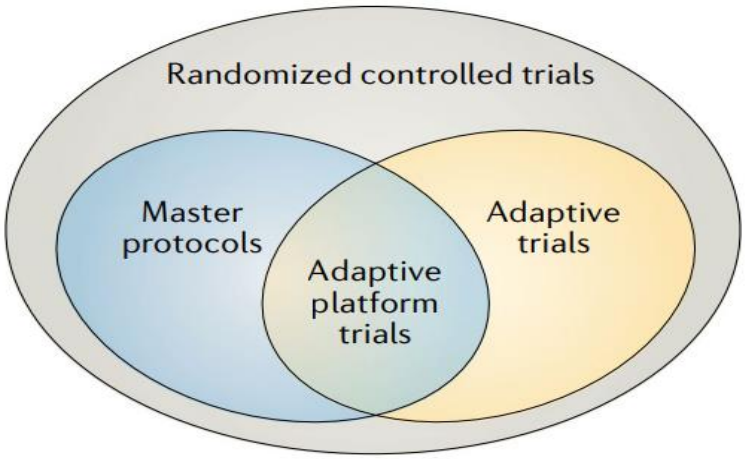

Figure 2 *Adaptive Platform Trials definition and context. Modified from APT Coalition, 2019.*

3.1.1. Rationale for the term 'adaptive platform trial'.

There are clear examples of platform trials under master protocols (for example, Lung-MAP35 (NCT02154490) or NCI-MATCH36 (NCT02465060)) and stand-alone trials that use Bayesian updating (for example, Sepsis-ACT37 (NCT02508649)) that would not be considered APTs. By combining elements of both, APTs generate a unique set of opportunities and challenges.

3.1.2. What kind of ethics issues do we encounter with APTs?

Regarding Randomized Control Trials (RCTs), there already is a lot of ethics literature and research ethics literature on clinical trials available but it is worth mentioning that all the conventional ethical principles apply, such as the declaration of Helsinki.

It is important to pay specific attention to issues that may raise further questions like:

- social contexts of vulnerability,
- the use of clinical trials during disease outbreaks
- post-trial access.

3.1.2.1. Including vulnerable populations

As regards to these, the WHO guidelines on ending TB strategy say: “Equity is a key value for managing latent TB infection, especially since both prevalence and risk for developing active disease is higher among already marginalized groups – prisoners, homeless persons, illicit drug-users and persons living with HIV/AIDS.

This inclusion of vulnerable populations in the UNAIDS WHO guidelines on HIV prevention trials, is referred to as social context of vulnerability and it is also relevant in the TB context. If trials are carried out with these groups (UNAIDS guidance document for HIV, guidance point 6), there is a need to be mindful. Indeed, all stakeholders should be mindful of people in populations living in a social context of vulnerability. Work with communities and relevant civil society stakeholders, and take measures to protect the safety, dignity, human rights, and the welfare of participants. Recognize that participation in research may increase the risk of social, psychological, legal harms. Even though this is a very general point, it is good to take it into account when considering these trials in a Low- and middle-income countries (LMIC) context. There's also some specific guidance on the relation between people who inject drugs and where there might be co-infections and comorbidities such as TB. That was already part of the HIV guidance documents so there is awareness of TB from an HIV perspective.

3.1.2.2. Conduct research in disease outbreak context

In the CIOMS 20 guidelines there is a specific guideline for disaster and disease outbreak. TB is not new, like COVID-19 but some of the ideas that have been written in that guidance point may apply to the TB context. RCTs are recognized as the gold standard but in a disaster, in a disease outbreak context, it is sometimes an idea to explore alternative designs. The guidelines insist that sponsors explore alternative trial designs that may increase trial efficiency and access to promising experimental interventions. The trade-off here is still to maintain scientific validity and therefore, the methodological and ethical merits of alternative trial designs always need to be considered and assessed before using those trial designs. When using alternative trial designs a careful assessment should be performed against validity and the ethical challenges.

CIOMS 20 also talks about a generic research protocol. This was all written before COVID-19, however, in these cases, it was decided that it might be helpful to submit a partial study protocol for ethical pre-screening to speed up the ethical review process. We have witnessed, in the COVID-19

period, that research approval can be done quicker. You can have an international network of specialists, but the ethical review process can be pre-screened and pre-assessed in advance.

3.1.2.3. Post-trial access

Post-trial access is often debated also for general clinical trials. The point about post-trial access is that you should make commitments to it in advance of the trial. When ensuring good collaboration between all the various stakeholders, part of that collaborative process should also be what to do with post-trial access. Researchers and sponsors must make plans for providing continued access to study interventions that have demonstrated significant benefit; and consulting with other relevant stakeholders, if any, to determine everyone's responsibilities and the conditions under which participants will receive continued access to a study intervention, such as an investigational drug, that has demonstrated significant benefit in the study.

