Imperial College London

Imperial Bladder 1 (**IB1**) - Fluorescence **CO**nfocal **M**icroscopy for ra**P**id evaluation of detrusor muscle at primary transurethra**L** rs**E**ct**T**ion of bladd**E**r tumours

Statistical Analysis Plan (SAP)

Version 1.0

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Name & Role	Date
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1.0 Statistical Methods

IB1 is an external pilot trial testing the feasibility of obtaining sufficient digital FCM images for the identification of detrusor muscle from transurethral resection of bladder tumor (TURBT) samples. Progression criteria are mapped from feasibility objective(s) using the traffic light approach (Eldridge et al. 2016, Mellor et al. 2023) and are prespecified in the Statistical Analysis Plan (SAP).

Additionally, the study aims to explore the diagnostic accuracy of FCM in determining presence of detrusor muscle (dichotomy) against the reference standard histopathological evaluation, with blinded evaluation and a paired design. The Area Under the Receiver Operating Characteristics curve (AUROC) will be estimated using DeLong's (nonparametric) method, alongside its 95% confidence intervals. Measures of sensitivity, specificity, and predictive values are to be estimated at different ROC coordinates. An exploratory test of the alternative hypothesis H1: AUC > 0.5, will be done using a Z test.

A supplementary estimand targeting the estimation of agreement between FCM and histopathology will use the kappa statistic to account for chance agreement and will be interpreted following J. Cohen's original recommendations.

The analysis set for diagnostic accuracy includes cases with an available result for both FCM and histology. No missing data imputation will be made.

2.0 Sample size

A total sample size of 35 tissues is expected to be collected and analyzed during a 6-months recruitment period. Given the pilot nature of the study, this was not calculated to power any specific hypothesis, but only to provide feasibility data to be able to conduct a more definitive trial.

Thirty-five patients would allow us to encounter substandard processes with a high probability (97.5%) when there is a 10% chance of any occurring in a given sample. (Viechtbauer et al. 2015) It will also provide us with a range of plausible AUC values and nuisance parameters (such as the prevalence of muscle invasiveness in this population) to be able to carefully plan a larger study.

3.0 References

Eldridge, S. M., Chan, C. L., Campbell, M. J., Bond, C. M., Hopewell, S., Thabane, L., Lancaster, G. A., & PAFS consensus group (2016). CONSORT 2010 statement: extension to randomised pilot and feasibility trials. *BMJ (Clinical research ed.)*, *355*, i5239. https://doi.org/10.1136/bmj.i5239

Mellor, K., Albury, C., Dutton, S.J. *et al.* Recommendations for progression criteria during external randomised pilot trial design, conduct, analysis and reporting. *Pilot Feasibility Stud* **9**, 59 (2023). https://doi.org/10.1186/s40814-023-01291-5

Viechtbauer, W., Smits, L., Kotz, D., Budé, L., Spigt, M., Serroyen, J., & Crutzen, R. (2015). A simple formula for the calculation of sample size in pilot studies. *Journal of clinical epidemiology*, *68*(11), 1375–1379. https://doi.org/10.1016/j.jclinepi.2015.04.014