Enrolling men in clinical trials: An analysis of recruitment strategies and processes in the T4DM diabetes prevention trial

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Statement of originality

This is to certify that to the best of my knowledge, the content of this thesis is my own work. This thesis has not been submitted for any degree or other purposes.

I certify that the intellectual content of this thesis is the product of my own work and that all the assistance received in preparing this thesis and sources have been acknowledged.

Karen Bracken

25 June 2019
Abstract

Participant recruitment is a crucial component of clinical trial conduct yet an estimated 50% of trials fail to recruit to target. Trialists seeking strategies to boost participant recruitment are faced with a lack of good-quality evidence to guide their decision-making. In this context, recruitment activities are often conducted in a trial-and-error manner, resulting in wasted time and resources, and risking trial failure. Men have a lower life expectancy than women, and are also at increased risk of a number of chronic diseases including diabetes. Nevertheless, men have been underrepresented in diabetes prevention trials, and the published literature on how best to engage men in trials is limited.

The aim of this research was to identify and evaluate strategies to recruit men into clinical trials. The research was set with the Testosterone for the prevention of Type 2 Diabetes (T4DM) study, a large, multi-centre, phase III, double-blind, placebo-controlled two-year trial of testosterone therapy combined with a lifestyle intervention (Weight Watchers®) compared to the lifestyle intervention alone for the prevention of Type 2 diabetes. Between January 2013 and February 2017, 19,022 participants were screened and 1007 randomised to the T4DM study. The final study visit was conducted in May 2019.

A systematic review of strategies to recruit men aged 50 years and over to clinical trials was conducted. In the included studies, the most effective strategies for identifying prospective participants were referral from an affiliated health service, media coverage and mass mailing. Identification of participants through community outreach activities such as displaying posters and attending local community events was not effective. Site staff training that focused on trial-specific recruitment challenges was also effective in increasing recruitment. Of the 16 included studies, only one was assessed to be of good quality. The most common sources of bias in fair and poor quality studies were inadequate description of recruitment interventions, and failure to report cost data.

Next, a program of three recruitment evaluations was conducted within the T4DM study. First, a range of promotional strategies to identify prospective T4DM participants was developed and evaluated. Repeated, high frequency bursts of radio advertising, infrequent but high reach television
news coverage, and direct mass mail outs by a government health agency were the most effective recruitment strategies. Promotions through community groups and businesses, online advertising, referral by general practitioner, coverage on newspaper and radio news bulletins, and newspaper advertising were also implemented but were evaluated to be less effective. Promotional activities cost an average of AUD$594 per randomised participant (ranging from no direct cost for television, radio and newspaper news coverage to AUD$1941 per randomised participant for newspaper advertising).

Second, a centralised, semi-automated approach to screening and enrolling T4DM participants was implemented and evaluated. The sequential screening process comprised: (i) web-based pre-screening, (ii) laboratory eligibility screening at a network of third-party pathology centres, (iii) final on-site clinical screening. This approach delivered high-volume screening at low cost and required few staff. Efficiencies were achieved by pre-screening the majority of subjects (95%) online, automating email communications with prospective participants, outsourcing blood collection for laboratory screening to a third party pathology centre, and automating eligibility ascertainment up to the point of final clinical screening. Screening and enrolment cost on average AUD$1411 per randomised participant, including direct and indirect costs. This represented a considerable cost saving compared to previous studies in similar disease settings.

Third, a ‘study within a trial’ (SWAT) was implemented to address an identified roadblock in trial recruitment. Phone call and Short Message Service (SMS) reminders were designed to increase screening uptake in participants who did not attend a further screening assessment after completing pre-screening. In a randomised comparison (N=709), there was no significant difference in screening uptake between those who received an SMS reminder and those who received a telephone call reminder (18% (62/354) and 23% (80/355) respectively) (RR=1.29, 95% CI 0.96–1.73, p=0.09). Both SMS (95% CI 14%–22%) and telephone call reminders (95% CI 18%–27%) increased screening uptake compared to neither reminder (12%). SMS reminders cost substantially less than telephone call reminders (AUD$0.53 versus AUD$6.21 per reminder), making them an adequate alternative to telephone call reminders to boost screening uptake.
In total, this research provides a detailed and costed approach for recruiting men to diabetes prevention trials. The estimates of cost and effectiveness reported in this research will be of use to trialists seeking to recruit similar participant populations. More broadly, the methods for implementing and evaluating recruitment strategies presented in this thesis will be generalizable to many trial settings.
Authorship attribution statement

I carried out the work presented in this thesis as a full-time PhD student at the NHMRC Clinical Trials Centre, The University of Sydney under the primary supervision of Professor Tony Keech, and co-supervision of Professor Gary Wittert, Professor Lisa Askie and Dr Nicholas Fuller.

This thesis is presented as a thesis including publications, comprising a traditional introduction chapter (Chapter 1), three chapters published as journal articles in peer-reviewed journals (Chapters 2, 3 and 5), one chapter presented as a manuscript accepted for publication and currently in press (Chapter 4), and a traditional conclusion chapter (Chapter 6). Details of included publications are provided in the following section, List of included publications.

Authorship of the included journal articles and manuscript reflects the collaborative nature of research conducted in the context of a large, multi-centre clinical trial. Notwithstanding the large number of co-authors, I was primarily and principally responsible for the conception, design, conduct, analysis and reporting of the recruitment research presented in the included papers. I wrote, and am first author on, all papers included within the body of this thesis. One additional paper on which I am a co-author is presented in Appendix A. Each paper is preceded by a preamble detailing my contribution to that particular piece of research.

Supervisor statement

As supervisor for the candidature upon which this thesis is based, I can confirm that the authorship attribution statements above are correct.

Professor Tony Keech

25 June 2019
**List of included publications**

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This recruitment research would not have been possible without funding and support from the NHMRC Clinical Trials Centre (‘CTC’), University of Sydney, and from the funders of the main T4DM study: an NHMRC project grant, Bayer, Lilly and University of Adelaide. In addition to being a PhD candidate at the CTC, I have also worked at the centre for almost 15 years as a clinical trial data coordinator, trial coordinator and, most recently, as a project manager. In that time, I have been privileged to work with many experts in clinical trial conduct and design. I hope that this doctoral work does justice to the excellent guidance I have received from my CTC colleagues over the years.