In an adaptive clinical trial where arms are dropped, the question arises as to what is owed to participants when some people, on an individual level, have a better quality than before participation. Does that drug intervention still need to be provided or should the possibility to switch to the most effective arm of the trial be offered. That is a question ethicist have not yet considered.

3.2. MPs Ethical aspects

In APTs you make use of Master protocols (MPs) but the ethics of MPs has not been intensively studied by ethicists. There is some literature, especially in the context of oncology trials and also in the context of COVID-19 trials.

The MP can be defined as a research process designed to take multiple target therapies in small sub trials or cohorts. It is a protocol that is prepared in advance, but it is not always clear which specific intervention will be tested as it depends on the outbreak/evolution of disease and there's this option to pre-screen.

At first glance, adaptive trials can be thought to be more ethical because pre-specified adaptations can be made and then more participants can be enrolled in the arm that is performing well.

However, there can be a lengthy period between enrolment and observation of clinical outcomes, while standalone trials could bring a rapid answer to an individual drug and if effective, it could be

made available faster to the whole community. If frequent interim analyses are carried out, a larger sample size than conventional trials may be required. APTs could also be complex and very expensive to plan and coordinate. It is worth bearing in mind that according to Spencer Hey (2015) we have to acknowledge that 'new treatments tend to deliver only small improvements over standard ones'.

3.2.1. The TB environment

Judging from the literature so far, there are potential questions and issues here for the TB context. For example, determining the relative merits of adaptive platform trials compared to conventional trial designs and also, looking at how TB compares and differs from oncology and COVID-19 in setting up and using MPs. In the oncology context, APTs are often used for phase 1 research and may have surrogate endpoints. For COVID-19, remember that WHO was involved in the Solidarity trial, which is the largest global platform trial at the moment. The Remap cap study in the UMC Utrecht was part of Solidarity. Another large adaptive trial was the Recovery trial in the United Kingdom. It is important to determine if those kinds of trials are comparable with TB or completely different as well as to look at the relevant moral differences between those contexts in which we have been using these trial designs.

Another key issue is that APTs can be costly and complex. It is not clear who can build an infrastructure when there is already a shortage of funding. The University Medical Centre Utrecht was involved in the Remap cap trial and so they were able to easily scale up with remaining funds when there was a COVID-19 outbreak and to link their protocols with the WHO solidarity trial. However, massive investment of hospitals, research centres or pharma is required to invest in the necessary infrastructure and if it is not already a priority, especially not for an LMIC, there is a problem.

Platform trials can help progress and also indicate promising interventions, but classic trials are usually still required to make policy recommendations (Phillips et al 2019) . Often, it is not enough to only do the trials within the MP context.

Finally, there is a need to uphold the WHO End TB strategy 2017, which states that more strategies are needed to end TB: "Tackling TB requires addressing the underlying social, economic and political conditions that lead to infection and disease, and that prevent those affected from fully benefitting

from existing effective measures, including current diagnostics and drugs." Innovative tools including APTs are clearly an element that could contribute to end TB, but eventually we will need multiple strategies to end TB.

3.3. Ethical committee review. How to reduce time from submission to approval?

Given the level of suffering that it causes, DR-TB and DS-TB is still a very important public health issue in LMICs that lacks the appropriate level of attention or innovation. The ethics review process has contributed to delays in trial approvals, as experienced recently in the TB Practecal trial, a DR phase II trial over the last four or five years that has been running in Uzbekistan, Belarus and South Africa.

Designing a successful trial is not only about the MP, but also about the community engagement and social acceptance. The ethical boards within the communities that the participants will come from have not always been a specific stakeholder right at the start of that community engagement process and that would be something that's very important for sponsors or even clinical trial networks, like in a platform trial network, to start to think about.

3.3.1. Include the ethical boards/infrastructure in a particular country/jurisdiction in the community engagement planning right from the start

Planning takes resources, experience and time and the engagement of a sponsor, or a group of sponsors, within the ethics infrastructure in any particular place, is a key element in that planning process. Early dialogue with regards to the design of trials is required, including the risks for affected people in the community. Early dialogue may even be possible with the ethical committee there so familiarity can be built up with them as an organization, and more specifically on any protocol design. It is quite possible that investing in this relationship early on will help to solve things down the line. This dialogue is not restricted to building decision points into an adaptive protocol and making them very clear in the MP or the sub protocols, but it may also include a discussion at a very early stage,

whilst the protocol is being developed with the ethical boards. Sponsors would do well to invest a little more in dialogues such as these early on.

