

CAF/26/117 - Testosterone replacement therapy in boys and men with Klinefelter syndrome

Klinefelter syndrome (KS) is a very common genetic condition caused by an extra sex chromosome, affecting 1 in 600 males. It can lead to a range of physical, developmental and hormonal changes. These may include tall stature, small testicles, breast tissue development, learning difficulties, behavioural challenges in childhood, infertility in adulthood, and low levels (deficiency) of testosterone, the male sex hormone. Testosterone deficiency can impact mood, bone strength, and heart health. Despite these known effects, current clinical guidelines for testosterone replacement therapy in KS are not based on strong evidence.

This research project aims to add to the evidence by exploring how testosterone therapy affects health in children and adults with KS. It will also investigate the best timing to start treatment, helping healthcare teams and families make informed, personalised decisions.

The project is structured into three work packages:

- Work Package 1 will analyse existing data from SDMregistries, a global database of people with KS. This study will examine how testosterone therapy has been used throughout the world — including the age treatment was started, the type of testosterone formulation used, how often patients were monitored, and what tests were performed to check it was working for the patient. By comparing practice around the world, this work will identify patterns that may inform future guidelines.
- Work Package 2 will invite boys with KS between the ages of 12-18 years to come for some tests to look at their heart health, learning, mood and quality of life according to whether or not they are on testosterone therapy. We will also compare the 2 different types of testosterone therapy. We will do this project in the West of Scotland and with colleagues in other centres around the world using networks within the SDMregistries. We will follow boys up for 18 months and this will tell us about the short-term effects of testosterone.
- Work Package 3 will focus on long-term outcomes using anonymised data from Public Health Scotland, which is collected routinely by the government. These data include hospital and outpatient records, information about prescriptions, death records and school attainment. By finding men with KS and comparing those who received testosterone therapy with those who did not, we can look at differences in health outcomes (such as hospital admissions and causes of death) and life outcomes such as education. This will help determine whether testosterone therapy has long-term benefits beyond physical health.

Together, these three work packages will provide a detailed picture of testosterone therapy in KS across the lifespan, from early adolescence to adulthood. The findings will support the development of evidence-based guidelines and help people with KS

and their healthcare teams tailor treatment decisions. Ultimately, this research aims to improve quality of life and long-term outcomes for individuals with KS by ensuring care is timely, effective, and personalised.