I am extremely grateful to my team of supervisors: Professors Tony Keech, Gary Wittert, Lisa Askie, and Dr Nick Fuller. Each has generously and patiently shared their expertise with me and I have felt guided and encouraged throughout the entire process. I would like to especially thank my primary supervisor, Tony, for his ongoing support of this research project.

I would also like to acknowledge my mentor, Dr Wendy Hague. Wendy was my manager for many years and I am proud to say, is now also my friend. Her unwavering belief in my capacity to complete this work, her kindness, her candidness, and her depth of knowledge in the field of trial conduct, have provided me with the solid foundation needed to push through the challenges of completing a doctoral program.

This work would also not have been possible without the support of the T4DM study investigators. It has been a unique experience to be part of such a cohesive and collaborative trials team, thanks to the leadership of our study chair, Professor Gary Wittert. I have been fortunate to receive input and wise counsel in my research from this expert team, and I look forward to collaborating with this outstanding group of academics on future projects.

Of course, an excellent trials team would be nothing without our T4DM study participants. These men have generously provided their time to the study in the hope of advancing men’s health. Under normal circumstances trial managers do not speak directly to trial participants. However, the centralised nature of the T4DM screening process has given me the privilege to speak directly to perhaps
hundreds of participants and prospective participants. They have openly, and often very amusingly, shared their perspectives on the trial. I have learnt so much from them and I will take their invaluable insights with me into my future clinical trial endeavours.

There have been many other people who have contributed to this work. I thank Caitlin for being my wonderful T4DM sidekick and for deflecting the flow of T4DM emails and phone calls long enough for me to finish writing this thesis; Sandra for her superior staffing of the T4DM information line, her affinity with our participants and her wonderful common sense in all things work and life related; Seshu, Colin, Anh Tai, Salma, Thuyen and Mark for working so hard to build and maintain the T4DM data systems that made this research possible; Kristy, Simone and Adrienne for their statistical expertise, and for not laughing at my early, inelegant attempts at SAS coding; Sherilyn for patiently ushering this novice author through the publishing process; Susan for being admirably unflappable and always squeezing in time for me to meet with Tony; and last but not least, Glenda, Jenny, Jody, Fiona, Lee and Chyn, the incomparable T4DM study nurses. I will miss working with each of you.

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List of frequently used abbreviations

CINAHL  Cumulative Index to Nursing and Allied Health Literature
CTC    Clinical Trials Centre (refers to the NHMRC CTC, the University of Sydney)
DHS    Department of Human Services
DPP    Diabetes Prevention Program
GP     General Practitioner/General Practice
GRADE  Grading of Recommendations, Assessment, Development and Evaluations
ICER   Incremental Cost Effectiveness Ratio
IWRS   Interactive Web Response System
NHMRC  National Health and Medical Research Council
OGTT   Oral Glucose Tolerance Test
ORRCA  Online Resource for Recruitment Research in Clinical Trials
PPI    Patient and Public Involvement
PRioRiTy Prioritising Recruitment in Randomised Trials
PRISMA Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QuinteT Qualitative Research Integrated within Trials
RCT    Randomised Controlled Trial
SEAR   Screened, Eligible, Approached, Randomised
SMS    Short Message Service
SWAT   Study Within A Trial
T4DM   Testosterone for the Prevention of Type 2 Diabetes study
TiDiE R Template for Intervention Description and Replication checklist
URL    Universal resource locator
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1.1. Overview

Recruitment of participants to clinical trials is a crucial but challenging component of trial conduct. An estimated 50% of trials fail to reach their recruitment targets in terms of the number of participants to be enrolled and/or the duration of recruitment\(^1\)\(^-\)\(^3\). Recruitment failure has serious consequences. First, trials that fail to recruit sufficient participants are at risk of failing to answer their scientific question for lack of power. This may result in promising new treatments being rejected due to lack of evidence of effectiveness. Second, trials that have recruitment delays may face trial budget problems and are likely to be slower to produce results, retarding the pace of research and the implementation of new treatments. Despite the importance of participant recruitment to trial conduct, the evidence on how best to recruit participants is limited\(^4\). To date, published accounts of recruitment have been predominantly post hoc, lacking in detail and methodologically problematic\(^5\). Few recruitment strategies are backed by good-quality evidence of effectiveness and, as a result, trial recruitment is often conducted using a trial-and-error approach. Furthermore, although experienced trialists within some academic trial units employ sophisticated recruitment methods, this knowledge is not being effectively disseminated, resulting in wasted time for researchers and participants, and wasted trial funding\(^4\).

Within the recruitment literature, the evidence on how best to recruit men to clinical trials is scarce. Men have a lower life expectancy than women and experience higher rates of several preventable conditions including coronary heart disease, diabetes, and injury\(^6\). In the past, men have been characterised as uninterested in their own health, and by extension, in participating in trials that could improve their health. Men have been underrepresented in recent disease prevention and lifestyle intervention trials\(^7\). However, there is now consensus that men will engage willingly with health services that address their needs\(^8\)\(^-\)\(^9\). Numerous studies have been conducted to explore men’s healthcare preferences to guide the development of gender-sensitised approaches to healthcare
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delivery\textsuperscript{10-12}. However, there is little evidence on how best to engage men as participants in clinical trial research. If the health inequalities experienced by men are to be addressed, inclusion of men in clinical trials, particularly disease prevention trials, is vital\textsuperscript{13}. In this thesis I aim to identify and evaluate strategies to recruit men to clinical trials, based on experiences from a large, Australian men’s diabetes prevention trial, the Testosterone for the prevention of Type 2 Diabetes (T4DM) trial.

1.2. The importance of participant recruitment

Clinical trials, specifically randomised, double-blind, placebo-controlled trials, are the gold standard in health and medical research\textsuperscript{14}. Good-quality trials are those that are well-designed, rigorously conducted and accurately analysed. These are the trials that produce reliable data to guide evidence-based healthcare. Unfortunately, clinical trials are not always well-conducted and an estimated 85\% of all research funds are wasted due to poor trial conception, design, methods and reporting\textsuperscript{15}. Indeed, as noted by Gheorghiade below, the very trials that seek to produce high-quality medical evidence are not themselves conducted in an evidence-based manner\textsuperscript{16}.

There is a peculiar paradox that exists in trial execution—we perform clinical trials to generate evidence to improve patient outcomes; however, we conduct clinical trials like anecdotal medicine: (1) we do what we think works; (2) we rely on experience and judgement; and (3) limited data to support best practices\textsuperscript{16}.