3.3.2. Identify the key interconnection between the sponsor and the ethical board

It is important to determine who is responsible for the discussions with the ethical committee in the country concerned. In some contexts, this could be a research organization or a clinical research organization, or it could be the Ministry of Health. It depends on country to country but having someone on board, that has administrative experience of actually communicating with the committee, can facilitate the process, ie: the best way is to approach amendments and so on.

If it's the first time the sponsor has contacted this committee, or it's the first time that the committee has reviewed platform trials, then a lot of upfront specific content can be created for the ethics committee. Although they do have set processes in many jurisdictions about what you can submit, they are generally open to additional information and additional documentation and even offers of meetings to discuss particular protocol designs. Any additional materials that you send to help smooth the process is a good idea.

3.3.3. Try to open a dialogue with the governmental infrastructure surrounding the ethics committees to try to introduce specific knowledge into their training development.

If the trial forms part of a longer-term setting up of a platform, like an integrated platform network, the investment in talking to ethics committees is crucial. It may be possible to introduce specific knowledge into their training development and having a dialogue with the governmental infrastructure surrounding the ethics committees. They are not only part of the research community landscape, but they are also a key part of the government. This will help to encourage regulators to have a supernational connectivity around clinical trials.

It could also be an idea to have global, EU or American networks of ethical boards so they could discuss best practice and also learn about what the main ethical considerations are for platform trials, to avoid starting this discussion afresh every time there is a new board. There are huge benefits to doing that and if this investment is made early on by a platform, the benefits should come with time.

3.4. Improving recruitment rate in an ethical and fair way in APTs

The education and sensitization of a community needs to start with an understanding of what drug development is and why it is done. In order to be fair and ethical in the implementation of any protocol, the engagement process needs to start long before scripting it. This includes dealing with questions for diseases that are managed like HIV, what is HIV? For diseases like TB that is cured, what is TB and why is the different from HIV? What is the difference between treating and curing? Those elements of involving a community take a long, long time.

It is a slow process but for entities like the TB Alliance, that has a specific community engagement team that plays a critical role in sensitizing the communities where they conduct their clinical research, the efforts over the last 4 to 5 years are paying off. They have put in huge amounts of effort into the wider community engagement efforts and there has definitely been a different attitude, a different perception of clinical trials, even towards the TB alliance. It is not unusual for them to participate in a Community Advisory Board (CAB) meeting and discuss how to review a protocol or an informed consent. The ‘need to know’ that the protocols implemented in the communities are relevant and that they are of benefit to the community and the wider TB community is now clear.

In addition, in each community, the stakeholders are different and knowing who those stakeholders are, building relationships with them and building up trust is vital. At the end of the day, sponsors need to ensure that wherever they are, they are working proactively to gain the confidence, the respect and the trust of the people who manage affected individuals at the TB clinics. Without referral from the TB clinics, there will be no trial participants.

3.5. The role of advertising

It is not clear whether advertising publicly will help improve recruitment rates because the relationship between the teams who run the TB clinics and those who oversee the management of the people affected by TB while they are ill and on treatment is such a close and unique one, that maybe another poster on the wall for a particular trial is not going to be particularly helpful. There are already many posters on the walls. The relationship between the clinical site and the referring TB clinic is, again, a very personal one. It's not an impersonal advertisement or a pamphlet that is handed out. Once more,

those relationships are started long before starting to write a protocol and they go on in between the clinical trials.

3.6. Informed consent

3.6.1. The importance of quality reading material in the informed consent

Sometimes, once a potential participant is identified at the TB clinic and is then referred to the site, the material that they are given to read is not appropriate. The informed consent can be really difficult for them to understand and, if the Flesch-Kincaid readability grade is run on it.

Often the outcome is that only somebody with a university level of education can read, uptake the information and understand what they are signing. Sometimes sponsors have to accept that, as a clinical group, it is not possible to write in plain language. Working with linguists, who do not make assumptions about the medical or clinical research jargon so often used, the readability grade can be brought right down. Between grade 6 and a grade 8 is really what the ethicists and the ethics committees require in these cases.

3.6.2. New and more efficient ways of handling informed consent

In some settings it can be hard to keep formal papers with the signature of the participants safe and they could get lost during the clinical trial, so now there are more secure ways of ensuring the safekeeping of the signature of the participant. These include electronically signed consent or fingerprint-based consent in case of illiteracy. With the advent of COVID-19, digital informed consents have become a standard part of obtaining informed consents. Indeed sometimes, again as with COVID-19, there has been a preference for deferred consent, meaning involving participants first and then asking for the informed consent. In large, observational studies, researchers have a preference for not asking informed consent when there is minimal risk and standard treatments. There has also been a lot of experience with alternative forms of informed consent and videos and so on but ethically the most important slogan is potentially to ‘tell it like it is’. If the sponsor has the dual role of both treating physician and researcher, there is a need to take more time to sit down and talk with the

participants.

