R24

Hub North West	Host University Lancaster University
Supervisor Thomas Jaki t.jaki@lancaster.ac.uk	Co-supervisors James Wason, Peter Horby
Is the project clinical or non clinical? Non clinical	
Title of PhD project Evaluating treatments for infectious diseases that could potentially become epidemic	

Background
In early 2014 the World Health Organization (WHO) was notified of an outbreak of the Ebola virus and around half a year later the WHO declared the epidemic to be a "public health emergency of international concern"[1]. In the time that followed frantic efforts where undertaken by different groups around the world to evaluate treatments to cure the disease[2].

With hindsight, it seems strange that no treatments were evaluated prior to the epidemic. Upon closer inspection, however, some of the reasons for this become clear. Firstly, without an epidemic, there are no or hardly any patients who could participate in a formal evaluation of a treatment. Secondly, the large number of pathogens (e.g. Avian flu, Swine flu, MERS-CoV, …) that could potentially lead to an epidemic makes it difficult to choose which disease should be the focus of the research.

The project
The goal of this project is to develop a statistical framework that allows evaluation of treatments for diseases that occur in outbreaks and have the potential for an epidemic. In such a setting learning about a treatment's effect can happen in two ways: Through a sequence of small (contained) outbreaks and during an epidemic.

In the first instance the project will develop methods that allow learning about the effectiveness of a treatment across several small outbreaks through a sequence of small clinical trials. The primary challenges here is the uncertainty about the number of patients recruited during each outbreak together with the potential of regional and other differences. The project will consider how to incorporate these differences and explore suitable stopping criteria.

The second part will consider adaptive methods that allow the design of these small clinical trials to be altered in the event of an epidemic. The initial challenge is to establish when a change in design should be triggered; i.e. when does an outbreak become an epidemic. We will begin by considering changing the rules for stopping the evaluation of a treatment to ensure that treatments reach patients faster. Due to the markedly increased speed of recruitment, designs that allow adapting the primary endpoint will be considered as long term endpoints are unsuitable during an epidemic. These adaptations will ensure decisions about the suitability of a treatment are made quickly and therefore ensure that suitable treatments are found in a timely manner.

The project will be informed by the experiences during the recent Ebola outbreak for which Prof Horby led one of the groups seeking to find treatments. Open source software for the designs developed will be made available.

Supervision arrangement
TJ will be the main supervisor and meet weekly with the student to provide ideas and to help overcome obstacles. JW will provide input and advice on the statistical aspects and PH, Professor in Emerging Infectious Diseases, University of Oxford, will provide clinical insights to the project and ensure that the project is undertaken within practical constraints and methods are suitable for real world applications. Joint quarterly supervisory meetings are planned with at least one meeting a year in person. In addition, the student will also have to opportunity for a secondment of at least 2 weeks to Prof Horby's group.

[1] WHO Ebola Response Team. "Ebola virus disease in West Africa—the first 9 months of the epidemic and forward projections." N Engl J Med 2014.371 (2014): 1481-1495.
[2] LE Dodd "Clinical Trials During the Ebola Crisis: A Series of Articles and Commentaries Describing the Challenges of Conducting Clinical Research During a Lethal Epidemic" Clin Trials 13(1) (2016) 1-111.

R24

Supplementary information

1. Describe the alignment of the project with the HTMR Network strategy

Core to this project is its collaborative nature that brings together the expertise from two different Hubs and supplements it with clinical expertise. The project also contributes to the Global Health strategy of the MRC. Finally, it encourages the use of novel methods through dissemination of the work via open source software.

2. Does this project align with the work of a HTMR Working Group; if so, which?

The core of this project is to develop adaptive methods and hence it is closely aligned with the adaptive designs working group. TJ is currently co-chairing this working group and JW is a member and the student would be expected to join the working group.

3. Describe how this project aligns with the host Hub strategy

The host Hub comprises of 3 distinct work-streams, one of which is on early phase designs. Given the context of evaluating treatments for the first time the project naturally falls into this stream and hence is in perfect alignment with the host Hubs strategy. Additionally, the BSU Hub has a work package on adaptive methods which this project also fits well with.

4. Detail of any Project specific training offered in the studentship

Lancaster University offers highly specialised courses on adaptive methods and early phase trial design to external participants. The student will be expected to take part in these short-courses to supplement and broaden their technical skills. In addition, the student will be offered to take part in the APTS which is a series of four week-long courses tailored for PhD students in Statistics that focuses on theoretical and computational statistical methods.

Finally, the student will get the opportunity to spend some time at the BSU and the University of Oxford.

5. Are there any prerequisite qualifications or experience for this studentship?

Candidates for an MRC-funded studentship must meet residence eligibility and hold qualifications in a relevant subject at the level of, or equivalent to, a good honours degree from a UK academic institution (see methodology website for more details- www.methodologyhubs.mrc.ac.uk).

For this project: A master's degree in Statistics, Mathematics or related subject.