Because of this lack of evidence, many trials are poorly designed and conducted and there are now growing calls to address this deficiency through trial methodology research\textsuperscript{17}. Trial methodology research aims to reduce waste in the conduct of trials by building the evidence base for trial management decisions. While evidence is lacking in many areas of trial conduct, recruitment methods have been identified as the highest priority in methodology research by clinical trial unit managers\textsuperscript{18}.

Clearly, a clinical trial cannot be successful without recruiting trial participants. Each clinical trial has a pre-specified recruitment target based on statistical power to address the primary research question.
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Failure of a trial to meet its recruitment targets has serious ramifications. Trials that fail to enrol enough participants are at increased risk of Type II error; a failure to find evidence of a treatment effect where one truly exists. Not only may low power result in promising new interventions being dismissed, but research time and money will also have been wasted on a trial that has failed to answer its scientific question. Recruitment failure also has ethical implications; trials that fail due to lack of power place their participants at risk of harm needlessly. Unsuccessful trials squander not only research funds but also the time and goodwill of participants. Recruitment problems may also lead to prolonged recruitment duration. This, in turn, may delay trial completion with flow-on delays for future research and the availability of new treatments. Slow recruitment also tends to increase costs, diverting funds from other trial functions, and from other trials. Ultimately, if trials cannot be effectively and efficiently conducted due to recruitment failure there may be long-term consequences for the sustainability of medical research funding.

1.3. How common is recruitment failure?

Estimates of the prevalence of recruitment failure depend on how recruitment failure and recruitment success are defined. If we define recruitment success as enrolment of 100% of the planned target within the planned duration, then only an estimated 26% of trials are successful. Allowing for an extension of recruitment duration, this estimate increases to approximately 50% recruitment success. More encouragingly, 52% of a sample of US-based trials achieved 85% of their recruitment targets allowing for a 6-month extension, and this proportion was 78% in a sample of UK-based trials with no limit placed on recruitment duration. However, these estimates were based on trials funded by competitive grants from a number of large UK- and US-based funding agencies and may therefore represent a subgroup of trials that are most likely to be well-designed, well-conducted and adequately funded. Thus, these figures may actually overestimate the true rate of recruitment success in trials more generally. Even in trials published in six leading medical journals, a sample enriched for recruitment success by virtue of publication, only 79% of trials reached their recruitment targets.
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The Australian National Health Medical Research Council (NHMRC) allocates AU$800 million per annum to health and medical research, including clinical trials. If between 22% and 48% of trials fail due to poor recruitment, this represents millions of dollars of research funding wasted each year in Australia, and perhaps billions of dollars wasted internationally. Therefore, advances in recruitment methods have the potential to translate into substantially greater value in research overall.

1.4. Why do trials fail to recruit?

The majority of Australians say they would be willing to participate in a clinical trial and this is consistent with international findings, yet still many trials fail to recruit. Recruitment problems are most commonly explained by barriers inherent within the design or marketing of clinical trials. The most commonly cited reason for recruitment failure is overestimation of the size of the eligible participant pool. Known as Lasagne’s Law, this is the oft-lamented phenomenon that the actual number of participants available for recruitment will turn out to be substantially lower than expected. In fact, the problem may be a combination of overly optimistic recruitment estimation, narrow trial eligibility criteria and lower than expected rates of participant consent. The literature proposes a number of reasons that trials fail to meet their recruitment targets, broadly categorised into participant-related, clinician-related, and protocol-related barriers to recruitment. Participant-related barriers include the inconvenience and cost of participation, particularly the possible requirement to miss work and to travel some distance to the study clinic. The possibility of physical discomfort and harm may also deter people from participating in trials. Clinician-related barriers include time constraints, lack of staff and training, worry about the impact on the doctor-patient relationship, concern for patients, loss of professional autonomy, difficulty with the consent procedures, lack of rewards and recognition, and an insufficiently interesting question. In some trials access to a pool of potentially eligible participants was also identified by clinicians as a barrier. Protocol-related barriers are factors inherent in the design of the trial which reduce the willingness of patients to take part in the research, such as randomised allocation of treatment, blinded allocation of...
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treatment, the possibility of receiving a placebo, potential side effects of study treatments, and the frequency, number and duration of trial visits and assessments.

Although the barriers to recruitment are well-researched and understood, the best approaches to address these barriers while maintaining appropriate study design and rigorous study conduct are less clear.

1.5. Strategies to boost recruitment

A number of systematic reviews have considered recruitment strategies, including a recent, large Cochrane review of randomised evaluations of recruitment interventions. The Cochrane review identified 72 randomised recruitment comparisons but concluded that there was only enough evidence of effectiveness in two comparisons: (i) recruitment can be improved by adopting an open-label study design compared to a double-blind design, (ii) phoning people who do not respond to a postal invitation to participate in a trial improves recruitment compared to not phoning them. In a third comparison, tailoring the design of the patient information and consent sheet based on feedback from patients and the public appeared to have no impact on recruitment. The review used Grading of Recommendations, Assessment, Development and Evaluations (GRADE) criteria to assess confidence in the existing evidence and this aided the interpretation of the review’s findings. However, the inclusion of only randomised evaluations produced findings that are likely to be applicable to only a small proportion of trials. Other previous systematic reviews which excluded all non-randomised evaluations of recruitment strategies produced similarly limited results. Elsewhere, systematic reviews have focused on recruitment of specific participant groups (vulnerable populations, young adults, frail elderly) or recruitment within particular trial settings or interventions (palliative care, unscheduled hospital admissions, walking interventions). A number of frequently reported recruitment strategies were identified including: providing trial information to participants prior to hospital admission or attendance at the study site, partnering with staff who have an existing care relationship with prospective participants, providing at-home screening, identifying participants through social marketing activities such as mass mailing, media coverage and displaying posters.
40, and following up with prospective participants by telephone40. However, though these recruitment strategies were frequently reported, it was unclear from the included papers and the systematic reviews whether these strategies effectively improved recruitment. It was also unclear whether strategies would be effective or appropriate outside the setting in which they had been evaluated36. Furthermore, with the exception of the large Cochrane review, many systematic reviews did not perform formal risk of bias or quality assessments. Where quality assessments were performed these focused on the conduct and reporting of the host trial rather than on the recruitment evaluation36, or used quality criteria that did not translate well to methodology research20, 40, 41. For this reason, assessing the strength of the evidence presented in the recruitment systematic reviews is problematic. An upcoming Cochrane review of non-randomised evaluations of recruitment strategies may provide more clarity, although preliminary results from this review indicate that all 102 included studies were at serious or critical risk of bias42.