Possibly the most important thing is to explain that it is research. Related to APTs, the challenge is to take away the misconception that adaptive trials are beneficial per se to those who are enrolled, which is not necessarily the case. That might be the case, but it's not necessarily the case. So this idea that they are more ethical should not be, a slogan to get them to enrol in these platform trials. For APTs, the most important thing is to explain how the enrolment process works in an adaptive trial, clearing up doubts as to who's better off, who's worse off and whether you are really worse off if you enrol first, rather than later. Those kinds of issues have to be explained and it is a challenge, even for research status committees as they typically do not have the necessary experience in evaluating platform trials, thus making it more difficult. First of all, it is important to explain ethically what the difference is between this and conventional trials and if sponsors have that clear for themselves, it will also help them not to suffer from this therapeutic misconception when they go on to explain it to the participants.

3.6.3. Getting consent ethically

Informed consent has two parts, obviously informing participants first and then them giving consent but how that consent is obtained is important. Technology offers certain options, and they can be assessed on their efficacy in their own right, including video consent, fingerprinted consent, remote consent and there will be new options going forward. In terms of data protection mechanisms for fingerprint-based or video consent, we need to be especially careful, in particular when there are less strict protection regulations in the country where the study is performed. Specific attention should be paid to these issues as they require more thought.

The informed part is actually really quite difficult, and sponsors need to be mindful of the relationship between who is giving the information, who is receiving it and what kind of power relationship is happening between the healthcare provider and the participant. This is something that can be difficult in normal research, in all types of research, but it becomes even more difficult in clinical trials and trying to explain randomization and maybe trying to add different layers of complexity on top of that conversation, is not easy. Getting to a stage where there is a high confidence in assuming that the person is informed is difficult and will only come harder with these types of trials. That ethical cost has

to be balanced against any ethical benefit.

This comes even more into focus if the discussion is turned towards trying to get vulnerable groups and paediatric studies into clinical trials. There, the concept of information and informed consent requires a special attention. There are no easy answers but if sponsors make the effort to try and do a series of mini medical ethics studies for that population and try to come up with some very context specific, informed consent recommendations for that particular research in that particular locality per trial or per platform, it could provide an efficient way of lowering the risk of people entering the trial without being fully informed. It's very hard to enter without giving consent but it is quite common for people to go into a trial without being fully informed. That's something that is a risk for many ethical committees.

3.7. Ethics and Community: ‘Nothing about us without us’

In the AIDS conference in 2012, the slogan ‘nothing about us without us’ was widely used and it's a slogan that comes up within the TB activist groups and CABs on a regular basis, but not in the negative connotation. Now it is in the positive connotation and the appreciation that we submit our protocols, our documentation, our plan to develop new TB medications to CABs, because in the end the communities that they represent are the ones that will be affected by the new treatments and interventions. Therefore, it is important before writing the protocol, informed consent or starting the rollout, to visit the community where the clinical trial is to be implemented, to understand better what the community looks like as well as the cultural context.

Having a robust community engagement program that recognizes that the link between the community engagement team, the site investigator and the sponsor is critical to understanding the culture and the belief. Site investigators and community representatives are pivotal figures to include during the protocol writing, to finally draft a document that is relatable to the different communities. In community visits, the time needed to just listen may be considerable at times, but it is vital.

Sometimes there is more of a general operational feasibility process, like in Médecins Sans Frontières (MSF), whereby visits and discussions are initiated with the investigator, but also an attempt is made to start the public involvement in the design of materials as soon as possible. This can only be done in specific visits to get the views of the community and the staff there as early as possible into the

process. It's a mixture of trust and the relationship with the investigator, who has the drive and the enthusiasm, but then there's a whole other set of stakeholders behind that person that also need input into the process.

3.7.1. Perspectives from Brazil

In Brazil the ethical review committees were created in 1996 and they are linked to the national health council, part of the organizational structure of the Ministry of Health. They also include the participation of some non-governmental entities. Now, after 25 years, this organization has more than 800 ethical boards/committees, not exclusively dedicated to health, i.e.: education, psychology, anthropology, and then there are students, associations or workers from these areas.

3.7.1.1. The concept of 'social control' in health

This includes movements like non health professional organizations, social movements, service provider organizations, and very different institutions, not only from government and their role is to monitor and bring demands from the community to the health ministry. This ensures the representation of the social movement in the ethical boards. Each committee must have at least two members to represent the research interests of the research participants and they must be indicated by an organization or social movement. They are considered members of the social control. This idea of social control is very important in the Brazilian health system structure because the community can participate directly or via these representatives and help in consultations and decision-making.

