NICE National Institute for Health and Care Excellence

Expert testimony to inform NICE guideline development

Section A: Developer to complete	
Name:	Dr Michael Ni'Man
Role:	Practitioner and academic
Institution/Organisation (where applicable): **Contact information:**	Trans Gap Project Michael.niman1@nhs.net
Guideline title:	Type 2 diabetes in adults: management (medicines update)
Guideline Committee:	Advisory committee
Subject of expert testimony:	Transgender inclusion in guideline
Evidence gaps or uncertainties:	How to score transgender people with diabetes for cardiovascular risk (using QRISK) and potential changes to kidney function in transgender people with diabetes. Both may affect diabetes medications offered.

Section B: Expert to complete	
Summary testimony:	[Please use the space below to summarise your testimony in 250–1000 words. Continue over page if necessary]

There are estimated 14,000-19,000 transgender people in the UK aged 16 and over with diabetes (based on a diabetes proportion of the 2021 UK census transgender population (Office for National Statistics (ONS), 2023)) who may not be receiving specific diabetes care that will improve their quality of life and lower their cardiovascular risk. There is little available guidance on how diabetes control and risk is affected by hormone replacement in the transgender population. At TransGapProject, a research group across the UK, we sought to investigate this through a series of reviews, to better serve the autonomy of transgender people with diabetes (TPD). This will also result in improved safeguarding for clinicians in their practice in the UK.

Our findings

Diabetes review

The key takeaway for both transgender men and women with diabetes is that the evidence base appears to suggest there is not a clinically significant impact on their glycaemic control as a result of taking gender affirming hormone therapy (GAHT). However, whilst effect on HOMA-IR (Homeostatic Model Assessment for Insulin Resistance), insulin sensitivity and fasting glucose were on the whole inconclusive. There did appear to be significant changes to body fat and lean body mass within these studies. For transgender women, GAHT was found to have statistically significant increases in body fat. Nokoff *et al.*, 2020 finding that transgender women had a higher percentage body fat than cisgender males (28% ± 6% vs 20% ± 10%; P = 0.001), and had a body fat composition more comparable to cisgender women (31% ± 7% vs 35% ± 8%; P = 0.033). For transgender men on GAHT, their body weight increased but this was secondary to increases in lean mass (whereas transgender women typically saw reductions in the level of lean mass). Nokoff *et al.*, 2020 found transgender male lean mass increasing to be higher than cisgender women (29% ± 7% vs 33% ± 7%; P = 0.002) and in line with cisgender men (69% ± 7% vs 73% ± 8%; P = 0.029).

Kidney function review

GAHT appears to cause measurable changes in kidney function (towards affirmed gender baseline) from as early as 3 months. This change is then sustained through 24 months post-GAHT initiation, whereby kidney function either stabilises or continues to trend further towards affirmed gender reference ranges (changes do not revert back to pre-GAHT baseline). However, these changes are only significant in transgender men (likely due to the changes in lean mass and creatinine).

QRISK review

Our research did not appear to find a significant increase in cardiovascular risk in transgender men on GAHT; this is in line with male hypogonadism individuals receiving testosterone in the TRAVERSE trial being found to have no significant increase in major cardiovascular risk (Lincoff *et al.*, 2023). However, what is unique with transgender men with type 2 diabetes (T2D) compared to male hypogonadism individuals [and the general population], is that how women with T2D are well established to have a higher cardiovascular risk compared to men with T2D (Garcia *et al.*, 2016). QRISK is a cardiovascular risk score may underestimate this risk in TPD. Depending on the time in which the transgender man began taking GAHT, they may have had many years building up the pathological risk that would place them at greater risk of a cardiovascular account. For this reason, this population needs individualised risk profiling that does not omit this increase in cardiovascular risk.

Whilst for transgender women, there is a more outright connection with taking feminising GAHT and an increase in cardiovascular and stroke risk. Particularly with significantly increasing risk of VTE over time; the VTE risk is higher in oral GAHT compared to transdermal GAHT (Seal, 2019).