1.6. Recruitment research methods

It is widely recognised that the existing evidence in recruitment methods is inadequate33, 34, 36, 40, 43. However, simply calling for more recruitment research is unlikely to address this deficiency. Indeed, the Online Resource for Recruitment research in Clinical trials (ORRCA) database, which collates methodological research on recruitment, has identified 2804 reports of recruitment research published up to 201544. Hence, it is not the quantity but rather the quality and focus of recruitment research that is at issue. The bulk of the existing evidence comes from post hoc case studies of recruitment experiences in individual trials, recruitment research set within hypothetical trials, and brief accounts of recruitment reported alongside the host trial’s main results5. To date, innovation in recruitment processes has involved trial and error rather than systematic planning, data collection and analysis40 and few recruitment evaluations have been informed by theory5. Trial methodology research is, by its nature, secondary to primary clinical research. Recruitment research studies are typically embedded within a host clinical trial and must therefore be conducted to avoid damaging the scientific integrity of the host trial. To address this challenge while promoting
methodological rigor in trial methodology research, the UK-based initiative, Trial Forge, has proposed the Study Within A Trial (SWAT)\(^4\). SWATs are prospectively designed evaluations with formal, registered protocols. SWATs are often constrained in size and duration by their host trial and it is therefore important that SWATs are designed and reported to facilitate replication in multiple trials to generate adequate evidence. Methods for conducting SWATs are still developing. More work is needed to understand how best to produce quality methodological research with limited funding and resources, and within the constraints of clinical research.

Recruitment methodology research should address the complexity of the recruitment process. Characterisation of recruitment as a single activity with a single outcome (number of participants recruited) is overly simplistic. Recently, Wilson and colleagues\(^{45}\) have proposed the Screened, Eligible, Approached, Randomised (SEAR) framework incorporating four recruitment stages: (i) screening to identify prospective participants, (ii) assessment of participant eligibility, (iii) approach to the participant to seek consent, and (iv) randomisation. This framework provides a structure for the identification, investigation and remedy of recruitment challenges in trials.

### 1.7. Recruitment to diabetes prevention trials

#### 1.7.1. The importance of diabetes prevention

An estimated 425 million people worldwide have Type 2 diabetes (‘diabetes’) and a further 352 million are at increased risk of the disease due to impaired glucose tolerance\(^{46}\). Diabetes is a silent pandemic; sufferers often already exhibit signs of diabetes-related complications by the time they receive a diagnosis of diabetes\(^{47}\). In Australia, diabetes is the second highest contributor to disease burden in men and the fourth highest in women\(^{48}\), and is a contributing factor in 65% of cardiovascular deaths\(^{47}\). Furthermore, people with diabetes are at increased risk of numerous conditions affecting not only cardiovascular health but also the feet, eyes, and kidneys. Diabetes and its associated complications cost an estimated AU$6 billion per year in Australia including health service, care and government subsidies\(^{47}\).
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Risk of diabetes is associated with a number of modifiable risk factors including excess weight, poor diet, physical inactivity, smoking and impaired glucose tolerance\(^\text{46}\) and there is now international consensus that lifestyle interventions to improve diet and increase physical activity are effective in reducing the risk of diabetes\(^\text{49}\). However, further diabetes prevention research is needed if the substantial and growing disease burden and economic costs associated with diabetes are to be reduced.

1.7.2. Recruitment to previous diabetes prevention trials

Recruitment of participants to diabetes prevention trials is challenging. Recently, diabetes prevention trials have recruited participants with pre-diabetes as they are at highest risk of developing diabetes\(^\text{50-59}\). However, people with pre-diabetes are likely to be asymptomatic and undiagnosed, making them difficult to identify for trial recruitment. Instead, past trials have invited members of the public to be screened for pre-diabetes as the first step in trial screening. This non-targeted approach has resulted in screening failure rates as high as 98\% in past trials\(^\text{51}\). It is therefore crucial that diabetes prevention trials can screen large numbers of participants cheaply and efficiently to control recruitment costs and avoid recruitment delays.

Of the many trials evaluating interventions to prevent diabetes, 13 have reported their participant recruitment methods. Seven of these trials published stand-alone recruitment methods papers\(^\text{51, 52, 55, 58-61}\); a further six trials published a brief account of recruitment methods within the study design or main study results papers\(^\text{50, 53, 54, 56, 57, 62}\). Trial participants were most frequently identified through referral from health service providers\(^\text{55, 56, 58, 59}\), screening at community-based events\(^\text{53, 56, 58, 59}\), media coverage\(^\text{54, 56, 58}\) and mass mailings\(^\text{54, 56, 58, 59}\). However, it was unclear which of these strategies were most effective. Few papers reported the numbers of people identified through each strategy, and where these results were reported they appeared to be inconsistent between trials. In some trials most participants were identified through media coverage and mass mailings, yet in others these approaches resulted in few enrolments. Elsewhere, strategies appeared to be strategically targeted. For example, one Indian trial screened large numbers of participants at events held in residential complexes\(^\text{52}\), and
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one, small American trial successfully recruited participants of Mexican descent at church-based screening events. However, it was unclear whether these recruitment strategies would be effective in other participant populations. Comparisons between trials were also hindered by lack of detailed reporting of recruitment activities. Activities were often reported in a single sentence with no indication of the intensity, resource use, setting or content involved.

Only four studies reported the costs and/or resource use associated with screening and enrolling participants. However, comparing costs between studies is problematic as the methods for measuring and reporting costs were not well-described. In three trials, recruitment, screening and enrolment activities required 69, 91 and 98 hours per participant randomised. The largest of these trials, the US-based Diabetes Prevention Program (DPP), required 373,000 hours of site staff time to randomise 3819 participants, not including the time spent on recruitment activities by coordinating centre staff. One additional trial reported that only six hours of staff time were required per randomised participant. However, this study was small (58 participants) and did not require participants to be pre-diabetic for trial enrolment, perhaps explaining the discrepancy with the other studies. The direct cost of recruitment was AU$2747 per participant in the DPP and substantially less (AU$239) in a smaller, community-based translational follow-up trial to the DPP although these estimates seemingly included only recruitment promotions and excluded screening and staffing costs.