3.7.1.2. The special case of research with humans

When there is an ethical review for research with human beings, there are always community representatives. These are people with different backgrounds and a history of participation in a social or community movement, and this participation is not only limited to the health area. For example, it can be from educational background, other social movements, elderly, children, people deprived of liberty, housing movements, human planning, different situations where social movements can be organized. The representative must be able to express the points of view and interests of these individuals or groups, in order to represent the collective interest. The representatives cannot represent individual interests, only the collective. They have the opportunity to participate in the

meetings, at the training courses, and so on and they can contribute to the ethical evaluation of the protocols.

Some researchers may want to discuss some issues in the ethical board prior to development. For example, how to make contact with the community, how to do the consent process, how to write the explanatory information to obtain informed consent in this specific group or culture. The way the system is set up means there are specific representatives that can help, and different interests can also be represented, for example, there are representatives from patients' associations from specific diseases that can be called upon if there are specific issues to be addressed.

3.8. Take home messages

- **All stakeholders should be mindful of people in populations living in a social context of vulnerability**. By working with communities and relevant civil society stakeholders, measures should be taken to protect the safety, dignity, human rights, and the welfare of participants. It should be recognised that participation in research may increase the risk of social, psychological, legal harms, especially considering these trials are run in an LMIC context
- **Post-trial access require special attention and you should make commitments to post-trial access in advance of the trial.** When ensuring good collaboration between all the various stakeholders, part of that collaborative process should also cover post-trial access. This is especially important in APTs where arms can be dropped and some participants, on an individual level, may have had a better quality than before participation, for example. A decision would need to be made as to whether that drug intervention would still need to be provided or if they should be offered the most effective arm of the trial.
- **There is a common therapeutic misconception that affects transparency in the informed consent** and that is that APTs are beneficial *per se* to those who are enrolled, which is not necessarily the case. It is still research and has to be explained as such, rather than describing it as the best available treatment. The most important thing is to 'tell it like it is'. If a sponsor has a double role, of both the treating physician and researcher, they should

take more time to sit and explain it to the participant.

- **Include the ethical boards and community representatives of the country/jurisdiction of the study from the start.** If early dialogue with the ethical committee with regards to the design of trials and the risks for participants in the community is established from the outset, and if familiarity is built up with the committee, both as an organization and specifically on any protocol design, it is quite possible this will help to solve things further down the line.
- **Identify the key interconnection between the sponsor and the ethical board.** This entity changes from country to country but it should be someone that has administrative experience of actually communicating with the board, that can then discuss what the best way is to approach amendments, etc.
- **Educate the national ethical institutions**. If it is the first time the sponsor has contacted this committee, or it is the first time the committee has reviewed platform trials, then a lot of upfront specific content can be created for the ethics committee. This will help them in their assessments.
- if your trial is long term, try to **open a dialogue with the governmental institutions** surrounding the ethics committees to try to introduce specific knowledge into their training development. The investment in talking to ethics committees and having a dialogue with the governmental infrastructure surrounding the ethics committees should pay off in time. They form part of the research community landscape and part of the government so this will help to encourage regulators to have a supernational connectivity around clinical trials.
- **The personal relationship between the various players in LMICs is a close and unique one**, from the teams who run the TB clinics and who oversee the management of the people affected by TB while they are ill and on treatment, to the one between the clinical sites and the referring TB clinic. The relationship with them needs to be started long before starting to script the protocol and maintained in between clinical trials.
- **Ensuring quality and appropriate language adaptation in the reading material in the informed consent is crucial**. Work with linguists who don't make assumptions about the medical jargon or clinical research jargon to bring readability right down. This is something the ethicists and the ethics committees have required but have not always enforced. It's critical to really ensure that the participants know what we are asking them to consent to.

- **Keep informed consent very context specific, including recommendations for that particular research in that particular locality**. Per trial or per platform, aim to do a series of mini medical ethics studies for that population in order to lower the risk of people entering the trial without being fully informed. This is a risk that needs to be mitigated for ethical committees.
- **Work towards having global, EU or American networks of ethical boards,** to discuss practice and gain a common knowledge base regarding the principle ethical considerations of platform trials. In the future, this would help to avoid starting the discussion afresh every time, lead to shorter timelines and improve the guidance from the ethical committees.

