Background In 2012, WHO published a roadmap, for ‘Accelerating Work to Overcome the Global Impact of Neglected Tropical Diseases (NTD)’, which set out control and elimination targets for five NTDs that were considered tools-ready. Lymphatic filariasis, onchocerciasis, schistosomiasis, trachoma and soil-transmitted helminthiasis are amenable to the preventive chemotherapy (PC) strategy and manageable through the implementation of available diagnostic products, and safe and effective medicines. The optimism for achieving the WHO 2020 targets for control and elimination for these PC NTDs was crystallised by the London Declaration of 2012 – a pledge by leaders of several major global health and development organizations, together with industry partners to unite efforts to achieve the targets by 2020. Clinical research involving human subjects is driven primarily by the need for novel products, devices or interventions. The question remains whether clinical trials have a role in the fight against NTDs that are tools-ready. Can an investment case be made for vaccines or new drugs for the five PC NTDs? Four of the five PC NTDs are vector-borne diseases, but clinical trials are not normally designed to measure vector outcomes and there is little information available for the conduct of clinical trials involving entomological tools and products. Moreover, human and laboratory capabilities for conducting clinical trials in the countries most affected by NTDs in sub-Saharan Africa are limited. Nonetheless, alternative intervention strategies based on new drugs, vaccines and novel devices have been proposed as additional tools that could fast-track the fight against the PC NTDs. The role of clinical trials in defining these new strategies will be discussed.