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and development pipeline. Using onchocerciasis as an example, we demonstrate the utility of clinical trial simulation with illustration from an individual-participant simulator of a novel (hypothetical) macrofilaricidal drug. We show how predicted participant outcomes based on desired pharmacodynamic properties inform the target product profile; the choice of where to conduct trials; how many patients should be recruited; which parasite stages should be sampled from the patients, and when these patients should be followed up to maximise statistical power for demonstrating superiority over existing treatment(s). We also consider how simulations can help to resolve the unique complications that arise when designing clinical trials that are to be conducted in a backdrop of MDA and ongoing transmission.

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THE ADDITION OF ALBENDAZOLE TO IVERMECTIN DOES NOT REDUCE FEMALE WORM FERTILITY IN ONCHOCERCIASIS

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A randomised open-label clinical trial was performed in an endemic area of Central Ghana to address the question whether ivermectin (IVM) combined with albendazole (ALB) at higher doses and given more than once per year might generate sustained reduction in microfilariae (Mf) by reducing female fertility or by killing adult worms in onchocerciasis. In total 272 Mf-positive participants, with at least one palpable onchocercoma were treated with either 1) IVM 200µg/kg annually (0, 12, 24 months; N = 68), 2) IVM 200µg/kg biannually (0, 6, 12, 18, 24 months; N = 68), 3) IVM 200µg/kg plus ALB 800mg annually (N = 70) or 4) IVM 200µg/kg plus ALB 800mg biannually (N = 66). 76 participants had not taken part in previous mass drug administration (MDA) of annual IVM, the other 198 had done so in at least one round (median 2 (1 – 10)). 36 months after treatment start, 218 patients (80%) got their onchocercomata surgically removed. Skin snips were taken at 0, 6, 18 and 36 months. Histological analysis showed normal embryogenesis in 15/135 (11% [7-18, 95% CI]) adult female worms in the IVM annual group, compared to 22/155 (14% [10-21]) in the IVM biannual, 35/154 (23% [17-30]) in the ALB+IVM annual and 20/125 (16% [11-23]) in the ALB+IVM biannual group (p = 0.1229, comparison over all 4 groups). With a range of 55 - 59% the proportion of dead worms did not differ between the 4 groups. The proportion of individuals that completely cleared Mf at 36 months (after 3 annual/5 biannual treatments) was 35/56 (63% [49-74]) in the IVM annual, 42/59 (71% [59-81]) in the IVM biannual, 39/64 (61% [49-72]) in the ALB+IVM annual and 43/53 (81% [69-89]) in the ALB+IVM biannual group. In the subgroup without prior IVM, there was a trend to more Mf-negative individuals in the ALB+IVM biannual group. In conclusion, addition of ALB to IVM did not improve the efficacy against female worm fertility or the macrofilaricidal effect. However, the increase from annual to biannual drug administration resulted in a sustained increase of Mf negative individuals (annual: 62% [53-70], biannual: 76% [67-83], p = 0.024). It will be interesting to compare these results to an ongoing trial with a similar design in Eastern Ghana.

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DETECTING ALBENDAZOLE METABOLITES IN SERUM AND URINE: A FIRST STEP IN DEVELOPING AN INDICATOR OF MDA COMPLIANCE IN HUMANS

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The neglected tropical diseases are a group of pathogens affecting individuals in the poorest regions of the world. Among them, Soil Transmitted Helminth infections directly impact nutritional status, educational development, individual productivity, and physical and mental development in human populations. Currently, these infections are controlled through mass drug administration (MDA) programs using albendazole (ABZ) or mebendazole. However, not all programs have demonstrated expected impact on prevalence or intensity of infections. These failures may be related to poor programmatic coverage, suboptimal adherence or the exposure of parasites to sub-therapeutic drug concentrations due to poor drug dissolution, insufficient gastrointestinal absorption and/or systemic availability of the active ingredient. Accordingly, improved knowledge of the basic pharmaco-kinetics of ABZ in treated people is critical. As part of the DeWorm3 project, we sought to characterize the serum disposition kinetics and pattern of urinary excretion of ABZ and its metabolites (ABZ sulphoxide (ABZSO) and ABZ sulphone (ABZSO2)) in human volunteers. In addition, we sought to determine the duration and optimal timepoint where ABZ/ metabolites can be measured in urine as an indirect assessment of an individual's adherence to treatment. Venus blood and urine samples were collected from eight (8) volunteers between 2 and 72 h (serum) and 4 and 72 h (urine) for HPLC analysis following administration of a single postprandial oral dose of ABZ (400 mg Glaxo SmithKline). The ABZSO was the main analyte recovered either in serum and urine samples. ABZSO serum concentrations reached its peak concentration (Cmax= 1.20 ± 0.44 µg/mL) at 4.75 h post-treatment. In urine ABZSO Cmax value was 3.24 ± 1.51 µg/mL, reached at 6.50 h post ABZ administration. The urinary AUC value, resulted higher (2.3 fold) compared to that measured in serum. The overall, PK-based information reported here demonstrates that the measurement of ABZSO concentrations both in serum and urine could be useful to confirm compliance to ABZ treatment and an objective measurement of program coverage.

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FURTHER EVIDENCE OF COLLATERAL IMPACT OF CDTI ON STH PREVALENCE AND INTENSITY: IMPLICATIONS IN DEWORMING STRATEGIC PLAN AND GLOBAL ELIMINATION

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Soil-transmitted helminthiases (STHs) are among the most prevalent afflictions of the developing world, responsible of physical and mental growth retardation and hindrance of economic development. Periodic deworming with Albendazole or Mebendazole of high-risk groups (school-age children, preschool children, and pregnant women) can significantly lower the levels of infections below the threshold associated with morbidity. Control efforts are mostly focused on school aged children. However, it was shown that age groups other than school-age children