3.9. References:

International Ethical Guidelines for Health-related Research Involving Humans, prepared by the CIOMS in collaboration with WHO

https://www.who.int/docs/default-source/ethics/web-cioms-ethicalguidelines.pdf?sfvrsn=f62ee074_0

Ethical considerations in HIV prevention trials, UNAIDS and WHO guidance document

https://reliefweb.int/report/world/ethical-considerations-hiv-prevention-trials

Ethics guidance for the implementation of the end TB strategy, produced by WHO

https://www.who.int/publications/i/item/9789241512114

The end TB strategy

https://www.who.int/publications/i/item/WHO-HTM-TB-2015.19

Adaptive Platform Trials Coalition. Adaptive platform trials: definition, design, conduct and reporting considerations. Nature reviews Drug discovery vol. 18,10 (2019): 797-807. doi:10.1038/s41573-019-0034-3

https://pubmed.ncbi.nlm.nih.gov/31462747/

Syn NL, Yong WP, Goh BC, Lee SC. Evolving landscape of tumor molecular profiling for personalized cancer therapy: a comprehensive review. Expert Opin Drug Metab Toxicol. 2016 Aug;12(8):911-22.

https://pubmed.ncbi.nlm.nih.gov/27249175/

Hey SP, Kimmelman J. Are outcome-adaptive allocation trials ethical? Clin Trials. 2015 Apr;12(2):102-6. doi: 10.1177/1740774514563583.

https://pubmed.ncbi.nlm.nih.gov/25649106/

van der Graaf R, Roes KC, van Delden JJ. Adaptive trials in clinical research: scientific and ethical issues to consider. JAMA. 2012 Jun 13;307(22):2379-80. doi: 10.1001/jama.2012.6380.

https://pubmed.ncbi.nlm.nih.gov/22692169/

Phillips, Patrick P J et al. “Keeping phase III tuberculosis trials relevant: Adapting to a rapidly changing landscape.” PLoS medicine vol. 16,3 e1002767. 22 Mar. 2019, doi:10.1371/journal.pmed.1002767

https://pubmed.ncbi.nlm.nih.gov/30901331/ https://pubmed.ncbi.nlm.nih.gov/30901331/

Kincaid, J.P., Fishburne, R.P., Rogers, R.L., & Chissom, B.S. . Derivation of new readability formulas (automated readability index, fog count, and flesch reading ease formula) for Navy enlisted personnel. 1975. Research Branch Report 8–75. Chief of Naval Technical Training: Naval Air Station Memphis.

https://stars.library.ucf.edu/cgi/viewcontent.cgi?article=1055&context=istlibrary

TB PRACTECAL TRIAL

A 24-Week, All-Oral Regimen for Rifampin-Resistant Tuberculosis

https://www.nejm.org/doi/full/10.1056/NEJMoa2117166

Berry C, du Cros P, Fielding K, Gajewski S, Kazounis E, McHugh TD, Merle C, Motta I, Moore DAJ, Nyang'wa BT. TB-PRACTECAL: study protocol for a randomised, controlled, open-label, phase II-III trial to evaluate the safety and efficacy of regimens containing bedaquiline and pretomanid for the treatment of adult patients with pulmonary multidrug-resistant tuberculosis. Trials. 2022 Jun 13;23(1):484. doi: 10.1186/s13063-022-06331-8. PMID: 35698158; PMCID: PMC9190445

https://www.burnet.edu.au/publications/7130_tb_practecal_study_protocol_for_a_randomised_controlled_open_label_phase_ii_iii_trial_to_evaluate_the_safety_and_efficacy_of_regimens_containing_bedaquiline_and_pretomanid_for_the_treatment_of_adult_patients_with_pulmonary_multidrug_resi

stant_tuberculosis

REFERENCES FOR NON TB TRIALS:

Solidarity Trial

https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments

Remapcap Trial

https://www.remapcap.org/

Recovery Trial

https://www.recoverytrial.net/

4. Consensus on Community Considerations for TB Platform Trials

4.1. Community engagement in TB Clinical Trials

We owe it to the community to ensure that the whole process is empowering and not discriminatory. There's always a distinction between the researchers and the community. They are often at the two ends of the spectrum and the closer they become, the better it will be for research, for development, for acceptance, and for better results. Despite current efforts, there still seems to be a gap between the researchers and the community and to avoid problems as well as improve and enrich the research, researchers need to be prepared to proactively work with the community to close that gap. When researchers go out to the community, besides visiting the clinic, an opportunity to engage with the community is opened up and should be taken. There is a need for research that is inclusive, that is empowering, that leads to outcomes that benefit not just one group of people, but the whole community.

4.1.1. Communication with the community is crucial

Community engagement refers to a variety of aspects to be considered in these groups. It is crucial to clearly present the risks and benefits to the participants as they need to understand the design of the protocol and, with platform trials, and it can be especially difficult for them. Good communication is always very important but especially in communities with socioeconomic vulnerabilities. The difference between the participant's healthcare and the objective of the clinical trial must also be clearly explained because they are not the same thing. The utility of post study medications is also sometimes unclear. Finally, it is vital to ensure stakeholder involvement and in each community the stakeholders are different. Knowing who those stakeholders are and building relationships with them to build up trust is crucial to trial success.

