Clinical trials design and methodology

OC - (8561) - RAPAED TB – AN INNOVATIVE CHILD TB DIAGNOSTIC VALIDATION STUDY

Olbrich, Laura (Germany)1; Zar, Heather (South Africa)2; Graham, Steve (Australia)3; Sabi, Issa (Tanzania)4; Ntinginya, Nyanda (Tanzania)4; Bhatt, Nilesh (Mozambique)5; Nliwasa, Marriott (Malawi)6; Corbett, Elizabeth (United Kingdom)7; Song, Rinn (United Kingdom)8; Denkinger, Claudia (Switzerland)9; Hölscher, Michael (Germany)1; Heinrich, Norbert (Germany)1

1- Division of Infectious Diseases and Tropical Medicine, Medical Center of the University of Munich (LMU); 2- Red Cross War Memorial Children’s Hospital, MRC Unit on Child and Adolescent Health Unit, Cape Town, South Africa; 3- University of Melbourne; 4- NIMR-Mbeya Medical Research Programme; 5- Instituto Nacional de Saúde (INS) - Mozambique; 6- Malawi College of Medicine, Blantyre; 7- London School of Hygiene and Tropical Medicine; 8- Oxford Vaccone Group, University of Oxford; 9- FIND (Foundation for Innovative New Diagnostics)

Background: Children account for an estimated 1 million new cases of TB every year, representing roughly 7% of the total disease burden. Every year, around 209 000 children die from TB, half of those cases are in Africa. The main issue continues to be timely and accurate diagnosis, as treatment outcomes – even in the case of drug resistance – are significantly better than in adults.

Clinical diagnosis in the absence of laboratory confirmation is hampered by non-specificity of symptoms. Diagnostics validation studies in children are difficult - in most studies, very few of the symptomatic children achieved microbiological disease confirmation, resulting in imprecise estimates for test sensitivity.

Design/Methods: With the RaPaed TB study funded by EDCTP, we are preparing an improved diagnostic validation study design to improve on the traditional approach of a single-gate, double diagnostic study in the target population. The project will evaluate multiple new tests on the same patients, to determine algorithms of screening and confirmatory tests. Most novel tests in this study use non-sputum samples, and are therefore more suitable for children.

Allocation of patients into standardized groups will follow NIH-convened consensus panel recommendations on case definitions of paediatric TB diagnostic studies. Using an endpoint review committee will allow blinded review of those new-positive cases, plus matched controls, and determine their likelihood of disease based on clinical data including follow-up, and X-ray. This will improve the quality of evaluation of false positive vs. true positive results of new tests and therefore improve the assessment of specificity.

To improve on sensitivity assessment, the study includes partners with a high number of confirmed cases in past studies, and plans to draw in cases of confirmed disease from other diagnostic facilities.

Conclusion: This improved methodology will lead to more meaningful and applicable results of diagnostic validation studies.