PETTS Data Analysis Plan

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Analysis, Publication of Results

- **Framework with 3 levels:**
  - **Primary:** 4 reports focusing on main objectives of PETTS
  - **Secondary:** Multiple other analyses & publications initiated by partners
  - **Site-specific analyses, publications & presentations (oral, posters, abstracts)**
PRIMARY ANALYSES AND REPORTS
Primary Analyses and Reports

- #1 - Prevalence of and risk factors for baseline drug resistance
  - To determine baseline prevalence of and clinical, epidemiological, and microbiological risk factors for resistance to second-line drugs (SLD)

- Comments
  - Manuscript in CDC clearance!

- Point of contact (POC)*
  - Tracy Dalton, Peter Cegielski

*POC will work with the coordinating center team to finalize data, and will work with coordinating team and country representatives on data analysis and report writing
Primary Analyses and Reports

- **#2 - Incidence of and risk factors for acquired drug resistance**
  - To determine the incidence of and risk factors for amplification of drug resistance

- **Comments**
  - Per protocol, genotyping was to be based on comparison of DST results of all drugs
  - SM, EMB, PZA, THA, PAS – poor reproducibility of DST results
  - Should genotyping isolate-pairs with differing DST results be limited to INH, RIF, FQ, SL-INJ?

- **Point of contact (POC)**
  - Peter Cegielski, Tracy Dalton
Primary Analyses and Reports

- **#3 - Effect of acquired drug resistance on treatment outcomes**
  - To describe MDR-TB treatment outcomes and to determine risk factors for poor treatment outcomes
  - To evaluate time to and identify independent predictors of time to sputum culture conversion
  - To assess impact of acquired drug resistance and delayed sputum culture conversion on treatment outcome

- **Point of contact**
  - Peter Cegielski, Tracy Dalton, Ekaterina Kurbatova, Julia Ershova
Primary Analyses and Reports

- **#4 - Timing of acquired drug resistance in relation to specific mutations**
  - To determine time to change in drug resistance and risk factors for faster amplification of resistance
  - To assess if specific mutations are associated with time to resistance amplification

- **Comments**
  - DST and genotyping for those with different baseline & final DST (INH, RIF, FQ, SL-INJ) will be done selectively according to an algorithm

- **Point of contact**
  - Tracy Dalton, Peter Cegielski, Ekaterina Kurbatova, Julia Ershova
SECONDARY ANALYSES AND REPORTS
Secondary Analyses and Reports

- **HIV infection: acquired resistance and treatment outcomes in relation to CD4 count and antiretroviral therapy**
  - To better characterize the subset of HIV-positive patients with MDR-TB
  - To assess if HIV infection is a specific risk factor for acquired/amplified resistance to SLD, and longer time to culture conversion, compared to HIV negative patients
  - To assess impact of use of antiretroviral (ARV) therapy and co-trimoxazole preventive treatment (CPT) on mortality among HIV-infected patients

- **Point of contact**
  - Charlotte Kvasnovsky, Ekaterina Kurbatova, Melanie Wolfgang, Julia Ershova
Secondary Analyses and Reports of Aggregate Data

- **Genotyping differences in sequential isolates of *Mycobacterium tuberculosis* from same individuals**
  - To describe rates and probable reasons for changed genotyping profiles (exogenous re-infection, lab cross-contamination, mixed infection).

- **MDR-TB with 2 or more strains**
  - Reasons for change in genotypes between baseline and final isolates, e.g., reinfection, mixed infection, cross-contamination
  - Impact on treatment outcomes

- **Point of contact**
  - Ekaterina Kurbatova, Peter Cegielski
Association between molecular genetic basis of drug resistance and treatment outcome

To determine whether there is an association between specific genetic mutations that confer drug resistance (GenoType MTBDRplus, HAIN Lifescience) and clinical outcome, specifically the outcomes of development of additional drug resistances and duration of persistent positive culture.

Point of contact

Eleanor Click, Heather Alexander, Tracy Dalton
Secondary Analyses and Reports

- **Evaluation of GenoType MTBDR\textit{plus} and MTBDR\textit{sl} (HAIN Lifescience)**
  - To determine the accuracy of the \textit{MTBDRplus} assay (HAIN Lifescience) for detection of Rif-resistance, INH-resistance and MDR TB in clinical isolates
  - To evaluate the use of \textit{MTBDRplus} for differentiating between high- and low-level INH resistance
  - To determine the accuracy of the \textit{MTBDRsl} assay for detection of resistance to injectable SLD, the fluoroquinolones, and EMB

- **Point of contact**
  - Heather Alexander, Tracy Dalton
Secondary Analyses and Reports

- **Time-to-diagnosis of drug resistance and time-to-initiation of appropriate treatment: impact on acquired resistance and outcomes**
  - To determine if longer time to diagnosis and treatment of MDR-TB was associated with baseline drug resistance and poor treatment outcomes

- **Point of contact**
  - Peter Cegielski, Tracy Dalton, Ekaterina Kurbatova
Secondary Analyses and Reports

- **Impact of hospitalization on development of additional drug resistance due to re-infection with a different strain**
  - To determine effect of hospitalization on rates of drug resistance (baseline and acquired) because of re-infection, and association with nosocomial transmission

- **Point of contact**
  - Ekaterina Kurbatova, Peter Cegielski, Julia Ershova
Secondary Analyses and Reports

- Application of Molecular Detection of Drug Resistance (MDDR) service to PETTS isolates: rapid predictors of XDR-TB
  - To use DNA sequencing to further elucidate associations between genotypic and phenotypic SLD resistance in *M. tuberculosis* and clinical outcome in MDR-TB patients
  - To gain a better understanding of the extent of cross-resistance within drug classes and to further characterize mutations associated with cross-resistance
  - To identify potential novel mechanisms of resistance to the injectable SLDs (KAN, AMK, and CAP) and the fluoroquinolones (CIP, OFL, and MOX)

- **Point of contact**
  - Tracy Dalton
Secondary Analyses and Reports

- Baseline and acquired resistance to pyrazinamide (PZA) among MDR-TB patients - prevalence and effect on treatment outcomes
  - To describe rates and predictors of baseline and acquired resistance to PZA and effect on treatment outcomes

- Comments
  - Should we test for PZA resistance using a different method?
  - Should we select isolates for PZA testing according to some algorithm or decision rule?

- Point of contact
  - Peter Cegielski, Tracy Dalton, Lois Diem, Beverly Metchock, James Posey, Bonnie Plikaytis, Michael Iademarco, Ekaterina Kurbatova, Andrew Vernon
Secondary Analyses and Reports of Aggregate Data

- **Diabetes mellitus and MDR-TB outcomes**
  - To assess if diabetes is a specific risk factor for longer time to culture conversion, and for baseline and acquired/amplified resistance to SLDs.
  - To compare treatment outcomes between patients with/without diabetes.

- **Impact of body-mass index on treatment outcomes of patients with MDR-TB**
  - To determine the impact of low BMI on acquired resistance and treatment outcome.