CABs do exist to help but it’s not clear in all cases if they are genuinely linking the community with the clinical trials. For example, some communities are still insufficiently informed at the start of the trial and then later informed that it was a success. In cases like that, without the correct processes in place to inform the community, they may later hear that a new drug is being used but then it can be very hard to get them to take it. Sometimes the only people in the community that know the details are those that are already on it and also those that have already been cured. It might be an idea to take some representatives from this group and use them as patient advocates for the new drug, as was done in bedaquiline and other cases. When people from the community are directly involved in the communication process, they can help to inspire trust. The same issue occurs, for example, when details of the drugs regimen are changed, such as the timescale, and the community are not informed. WHO approved the shorter regimen, and the researchers know but those communities also need to know. Via a strong and committed community engagement, we can make them aware that we are now no longer using 18 months or 12 months for DR-TB, that it is now 6 months and that we no longer use these regimens for 6 months in DS-TB, but only for 4 months.

In addition, we cannot permit a situation whereby participants are enrolled to a study and then when they get to the clinic, they're given only partial information and do not get answers to any further questions they may have. This issue is only exacerbated when there are further problems down the line, for example, when the participant is having challenges, toxicity or collateral effect. Therefore, clear communication with the community is crucial.

4.1.1.1. Communication and engagement with the community needs to start early

Engagement with the community should begin very early on, right from the start, even before the protocol is put in place. Appropriate structures need to be set up as community engagement is not going to happen automatically. It requires deliberate, intentional exercise because otherwise good intentions will be reduced to all words and no actions. Community advisory boards or groups need to be established as well as a continuous dialogue, not just early on, but throughout the entire process. So before electing these CABs, the community itself could be asked to provide the people that will help impart the information. Where there is a 'leader' in the community, they could be called in to help choose someone from the community to help with community engagement. They can then report back to the researchers who will be deployed. The cultural heritage in each area needs to be respected in this way.

It is also important that the researchers go and check the participants' individual circumstances and the challenges in the community. In a past example of good practice from MSF, once the participant had enrolled, they started monitoring psychosocial support for the participant, with that support going above and beyond their time spent at the clinic. They did a home visit to check how the participant was living, who they were living with and how they were getting food. Supplying the medication when the person cannot take the medication without food does not make any sense without checking for a good food supply first. It is crucial to go into the community and check exactly what the settings and challenges are.

Another important community aspect is the value of support groups. Part of the success story is the medication to support the person medically but another, often overlooked part, is the need for support groups as the other affected people also help to support each other.

4.2. People centred research

Research needs to be focused on people. Often, when research is discussed, only the drugs are mentioned. As researchers or research literate advocates, it is extremely important to keep that people centeredness and especially in TB.

It is important to speak the community 'language' and respect their values. What is needed with any clinical trial, when you are trying to reach the community, is to use language that is easily understood,

that resonates with them. It is very important to explain all the processes, all the aspects of the research, to the community at *every* local site in a manner that is easily understood, in a language that they can identify with whatever it is.

In addition, it is vital to get to know the community, their beliefs and their values, because that varies from country to country and trust is crucial. So, the first way to approach that could be to have community members who look like the individual, who they can relate to and who they can believe in. To enrol participants in TB, individuals who are willing to share their life experience are also needed. If TB survivors speaks to their community, there is better acceptance than somebody coming from somewhere far away, who they do not know. So local is always better, closer to people is better. The community members should be themselves and really provide that personalized insight into what it means to either live with the disease, or temporarily be with the disease, so that affected people can see with their own eyes someone, who looks familiar, sounds familiar, who has experienced many of the same things and fears. If the community is made comfortable in this way, that would be a very important first step, especially when we are talking about platform design. Many do not understand the concept so it could be worth thinking about how to explain it to friends and family so they can understand exactly what it is. If that is done, it will translate better when it is time to inform the community.

It is vital to respect the culture of the community. If a study is organized, for example, in rural areas where there is a different culture, researchers should remember to be respectful when they visit.

For example, in South Africa, as a black community, it is believed that when you have TB, you have been cursed. Here is where community advisory groups and community advisory boards can play an excellent bridging role between the researchers, the scientists, and the communities. Investment into meaningful community engagement is never a waste of resources or time.

4.3. Ensuring well informed consent

A huge emphasis must be placed in the process of informed consent, ensuring the language and communication is aligned with the participants' characteristics and also on the way it is to be delivered, if it is written, a video or audio. The bottom line is that community needs to be *fully informed*. Efforts need to be made to ensure that the description of the research and activities that the participant must

undergo during the participation is clear as well as the separation between the healthcare needed and the trial objectives.

When there is no ownership of these tasks, the people in the community cannot directly ask for it. An investment needs to be made in the community to help them understand so that they are fully informed and empowered, and their capacity is built so that they can demand in a manner that really matters. Also, when the consent document and processes are developed, they need to be done with the community and with the community representatives.