Moreover, in general, transgender individuals may be at a baseline increased cardiovascular risk as a result of the minority stress model. As well as transgender

individuals typically experiencing higher rates of: smoking, alcohol consumption, lower participation in physical activity and higher BMI and higher rates of disordered eating - all of which worsen cardiovascular risk (Streed *et al.*, 2017).

Our advice

Our advice for NICE can only appropriately comment on the medically transitioning population that is receiving hormone therapy through their gender identity clinic i.e. not self-sourcing hormones, not surgically or socially [only] transitioning individuals.

For paragraphs: 1.7.5, 1.7.15, 1.7.16 - our advice to the committee would be for clinicians with transgender patients with T2D to calculate QRISK score (when considering assessing cardiovascular risk) using both genders and take the highest score to determine treatment. In other words, clinicians could use affirmed gender when it would NOT lower the risk output. This typically means using a male-based score for all patients. Clinicians would benefit from a conversation with their patients on why they are using a male-based equation if they identify as female and the risks involved in not doing so.

An example of said recommendation: “Transgender individuals may develop a high risk of cardiovascular disease as a result of gender-affirming hormone therapy. For these individuals, consider calculating QRISK as both male and female and use the higher score of the two to assess whether to consider SGLT2 inhibitor”.

For paragraph: 1.7.3 - our advice would be for an acknowledgement to seek specialist advice on how to accurately assess eGFR kidney function in transgender adults. As use of hormone therapy may affect eGFR eligibility for metformin.

If you were to have a 52 year old transgender man with T2D, being scored for consideration of a -flozin. They may be scored based on their assigned gender at birth (female) which would score them a 6% risk, or scored with their affirmed gender (male), which would see their score almost double to a 10% risk - which may then prompt a prescription of a -flozin. Conversely, a 52 years old transgender women with T2D would score 10% with their assigned gender at birth (male) and 6% with their affirmed gender (female), so may not be considered for a -flozin - despite per our research now holding a higher cardiovascular risk. Our advice covers both the transgender women who have an unaccounted higher cardiovascular risk as a result of their GAHT, and the transgender men who prior to transitioning will have had a higher baseline cardiovascular risk. TPD are not currently being offered the opportunity in the UK to make an informed decision on their diabetes care. This is well reflected in our PPI sessions whereby one of the participants commented: “It's difficult to find information on diabetes that's relevant when you're going to go into the clinic and have a conversation.”.

Due to anticipated discrimination, the established principle that transgender individuals do not seek healthcare opportunities as frequently as the general population due to the prejudice they anticipate they will (and typically do) face (Kcomt *et al.*, 2020). We as healthcare professionals should seek to maximise every opportunity with this population when they do attend clinics – and not further delay management of chronic diseases with needless/overzealous referrals. It is not uncommon for transgender individuals to wait many years to just see a doctor about being considered for GAHT.

The potential for ambiguity for clinicians is well exemplified in paragraph 1.7.15, whereby transitioning after age of 40 on GAHT may be interpreted as a change in personal circumstances. Which consequently would change their QRISK score (depending on what gender used) and therefore treatment. But there is no guidance for transgender individuals. Whilst, this case may be rare, it bears acknowledgement. In doing so, within the guidelines for all paragraphs mentioned above, it will hopefully lead to: a reduction in confusion and lack of clarity for clinicians on these decisions; better safeguarding for clinicians i.e. the medicolegal implications if a -flozin was not prescribed based on cardiovascular scoring and the individual went on to suffer from a cardiovascular event;

and improve the patient autonomy of transgender individuals, leading to more informed healthcare decisions.

This will have the positive effect on the main outcomes of this update being an improvement in health-related quality of life and reduction in cardiovascular events. As provided a guideline that acknowledges the calculation changes in the transgender cohort leads to an increased uptake of -flozins. These medications being used in a population that may have missed out on these medications will hopefully lead to improved outcomes in cardiovascular mortality, major cardiovascular events and renal events.