Most previous studies (9/13) reported screening participants in a multi-step process with less expensive and less invasive eligibility checks performed first to exclude as many ineligible participants as possible prior to more intensive screening tests, thus reducing testing of ineligible participants. However, this approach required prospective participants to return to the study site up to four times prior to randomisation, which was likely to have been resource-intensive, and inconvenient for potential participants, perhaps leading to the considerable participant drop-out rates reported during the screening process.

As in the general recruitment literature, reporting quality of recruitment interventions and outcomes in diabetes prevention trials was low. Few papers provided more than a cursory description
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of the recruitment strategies they employed, and it therefore remains unclear how to most effectively and affordably recruit participants to diabetes prevention trials.

1.8. Recruitment of men to trials

1.8.1. Understanding men’s healthcare needs

Men have a 70% higher rate of avoidable mortality than women and a lower life expectancy overall. Men’s higher rates of chronic diseases such as coronary heart disease, Type 2 diabetes, and road-traffic injury have been attributed to men’s poorer lifestyle choices and higher rates of risk-taking behaviours. Men are also more likely to delay seeking help for health problems. In the past, these observations have led to men being inaccurately labelled as under-users of healthcare and being ‘blamed’ for their poorer health outcomes. It is now accepted that this framing of the issue is overly simplistic; it fails to acknowledge the impact that both biological sex and gender norms have on health outcomes. Recent research in men’s health has sought to understand the social determinants of men’s help-seeking behaviours, and to consider how health services can be designed to meet men’s needs. Stereotypical masculine strengths such as problem-solving, control and self-reliance are not inconsistent with good health. Men may favour a practical approach, monitoring their own health and their ability to perform regular activities to determine if and when professional help is needed. Thus, the fact that men are more likely to delay seeing their doctor may now be understood, not as disinterest in health, but rather as a considered decision by men about their healthcare needs. Indeed, 89% of men reported visiting a general practitioner in a recent 12 month period, refuting previous claims that men are disengaged with healthcare. Men value convenience and anonymity in health service provision and men of working age may engage more effectively with services that are based within the workplace or that are offered outside working hours. Healthcare professionals can address men’s preferences by providing frank but empathetic healthcare advice and by alleviating the seriousness of a consultation with thoughtful humour and a laidback attitude. Men have shown willingness to attend health services and to engage with lifestyle interventions that are targeted to their needs.
1.8.2. Enrolling men in trials

Historically, it was women who were underrepresented in clinical trials. This underrepresentation, particularly in pharmacotherapy trials, resulted in trial results that could not be generalised to women, putting women’s health at risk. To combat this issue, research has focused on gender-sensitised approaches to including women in clinical trials. However, men are now underrepresented in disease prevention and lifestyle intervention trials and thus these trials may produce evidence that is not generalisable to men. This is of concern since men are at increased risk of many of the chronic conditions that such trials seek to prevent. As gender-sensitised approaches to delivery of men’s healthcare has improved engagement, it follows that gender-sensitised strategies to include men in clinical trials may also be promising.

1.9. The T4DM Diabetes Prevention Study

The Testosterone for Diabetes Mellitus (T4DM) study is a Phase IIIB, multi-centre, randomised, placebo-controlled trial of testosterone for the prevention of Type 2 diabetes or the reversal of newly diagnosed diabetes. The study design paper, of which I am a co-author, has been published and is included in Appendix A for further information. In brief, the study enrolled men aged 50 – 74 years, who were overweight or obese, had pre-diabetes (evidenced by impaired glucose tolerance) or newly diagnosed diabetes, and lowered testosterone. Participants received two years of treatment with testosterone or matched placebo (delivered by 12-weekly intramuscular injection), combined with a lifestyle intervention provided by Weight Watchers®. The study’s primary outcomes were: i) proportion of participants with 2-hour glucose in the diabetic range at two years, ii) mean change in 2-hour glucose from baseline to two years. The study was conducted at six endocrinologist-led, hospital-based sites in five Australian capital cities. The study was centrally coordinated by the NHMRC CTC, University of Sydney and sponsored by the University of Adelaide. The study recruited 1007 men over four years from January 2013 to February 2017 and the final patient visit was conducted in May 2019. The trial results are expected to be released in early 2020.
1.9.1. My contribution to the T4DM study

The T4DM study was funded by an NHMRC project grant commencing in 2012 and I joined the study as the project manager in January 2012. I have remained the project manager throughout the course of the study, with responsibility for: leading trial operations; managing the trial coordination team; producing trial documentation; designing trials data systems and maintaining data quality and completeness; developing, implementing, monitoring and enhancing recruitment and screening processes; overseeing and training site staff, in partnership with site investigators; managing the relationship with third party providers for drug distribution and pathology services; managing the trial budget; and reporting to the Trial Steering Committee.

1.10. Research aim and objectives

1.10.1. Research aim

To identify and evaluate strategies to recruit men to clinical trials, based on experiences from the T4DM diabetes prevention trial.

1.10.2. Research objectives

1. To systematically identify, review and synthesise the existing evidence on strategies to recruit men aged 50 years and over to clinical trials.

2. To identify and implement promotional strategies to invite men to participate in the T4DM study, and to evaluate the effectiveness and cost of these strategies.

3. To design, implement and evaluate a high-volume, low-cost process to screen and enrol participants identified through the strategies described in objective two.

4. Within the screening process described in objective three, to evaluate and compare, in a randomised fashion, the impact of telephone and short message service (SMS) reminders on screening uptake in prospective participants.
Chapter 1. Introduction

1.11. Thesis presentation

This work is presented as a ‘thesis including publications’, in accordance with the University of Sydney Thesis and examinations higher degrees by research policy 2015. The thesis includes four journal articles (Chapters 2 to 5). Published journal articles have been embedded within this thesis in their published format. The journal article that has been submitted for publication and is currently in press has been reformatted for consistency with the remainder of this thesis. A single reference list is presented at the end of the thesis, except in the case of the published articles which have self-contained reference lists. Supplementary materials referred to in journal articles are presented in the appendices.

The four journal article chapters make up the body of the thesis and are book-ended by this introduction chapter (Chapter 1), and a summary and conclusion chapter (Chapter 6). Taken as a whole, these chapters present a cohesive investigation of strategies to enrol men in clinical trials, using strategies and evaluations set within the T4DM trial. As each journal article describes a specific piece of research including the associated methods and results, stand-alone methods and results chapters are not presented in this thesis.