It is necessary to include local researchers in the design and planning too, to improve interactions with the community and build trust. They also bring a better understanding in terms of the language and culture. There are LMICs who have good researchers, good scientists, capable of doing high quality research. They need to be identified and sought out.

4.3.1. Methods of informed consent: community perspectives

The community preference regarding informed consent depends on the participant age, the level of literacy, etc. Sometimes the process of consent is providing all research information in different ways and granting some more time to the participants to discuss their participation with family or friends, not only with the researcher. Using a video may be better for a young participant but if you are looking at an older group, using technology may not be the best way, it may be face to face. There is a need to analyse the group, the target. However, before looking at all the avenues and mechanisms to communicate, it is important to look at the available infrastructure of the site, for example, video conferencing does not work in many countries because of load and cost of data.

The bottom line here is that the information needs to be given and understood in the best way possible. The community should understand what the trial means and have that trust. They should be in the centre. Researchers and scientists should not be out of reach, where the community cannot access them and there should not be any sort of a power play.

As to the method used, researchers need to use all their creativity, but certain principles need to be followed, especially with data protection, ensuring language that is non-stigmatizing and so on. Those are non-negotiable and if researchers respect those, whether they use a song and dance, a video or simply sit down with the participants to explain it, it does not matter. They should do whatever it takes

to get the message through. Nowadays there are so many different tools for communication available for use in the research, efforts should be made to make it both creative and effective.

4.3.2. Avoid stigmatising language

In TB research, the use of a stigmatising language is still an unresolved issue, for example the use of the term “patients” should be avoided in favour of “individuals”. That word is considered stigmatizing and to help move away from that useful language guides have been developed by the Stop TB partnership. These guides provide lists of stigmatizing words and expressions and suggest inclusive alternatives. As language is a pivotal element in TB research, it is important to remember that documents can fail ethical approval if they have language that uses terminology which is considered stigmatizing by the affected communities. The scientists and the researchers are focusing on doing good, implementing good science, and the lack of sensitivity sometimes may cause friction with affected individuals that can and needs to be avoided.

4.4. The inclusion of pregnant women, children or other vulnerable populations in the early stages of drug development

In general, TB research in children has not been conducted to the same degree as in adults as tools that work both for adults and children were not developed simultaneously. Innovative treatments and regimens are developed for adults and then adapted to be used in the paediatric population. Nonetheless, this process is lengthy and often takes several years after the drugs are developed. We need to define a simultaneous process to develop new regimens for adults and children, side by side.

Improved acceptance of studies involving children with the community can be achieved by researchers transparently communicating the risks involved. To this aim, it is important to define clear parameters for further study, helping in better understanding the risks for the paediatric population.

The same process should be applied for pregnant women. In this case, frequent monitoring of the wellbeing of the mother and the foetus are pivotal to ensure their security and safety during the trial. The monitoring should continue after the child birth for the mother and especially for the child for a

suitable a period of time. The period of time should be determined in such a way that collateral effects could be prevented or at least immediately identified.

4.5. Take home messages:

- **Use the community to ensure win: win in trials.** It might be an idea to take some representatives from the community that are already on a new drug or those that have already been cured by it to act as goodwill advocates for the new drug. If people from the community are involved in the communication process, they can help to inspire trust. The leader of the community can also be used to help provide local people that will help impart the information in the CABs.
- **Engagement with the community needs to start at the outset**, even before the protocol is put in place. Set up structures such as community advisory boards or groups to establish a continuous dialogue, not just early on, but throughout the entire process. They can play an excellent bridging mechanism between the researchers, the scientists, and the communities.
- **Check the participant's individual circumstances and the challenges in the community**. When you are doing research, it is not only giving the medication. Sponsors need to check the potential need for psychosocial support for the participant, going above and beyond what they receive at the clinic. For example, it is important to check food supply if the person can't take the medication without food.
- **Don't underestimate the value of support groups.** Part of the success story is the medication to support the affected person but another, often overlooked part, is the need for support groups as the TB community also help to support each other.
- **It needs to be all about people.** As researchers or research literate advocates, it is extremely important to ensure people centeredness and especially in TB.
- **Use the right words.** It is important to speak the community 'language' and respect their values. Choose words that are easily understood, that resonate with participants, a language that they can identify with, whatever it is. Moreover, stigmatizing language should never be used. Appropriate language guides have been developed and all researchers working in the

TB field should follow them.

- **How to include vulnerable populations.** We need to simultaneously develop tools that work both for adults and children. To improve community acceptance, the risks need to be honestly examined and appropriate limits set accordingly. For pregnant women, specific data is required, or some other means to assure them about their children's safety. Follow up programs are required to monitor the children of these pregnant woman in the future.

4.6. References:

Words matter language guide

https://www.stoptb.org/words-matter-language-guide