Paradigms and Paradoxes: Enigmas in Clinical Trials in Ghanaian Children

The tenets of evidence-based medicine mandates that medicines should be tested and shown to be safe and effective before licensing for use in the general population. Clinical trials remain the recognized methods for evaluating safety and efficacy of medicines. Conducted in three overlapping phases, a clinical trial may be defined as "a research study in which one or more participants are prospectively assigned to one or more interventions to evaluate their effects on health related biomedical or behavioural outcomes."

While medicines licensed for use in adults would be expected to have undergone evaluation through all three phases (except in specific situations), this may not be so for children. There is evidence to show that many medicines used for treatment in children are prescribed outside the terms of their product license in terms of dosing, indication, route of administration etc. This phenomenon, termed "off-label drug use," is a legal and acceptable practice, especially in situations when alternative treatments do not exist. It is also a means to respond to a specific patient's medical needs. The practice of off-label drug use, however, bypasses the safeguards of modern drug regulatory norms and has been linked to an increased risk of adverse effects of medicines. Off-label drug use also occurs in adults; however, it is typically based on new evidence that demonstrates the safety and efficacy of medicines for new indications. In children on the other hand, off-label drug use is often based on extrapolation in the absence of firm evidence. Thus, medicines that have been tested in and found to be safe and effective in adults but not tested prior to use in children would not be supported by the same level of high-quality evidence. This has the potential to perpetuate an anecdotal belief system and risk a false sense of assurance that does not encourage further rigorous testing, thus depriving children of high-quality evidence on medicines.

The relative absence of information on medicines in children was an unintended outcome of regulation intended to enhance drug safety. Outrage from the infamous disasters resulting from unintended but improper medication use in children resulted in landmark legislation such as the *Pure Food and Drug Act, 1906* (enacted to prevent adulterated and misbranded drugs from entering the market) the *Food, Drug and Cosmetic Act 1938* (enacted to ensure (for the first time) that medicines demonstrate safety and purity before marketing); and *Kefauver-Harris Amendments* 1962 (to ensure medicines demonstrate efficacy in addition to safety). Drug manufacturers resorted to including warnings in labelling to the effect that these medicines "were not recommended for children due to inadequate (or non-existent) data, and strategic

decisions to exclude children from clinical trials of new medicines following passage of these laws. Advocacy to the effect that lack of information on medicines in children was encouraging off-label practice and that treating children with untested medicines should be likened to uncontrolled experimentation and thus, potentially unethical, may have contributed to the establishment by the (US) National Institutes of Health (NIH), of the Paediatric Pharmacology Unit (PPRU) network (in 1994). The mandate of the PPRU was to stimulate collaborative research between academia, industry and healthcare providers to improve paediatric labelling of new and existing medicines. Subsequent legislation introduced from 1997 with a focus on initiatives and incentives like assurances of patent exclusivity for paediatric studies and labelling change mandates opened up the space for paediatric medicines research subsequently.

It was during the years when research on paediatric medicines were being encouraged that I began participating in and subsequently led and supervised several clinical trials with the overall focus to improve drug therapy in Ghanaian children. These trials investigated issues contemporary to the times, including studies in sub-populations with high morbidity and mortality, childhood populations recognized for lack of data on most medicines (such as newborns), or evaluation of the then novel drug combinations. Specific examples include trials to evaluate efficacy of quinine preparations in children cerebral malaria; artemisinin combination therapies in children with uncomplicated malaria, HIV infection or sickle cell disease; amikacin (an antibiotic) and aminophylline (a drug used to improve breathing in newborns) combination in newborns with sepsis; and cetirizine (antihistamine) and gabapentin (an anticonvulsant) combination for treating pruritus (itching) - a common disturbing symptom that compounds the affliction of patients recovering from burns.

Aside efficacy, our studies sought to generate evidence on relevant safety parameters, with a special focus on investigating “what the body does to medicines” in terms of their movement in and out of the body (i.e., absorption, distribution, metabolism and excretion) - otherwise known as pharmacokinetics (PK), and overall mechanistic effects of the respective medicines on the body - otherwise known as pharmacodynamics (PD). To overcome the clinical, logistical and ethical limitations of repeated multiple blood sampling required for conventional PK studies, which historically discouraged children from participating in PK/PD studies, we applied the novel (population) modelling approach that requires only 1-2 blood samples per patient to enable us to characterize the PK/PD profile of studied medications.

Beyond biomedical outcomes and in the spirit of multi- and inter-disciplinarity, our studies incorporated strong socio-cultural components to gain insights into relevant contextual factors. In collaboration with sociologists and bioethicists, we interrogated issues like the adequacy and appropriateness of informed consent procedures, parents' perspectives of their child's recovery from study medications and their views on the appropriateness of use of blood samples for further research.

Children are not small adults, and childhood is composed of a heterogeneous population. Children exhibit distinct developmental, maturational and physiological characteristics that differ from adults. Even the practice of scaling adult drug doses for children using body weight or surface area may be inappropriate because these are based on allometric scaling but human growth is not a linear process. There are also discordant age-associated differences in body composition and organ function at certain stages of growth that should be integrated into other considerations.

There are still critical gaps in knowledge on the role of maturational and ontogenic changes in drug disposition in children and there is still a lack of full understanding of the effect of these changes on drug metabolism. There is the need therefore, for comprehensive research on many old as well as new medicines used for treatment in children. This would require an intentional, comprehensive child centred paradigm.

In this inaugural lecture, I will present a synthesis of the findings from the various studies and discuss their relevance and implications for clinical practice and policy where applicable. I will also highlight unexpected findings that were deemed inconsistent with our hypotheses or conventional assumptions and share insights from the encountered operational challenges. I will also seek to interrogate these findings in the light of drug regulation in Ghana and share my perspectives on capacity needed to be developed strengthen the medicines research architecture to improve drug therapy for children in Ghana.