1.12. Thesis outline

In this introduction chapter, I have demonstrated the importance of participant recruitment to successful trial conduct and medical innovation, and have summarised the existing evidence on strategies to boost recruitment. As this work is set within the T4DM diabetes prevention trial, I have also summarised the recruitment approaches taken by previous diabetes prevention trials and have outlined the common recruitment challenges these trials have faced. As a men’s health trial, T4DM sought to develop a recruitment plan that addressed our male participants’ preferences and needs. In order to understand how best to enrol men in trials, Chapter 2 presents a systematic review of recruitment strategies in trials of men aged 50 years and older. This review categorises recruitment strategies according to the stage of recruitment they seek to improve, modified from the SEAR recruitment framework: identification of prospective participants, assessment of eligibility, and
Chapter 1. Introduction

provision of participant information and seeking of consent. Chapters 3 to 5 present original recruitment evaluations set within the T4DM study, categorised by recruitment stage in Figure 1.1.

Figure 1.1. Structure of thesis

As previously demonstrated, diabetes prevention trials seeking to recruit relatively healthy and asymptomatic participants are rarely able to identify enough participants through clinician referral alone and have instead employed a range of promotional recruitment activities. Although a number of previous trials have published their promotional recruitment strategies, it remains unclear which strategies are most efficacious and cost effective for boosting recruitment. Chapter 3 describes and evaluates the strategies used to identify participants to the T4DM trial. This chapter presents a detailed account of the range of traditional and online promotional activities employed, and an analysis of the efficacy and cost of these activities.

Identification of prospective participants through promotional activities has the potential to reach large numbers of the general public. However, this non-targeted approach to recruitment has resulted in high rates of screening failure rates in past trials. Screening out large numbers of ineligible
Chapter 1. Introduction

Participants has proven to be time-consuming and expensive. To address this problem, Chapter 4 presents the screening and enrolment process for the T4DM trial. It investigates a multi-step, centralised and semi-automated approach to deliver high-volume, low-cost screening. A detailed evaluation of the design, implementation, costs and screening outcomes is presented as well as a discussion of the advantages and disadvantages of this novel screening approach.

Disease prevention trials may experience high rates of participant attrition during screening if prospective participants perceive their risk of disease to be low and are unsure if the trial is suitable for them, increasing recruitment costs and putting trials at risk of recruitment failure\(^{31, 74, 75}\). Chapter 5 presents a randomised study within a trial (SWAT) of a reminder intervention intended to reduce participant attrition in the T4DM trial. This SWAT evaluates the effectiveness and cost effectiveness of telephone versus short message service (SMS) reminders on screening uptake in participants who failed to proceed past initial pre-screening.

Finally, Chapter 6 completes the thesis by summarising the main findings of each of the included evaluations. This chapter also presents the implications of this work to future recruitment practice, and suggests areas for future recruitment methodology research.
Chapter 2. Recruitment Strategies in Randomised Controlled Trials of Men Aged 50 Years and Older: A Systematic Review

2.1. Preamble

This chapter is a published manuscript presenting the results of a systematic review of recruitment strategies in trials of men aged 50 years and older.

The supplementary materials associated with this publication can be found in Appendix B (systematic review database search strategies) and Appendix C (systematic review PRISMA checklist).

2.1.1. Publication details


2.1.2. Contribution of authors

The review was conceived by KB and GW. KB performed the database searches. KB and GW performed eligibility checking. KB extracted the data from included studies and KB and LA performed the quality assessments. KB wrote the first draft of the manuscript. KB, LA, AK, WH and GW reviewed and refined the manuscript and approved the final manuscript.

2.2. Published manuscript
Recruitment strategies in randomised controlled trials of men aged 50 years and older: a systematic review

Karen Bracken, Lisa Askie, Anthony C Keech, Wendy Hague, Gary Wittert

ABSTRACT

Objectives To identify and review evaluations of strategies to recruit men aged 50 years and over to randomised controlled trials (RCTs).

Design Systematic review and narrative synthesis.

Data sources MEDLINE, EMBASE, CINAHL and ORRCA databases were searched to 1 December 2017.

Eligibility criteria Studies using quantitative methods to evaluate recruitment strategies to RCTs of men aged 50 years and older.

Data extraction and synthesis A single reviewer extracted data (for each strategy, number of participants approached, screened and randomised, and cost). Study quality was assessed using National Heart, Lung and Blood Institute Quality Assessment Tools and considered study design, description of interventions, description and measurement of outcomes, completeness of outcome reporting, performance of statistical testing and consideration of confounders. Recruitment strategies were categorised by the recruitment stage they addressed.

Results Sixteen studies (n >14,000) were included: one good quality, ten fair quality and five poor quality. Studies evaluated strategies to identify prospective participants, and to improve the processes for assessing participant eligibility, providing participant information and seeking consent. In good and fair quality studies, the most effective strategies for identifying participants were referral from an affiliated health service provider (two studies), mass mailing (five studies) and media coverage (two studies). Community outreach activities such as displaying posters and attending local community events were not effective (two studies). Trial-specific training of site recruitment staff, developed using qualitative analysis of recruitment visits (two studies), and provision of study information to prospective participants at a multidisciplinary, group information session (one study) both improved recruitment.

Conclusion Improved engagement of men aged 50 years and older in RCTs is needed. A gender-sensitised approach to RCT recruitment may help to address this need. We have identified several promising recruitment strategies that merit further evaluation.

INTRODUCTION

Randomised controlled trials (RCTs) are the accepted gold standard in health intervention research. Recruitment to RCTs can be challenging, and around 50% of RCTs fail to achieve their recruitment targets. The potential consequences of failed RCT recruitment are considerable and include wasted research resources, delays in the release of RCT results and increased likelihood of type 2 error. RCTs expose trial participants to potential risk and inconvenience, and trials that fail to recruit fully may waste the goodwill and commitment of the participants they do recruit. Clinical trial unit directors have identified the evaluation of strategies to boost recruitment as the highest priority in trial methodology research.

