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Differences between PARTICIPANTS AND NON PARTICIPANTS in a randomised controlled trial – LESSONS LEARNT FROM the ENGAGE study of referral for an exercise program in survivors of prostate cancer

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Dear Editor,

Randomised controlled trials (RCTs) provide the highest quality evidence for clinical practice. The broader applicability of RCT findings assumes that the study participants are representative of the population. However, systematic differences between study participants and non-participants may occur – in part due to stringent inclusion criteria. Recruitment into RCTs can also sometimes be difficult with many clinical trials reporting low recruitment rates for a variety of reasons.[1] The aim of this study was to compare the characteristics of eligible men with prostate cancer who did or did not consent to enroll in the ENGAGE study, a cluster randomized RCT to determine the impact of a clinician referred exercise program.[2]

The ENGAGE trial methodology and results have been reported in detail elsewhere.[2] In brief, patients who had undergone curative treatment for prostate cancer within the preceding 3-12 months at one of three major public hospitals and four private clinics located across metropolitan Melbourne, were recruited through outpatients' clinics between October 2011 and June 2013. Patients who were non-English speaking or who had a known musculoskeletal, cardiovascular, or neurological disorder were excluded. Consenting patients

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were referred to a defined exercise program or standard care with subsequent assessment of exercise participation, quality of life, depression and anxiety. The study received ethics approval from relevant Human Research Ethics Committees.

For this analysis, deidentified data were collected from the screening logs on all patients who were eligible for the ENGAGE trial, including patient demographics, (sex, date of birth, and postcode of residence), treatment characteristics, (public vs private health service and modality of treatment) as well as disease characteristics (clinical stage, biopsy grade and pre-treatment serum levels of the tumour marker prostate specific antigen / PSA). As a surrogate measure of the socio-economic status of patients, the socio-economic index for areas (SEIFA) was used with higher scores representing higher socio-economic status.[3]

One hundred and forty-seven (45.9%) of 320 eligible patients agreed to participate in the trial – patient characteristics are summarized in Table 1. Participants had a median age of 66 years (interquartile range [IQR] 61-73), slightly younger than non-participants, with median age 68 years (IQR 63-73), although the difference was not statistically significant ($p=0.098$). Trial participants also had a higher SEIFA score with a median of 1050 (IQR 1016-1076) compared to 1024 (IQR 982-1062) for non-participants ($p<0.001$).

Compared to participants, non-participants in the trial were more likely to have been treated at a public health service (73.5% vs 84.4%, $p<0.03$), to have undergone radiotherapy (49.0% vs 60.7%, $p<0.05$) or to be treated with androgen deprivation therapy (28.0% vs 52.4% $p<0.003$). There were no significant differences in PSA level at diagnosis, clinical stage or biopsy Gleason score between patients who enrolled and those who did not.

In this study, we found important demographic differences between participants and non-participants in this trial, which may have implications for the generalizability of study findings as well as trial design. We found that less than

half of the eligible patients participated in the trial, although this is a higher rate participation compared to similar trials that report recruitment rates around 20 to 30%.[4] Patient factors known to impact recruitment into RCTs, include competing demands, anxiety around randomization and lack of understanding of complex information. Clinician factors impacting recruitment include lack of resources, concerns over loss of autonomy and lack of interest in the study question.[5]

We found that participants in our trial were on average in a more socially advantaged position, as evidenced by higher area level SES (SEIFA) and more frequent treatment in private clinics, than non-participants, although with significant overlap in distribution. This is, however, consistent with other studies, which demonstrated under-representation in RCTs by patients from lower socio-economic status.[1] This may also reflect the nature of this trial, an exercise program. Evidence supports that, in population studies, adults living in areas with the highest levels of disadvantage were less likely than those living in areas of least disadvantage to meet the recommended physical activity guidelines (27% compared with 38%). Other factors that may also impact on participation, such as ethnicity or co-morbidities, unfortunately could not be assessed in this study.

Given the significant differences in demographic and treatment characteristics, we also expected to see some differences in terms of cancer characteristics, but none were seen. The pre-treatment PSA level was slightly lower among participants, but this difference was not statistically significant. Stage and grade distributions were similar regardless of trial participation.

The findings from this study contribute to the body of evidence that patients included in RCTs may not be entirely representative of the general population.[6] Given the voluntary nature of trial participation, some of this is inevitable, and a reflection of the patient's interest and ability to commit to the trial, and altruism. It is important to optimize trial design to overcome some of the known barriers to

trial participation as outlined above.[5] Clinical practice is guided by findings from RCTs, but our findings shows that care needs to be taken in this extrapolation - thorough and transparent reporting of recruitment details for RCTs can facilitate this process.

Conflicts of Interest:

Dr. Koonj Beharry reports grants from Australian Research Council and Prostate Cancer Foundation of Australia, during the conduct of this study. There are no other conflicts.

References:

TABLE 1: Characteristics of participants and non-participants

Characteristics	Participants 147/320	Non-participants 173/320	P-Value
Age (yrs) – med (<u>inter- quartile range</u>)	66 (61 – 73)	68 (63 – 73)	0.098
Socio-economic index for area – med (<u>inter- quartile range</u>)	1050 (1016 – 1076)	1024 (982 – 1062)	<0.001
Private Sector treatment, n (%)	39 (26.5)	27 (15.6)	<0.02
ADT, n (%)	25 (17.0)	47 (27.2)	<0.05
Surgery, n (%)	75 (51.0)	68 (39.3)	<0.05
PSA (ng/mL) – med (<u>inter- quartile range</u>)	7 (4.8 – 9.6)	7.3 (5.2 – 11.6)	0.07