CLINICAL INVESTIGATION

The challenges of conducting clinical trials for neglected tropical diseases

"Making an investment case for the R&D for vaccines of tool ready diseases have been challenging but researchers advocating for new products, including vaccines, are aware of these challenges and the low priority given to diseases that are amenable to the WHO preventive chemotherapy strategy."

Keywords: capacity building • clinical trials • London Declaration • low- and middle-income countries • neglected infectious diseases • neglected tropical diseases

Clinical research involving human subjects is driven mainly by the availability of novel products, devices or interventions that require further investigations to determine their safety and efficacy. The designs of clinical trials are critical to ensuring scientific validity and reproducibility of the results and it is essential that ethical approval is obtained by well-informed ethical committees in all participating countries. The WHO has developed a roadmap for 17 poverty related diseases, collectively called neglected tropical diseases (NTDs) [1]. However, the WHO focus NTDs do not include malaria, HIV/AIDs and tuberculosis which account for nearly two-thirds of all R&D funding associated with poverty related or neglected diseases. According to the 2014 G-FINDER survey report [2], in 2013, US$3.2 billion were invested in R&D for 132 poverty related diseases referred to as 'neglected diseases' [2]. The investment targeted 138 products that included drugs, vaccines, diagnostics, microbicides and vector control products. The big three diseases, HIV/AIDS, malaria and TB received 69% of the global neglected disease R&D funding and less than 10% was invested in the WHO focus NTDs. Of the US$2.1 billion contributed by the public sector, over US$2 billion were provided by high income countries (HIC) that influenced the diseases to focus on. This may partly explain the huge disparity between funding for the big three diseases and the 17 WHO focus NTDs. Nevertheless, in 2012 and 2014, 22 partners from the public and private sectors, including WHO, Bill & Melinda Gates Foundation, pharmaceutical companies and the US and UK governments committed through the London Declaration on NTDs 'to advance R&D through partnerships and provision of funding to find next-generation treatments and interventions for neglected diseases' [3].

Many of the WHO focus NTDs are considered tools ready, and targeted for eradication or elimination by 2020 [1]. These include Guinea worm disease, lymphatic filariasis, leprosy, human African trypanosomiasis and blinding trachoma. Other focus NTDs including schistosomiasis, soil-transmitted helminthiasis (STH), Chagas disease, visceral leishmaniasis and river blindness (onchocerciasis) are targeted for control as a public health problem by 2020. Alternative intervention strategies based on new drugs, vaccines and novel devices have been proposed as additional tools that could fast-track the fight against NTDs [4–7]. However, many challenges exist for the conduct of clinical trials that will determine the safety and efficacy of the proposed new products and interventions.

NTDs are diseases of neglected people living in low- and middle-income countries (LMIC) with little influence over the allocation of the substantial R&D funding required for the development of new products for

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treatment and diagnostics. It takes on average 7–10 years to develop a new drug at an estimated annual cost of US$15 million to US$30 million [8]. It can take up to 5 years and US$2 million to US$5 million per year before a new diagnostic product is fully developed and approved for use [8]. It is substantially more expensive to develop vaccines which require hundreds of millions of dollars of investment over 12–15 years [8].

Human and laboratory capabilities for conducting clinical trials in LMIC are limited and the involvement of vulnerable populations has its own ethical challenges. Obtaining informed consent for clinical trials in many of these resource limited settings can be particularly challenging because literacy rates are low and the value of clinical research is not clear to the affected population. The relevance of the end points of many clinical trials on NTDs are not always clear to policy makers in affected countries which causes challenges for translation of results into policy and ultimately hinders buy-in from the LMIC governments.

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Researchers from HICs have argued that the process of increasing clinical trial capacity should be led by the research sites, and trial designs should be tailored to the affected country's context [9]. A recent systematic review revealed that methodologies for the conduct and analysis of clinical trials on NTDs in resource-poor settings need to be standardized and the quality of research to be improved [10]. This is particularly true for the much neglected NTDs like cutaneous leishmaniasis, affecting people in the poorest settings. There is a clear need for simple approaches which can be implemented generally within the context of specific NTDs. A guideline for the designing, conducting, analyzing and reporting of clinical trials for the efficacy of leishmaniasis treatments was published in 2013 [10]. The paper included the definition of measurable, reproducible and clinically meaningful outcomes that can be used by clinical investigators working on other NTDs.

Many of the NTDs amenable to the WHO strategy of preventive chemotherapy are considered tools ready with regard to meeting the WHO NTD roadmap targets. Nevertheless, vaccines have been advocated for some NTDs including STH, Schistosomiasis, human African trypanosomiasis, Dengue, onchocerciasis and leishmaniasis. New genomic, proteomic, immunological and x-ray crystallographic data have resulted in the identification of promising candidate vaccine antigens for STH and schistosomiasis [5]. However, NTDs are chronic conditions with long term morbidity outcomes that make health impact difficult to measure. For example, measuring the impact of deworming on children's health can be challenging [5], and in the case of lymphatic filariasis, infected individuals develop symptoms very slowly from childhood [11].

Many NTDs are vector-borne diseases, but clinical trials are not normally designed to measure entomological outcomes and there is little information available for the conduct of clinical trials involving entomological tools and products. The release of transgenic mosquitoes to limit disease transmission is a novel vector control tool for dengue virus, and experimental studies have shown that the release of such mosquitoes in sufficient numbers can eliminate human-vector contact and impact clinical outcomes [12]. Another novel vector control strategy is the introduction of Wolbachia that can render the dengue vector partially resistant to infection with the virus [12]. A review of the designs and statistical considerations relevant to the conduct of clinical trials involving entomological tools and products was published in 2012 [12].

Conclusion

Many challenges exist for the conduct of clinical trials that will determine the safety and efficacy of the new products and interventions targeting NTDs. Having unified criteria for clinical trials for NTDs in resource poor settings will help strengthen evidence, optimize investments and enhance the capacity for high-quality clinical trials. Making an investment case for the R&D for vaccines of tool ready diseases have been challenging but researchers advocating for new products, including vaccines, are aware of these challenges and the low priority given to diseases that are amenable to the WHO preventive chemotherapy strategy. Some initiatives, like the Onchocerciasis Vaccine for Africa, are exploring other funding mechanisms through partnership with major foundations, public funding from HICs and private funding from major development banks committed to poverty reduction in sub-Saharan Africa. However in 2013, public funding from mainly HICs and the private sector fell by US$193 million.

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