Despite the importance of successful recruitment to the overall success of trials and the calls for research in this area, the published evidence on how best to conduct RCT recruitment is limited. Several large systematic reviews have found surprisingly few randomised evaluations of recruitment strategies with many randomised recruitment studies being underpowered, low quality or set within hypothetical rather than real-world RCTs. Other recent recruitment-focused systematic reviews have concentrated on specific demographic groups or disease areas. This approach recognises the diversity of trial populations, interventions and designs to build a greater understanding of how recruitment strategies may influence specific participant groups.
It is well-established that the differences in disease incidence and health outcomes observed in men and women are determined not only by biological sex differences but also by socially constructed gender roles and norms. There is an increasing focus on gender-sensitive health service delivery to address health inequities for both men and women. Women have been historically under-represented in clinical trials, and so gendered approaches to trial recruitment have often focused on the recruitment of women. However, research is also needed to better engage men in clinical trials. Men have a lower life expectancy than women, and men, especially those aged over 50 years, bear a greater disease burden. In the past, men have been characterised as disengaged with healthcare services but it is now recognised that men will engage willingly and effectively with healthcare that recognises, and is tailored to, men’s preferences. An exploration of gender-sensitised strategies to recruit men to RCTs may, therefore, be worthwhile, particularly since men may be under-represented in RCTs of disease prevention and health promotion.

Evaluations of online and social media recruitment strategies are becoming more common with promising results reported in the recruitment of adolescents and young people, and women. Facebook and other types of online promotion may achieve a broader reach and be more cost-effective than traditional recruitment methods such as newspaper advertising, media coverage and posters. However, a recent systematic review of recruitment using Facebook found little evidence of its effectiveness in recruiting participants aged over 35 years. It is therefore unclear whether online and social media strategies are effective in recruiting men aged over 50 to RCTs.

This review aims to identify and review evaluations of strategies to recruit men aged over 50 years to RCTs in order to guide recruitment planning for future men’s health RCTs.

METHODS

Eligibility criteria
Studies met our inclusion criteria if they evaluated a strategy or strategies intended to improve the recruitment of men aged 50 years or older to an RCT. Studies must have reported at least one of the defined, quantitative, recruitment outcome measures. Studies were eligible irrespective of whether they recruited patients or healthy volunteers.

An initial scoping of the literature revealed that recruitment studies set within RCTs of both men and women often failed to provide adequate detail to determine the effectiveness of recruitment strategies on male participants alone. Therefore, to assess the impact of recruitment strategies on men, studies were only eligible for inclusion if set within an RCT recruiting men only.

The review included RCTs recruiting participants aged 50 years and older. Where the age range was not specified, studies were included where the mean/median age was 60 years or older, or where the disease of interest was prevalent in older men (eg, prostate cancer).

Included studies needed to evaluate a specific recruitment strategy or strategies; papers describing barriers and facilitators to recruitment or discussing informed consent but not presenting a specific strategy or approach to recruitment were excluded. Similarly, papers providing a brief account of recruitment without describing or evaluating specific strategies or approaches were excluded.

The search strategy was restricted to papers published since 2000. Communication channels and data management practices are central to recruitment research. Both of these areas have been transformed in the past 18 years by the growth of internet access. Evaluations published before 2000 are therefore less likely to be relevant to current trial practices, particularly those reporting advertising and media-related strategies.

Search strategy
A search of four databases (Medline, Embase, CINAHL and ORRCA) was performed in July 2017 and updated in December 2017. Studies published in English from 2000 onwards were considered for inclusion. Individualised search strategies (available in online supplementary file 1) were developed for each database using a combination of keywords relating to recruitment, enrolment, men and RCTs. In addition, the reference lists of all included articles and other recruitment-related systematic reviews were searched by hand to identify other potentially relevant papers.

Study selection and data extraction
Citations and abstracts were exported to Endnote Version X8.2 and duplicates were removed. A 10% random sample of citations was selected for independent screening for eligibility by two reviewers (KB and GW), with disagreement resolved by discussion. The Kappa statistic for double-screened citations indicated substantial agreement (Kappa=0.66) and the remaining 90% of articles were screened by KB alone.

Data from the included studies were extracted by KB using a pre-piloted data extraction form. Studies were categorised according to disease area of the host RCT, type of host RCT (treatment, prevention or screening), number of participants in the recruitment study and recruitment study design. Where reported, the number of prospective participants who received the recruitment intervention and the number of those participants who went on to be screened and randomised to the host RCT were extracted. The costs incurred were also extracted.

Categorisation of studies
The Qualitative Research Integrated within Trials (QuinteT) group’s Screened, Eligible, Approached, Randomised (SEAR) framework was developed to map each stage of the recruitment pathway. We adapted this framework to categorise the included studies according
to the stage or stages of the recruitment process they addressed: identification of participants (‘Screened’ in the SEAR framework), assessment of eligibility (‘Eligible’ in the SEAR framework) and patient information and consent (‘Approached’ in the SEAR framework).

Outcome measures

Our primary outcomes were: strategy uptake (defined as the percentage of people receiving the recruitment intervention who went on to be randomised to the host RCT), strategy contribution (defined as the percentage of all participants randomised to the host RCT who were randomised as a result of a particular strategy) and strategy cost (defined as direct or indirect cost per participant randomised).

Assessment of study quality

Six tools to assess study quality or risk of bias were identified from recent systematic reviews of recruitment strategies and were piloted for suitability and usability. After piloting, the National Heart, Lung and Blood Institute Quality Assessment Tools were selected as they addressed all included quantitative study designs, assessed key quality components and could be easily adapted for the assessment of non-clinical data. The tools listed criteria for judging study quality including study design, description of recruitment interventions, description and measurement of recruitment outcomes, completeness of outcome reporting, the performance of statistical testing and consideration of confounders. Based on these criteria, studies were subjectively judged by KB, in consultation with LA, as being of good (least risk of bias), fair (susceptible to bias) or poor (significant risk of bias) quality. Since this review addresses a methodological rather than a clinical question, the fair quality category was broadly defined to include studies that provided useful evaluation data even where some flaws were noted in the quality assessment. Quality assessments were performed with respect to the quantitative, recruitment-related outcomes of interest in this review only. The qualitative components of included mixed methods papers were not assessed as they were outside the scope of this review.

Methods of analysis

All studies, irrespective of quality, were included in the descriptive analysis in order to describe the full range of strategies evaluated and to assist with hypothesis generation for future research. Outcome measures were only analysed for studies of fair or good quality. Estimates from poor studies were excluded except where no estimates
were available from studies of good or fair quality. In this case, the estimate is presented with a caveat that the study is of poor quality. We had planned to perform a meta-analysis if studies were sufficiently homogeneous in the target population and delivery of the intervention to do so.