I recognise there may be trepidation for including transgender specific guidance in this update. Let me address some of these:

Does not affect glycaemic control

- Whilst there may not be a direct effect on glycaemic control as a result of GAHT, there are clear changes in diabetes management as described through changes in kidney function and cardiovascular risk that need to be accounted for in TPD.

Too specialised

- Lowering the specialisation need for this cohort is key to health equity.
- Removing the need to involve specialist input in every decision.
- As our diabetes review appears to show, they should be treated the same as any other person with diabetes.

Population isn't big

- The TPD is estimated to be 14,000-19,000, a cohort larger than the cystic fibrosis population in the UK. There is some dispute over the accuracy of the 262,000 transgender population put forward by the UK census. However, if you were to remove all English second-language speakers there would still be a population of 200,000. Furthermore, some LGBT+ charities have said the original figure was an underestimate ('Response to census data on the size of the UK trans population – TransActual', 2023).

Not peer reviewed

- Our research was a scoping review, drawing from evidence that is peer-reviewed and pre-exists - building on established knowledge for the effects of hormone replacement in other population groups. We are also in the process of seeking publication for our work.

Concern about 'wokeness' 'sideism' 'politicisation'

- This would not be the first NICE guideline to acknowledge transgender individuals. This has been done in the recent Hybrid Closed-Loop guidelines (in regard to pregnancy). Having spoken to an individual involved in this guideline, they described how from their drafts and conversations the direct mention of transgender individuals ("women, trans men and non-binary people who are pregnant" vs people who are pregnant with diabetes) was preferred for reasons of visibility and that the ambiguity of a direct mention would lead to further confusion and therefore may worsen treatment for this population.

References to other work or publications to support your testimony' (if applicable):

Garcia, M. *et al.* (2016) 'Cardiovascular Disease in Women: Clinical Perspectives', *Circulation research*, 118(8), p. 1273. Available at: https://doi.org/10.1161/CIRCRESAHA.116.307547.

Kcomt, L. *et al.* (2020) 'Healthcare avoidance due to anticipated discrimination among transgender people: A call to create trans-affirmative environments', *SSM - Population Health*, 11, p. 100608. Available at: https://doi.org/10.1016/j.ssmph.2020.100608.

Lincoff, A.M. *et al.* (2023) 'Cardiovascular Safety of Testosterone-Replacement Therapy', *New England Journal of Medicine*, 389(2), pp. 107–117. Available at: https://doi.org/10.1056/NEJMoa2215025.

Nokoff, N.J. *et al.* (2020) 'Body Composition and Markers of Cardiometabolic Health in Transgender Youth Compared With Cisgender Youth', *The Journal of Clinical Endocrinology and Metabolism*, 105(3), pp. e704-714. Available at: https://doi.org/10.1210/clinem/dgz029.

Office for National Statistics (ONS) (2023) *Gender identity, England and Wales - Office for National Statistics*, *ONS website*. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/culturalidentity/genderidentity/bulletins/genderidentityenglandandwales/census2021 (Accessed: 28 December 2023).

'Response to census data on the size of the UK trans population – TransActual' (2023), 5 January. Available at: https://transactual.org.uk/blog/2023/01/05/response-to-census-data-on-the-size-of-the-uk-trans-population/ (Accessed: 21 October 2024).

Seal, L.J. (2019) 'Cardiovascular disease in transgendered people: A review of the literature and discussion of risk', *JRSM cardiovascular disease*, 8, p. 2048004019880745. Available at: https://doi.org/10.1177/2048004019880745.

Streed, C.G. *et al.* (2017) 'Cardiovascular Disease Among Transgender Adults Receiving Hormone Therapy: A Narrative Review', *Annals of Internal Medicine*, 167(4), pp. 256–267. Available at: https://doi.org/10.7326/M17-0577.

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