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist was completed and can be found in online supplementary file 2.

**Patient and public involvement**

Patients were not involved in the design or conduct of this systematic review. It is not possible to disseminate the results of this review to the participants of the included studies.

**RESULTS**

**Study selection**

Nine hundred and fifty-three unique papers were extracted. Of these, 16 recruitment studies were eligible for inclusion (figure 1). These 16 recruitment studies (listed in table 1) were conducted in the context of 12 RCTs since two RCTs hosted more than one recruitment study.

**Study characteristics**

The characteristics of included studies are described in table 2. As one might expect in trials recruiting exclusively older men, most selected studies reported recruitment to prostate cancer trials (11 studies plus one additional study in various cancers including prostate), with other studies reporting recruitment to trials in benign prostatic hyperplasia, low testosterone and suicide prevention. Three studies focused on the recruitment of men from minority ethnic groups. Recruitment studies ranged in size from 155 to 51085 screened participants and most commonly used a quantitative descriptive design.

**Quality assessment**

Most (10 of 16) studies were assessed as being of fair quality in relation to the recruitment outcomes of interest in this review. One study was evaluated as good, and five were evaluated as poor (tables 3–5). In general, all studies addressed a clear study question and enrolled a representative sample of participants. Recruitment outcomes were reliably measured and clearly reported, although few studies reported recruitment cost. However, the description and measurement of intervention delivery were often incomplete or missing. Some studies reported that interventions were delivered inconsistently across study sites, but this inconsistency was not accounted for in the reporting of outcomes. This limitation made comparisons within and between studies problematic. Possible confounding was also a common issue. Of the 16 recruitment studies, only three had a randomised design, and one additional, non-randomised study reported baseline demographic data by intervention group. In the remaining 12 studies, differences between the intervention groups in baseline characteristics could not be assessed. Therefore, differences in recruitment between groups may have been influenced by the characteristics of the individuals studied rather than the interventions evaluated. Furthermore, in some studies, several recruitment activities were implemented concurrently, but no study discussed the possible impact of this on the observed recruitment outcomes. Another common limitation was the lack of prospective study design. Three studies reported a prospective design; six reported a retrospective design and the remaining seven did not specify.

One study, which was otherwise of good quality, was assessed as fair due to inadequate sample size. Several studies incorporated both quantitative and qualitative designs, but were assessed for quality based on only quantitative analysis and outcomes.

**Stages of recruitment and associated outcomes**

The included studies addressed three recruitment stages: (1) identification of prospective participants, (2) assessment of eligibility and (3) provision of participant information combined with seeking of consent. The strategies addressing each stage of recruitment are summarised below along with their reported recruitment outcomes. Outcomes are shown in table 6 (studies that reported strategy uptake), table 7 (studies that reported strategy contribution) and table 8 (studies that reported strategy cost).

**Identification of prospective participants**

Participant identification strategies were evaluated in nine studies. Excluding poor quality studies, all studies reported the contribution of participant identification strategies to enrolment (shown in table 7) while only four studies reported strategy uptake (shown in table 6) and two studies reported strategy cost (table 8). Within the participant identification category, we further grouped strategies as mass mailings, media coverage and advertising, health service referrals or community outreach activities. This categorisation was adapted from previous recruitment research. The data from table 7 have been summarised in table 9 to aid comparison between studies. The most frequently evaluated strategy were mass mailings and community outreach strategies (seven studies). Media strategies were evaluated in six studies and health service referrals in five studies.

**Mass mailing**

Recruitment by mass mailing involved sending study information and a letter of invitation to the members of one or more acquired mailing lists. Seven studies sent postal invitations and one study also sent email invitations. Mailing lists were obtained from a variety of sources including the Department of Veterans Affairs database, Department of Motor Vehicles database, home owner database, participant lists from previous health research,
<table>
<thead>
<tr>
<th>Author, year</th>
<th>Host RCT</th>
<th>Therapeutic area</th>
<th>Recruitment stage studied</th>
<th>Recruitment study design</th>
<th>Screened/eligible /randomised* (n)</th>
<th>Intervention(s)</th>
<th>Summary of findings</th>
<th>Quality assessment†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bhar et al., 201338</td>
<td>Not specified</td>
<td>Suicide prevention</td>
<td>Identification of participants</td>
<td>Quantitative descriptive</td>
<td>233/48/33</td>
<td>Various mass mailing and health service referral strategies.</td>
<td>Seeking referrals from a co-investigator’s clinic was the most effective strategy and also had the highest uptake rate. Seeking referrals from non-collaborating health services and mass mailings were not effective strategies.</td>
<td>Fair</td>
</tr>
<tr>
<td>Cauley et al., 201539</td>
<td>T trials</td>
<td>Low testosterone treatment</td>
<td>Identification of participants</td>
<td>Quantitative descriptive</td>
<td>51,085/931/790</td>
<td>Various mass mailing, media and community outreach strategies.</td>
<td>Mass mailing was the most effective recruitment strategy and was also the lowest cost per man screened. TV, radio and print advertisements, clinicaltrials.gov listing, posters and flyers and presentations at events resulted in very few men being screened.</td>
<td>Poor</td>
</tr>
<tr>
<td>Chlebowski et al., 201040</td>
<td>SELECT</td>
<td>Prostate cancer prevention</td>
<td>Identification of participants</td>
<td>Quantitative descriptive</td>
<td>4022/NR/634</td>
<td>Mailing to male home owners vs mailing to previous female research participant spouses.</td>
<td>Mailing previous female research participants’ spouses resulted in higher recruitment uptake than mailing men and was also more cost-effective. Mailing women contributed fewer participants than mailing men due to the relatively small size of the past research participant mailing list.</td>
<td>Fair</td>
</tr>
<tr>
<td>Cook et al., 201041</td>
<td>SELECT</td>
<td>Prostate cancer prevention</td>
<td>Identification of participants</td>
<td>Non-randomised controlled trial</td>
<td>NR/NR/8532</td>
<td>Various site-directed minority-targeted recruitment strategies funded by minority recruitment enhancement grants.</td>
<td>Sites awarded grants increased recruitment of African-American men significantly more than matched comparison sites. Overall recruitment was also increased at grant sites.</td>
<td>Poor</td>
</tr>
<tr>
<td>Heiney et al., 201042</td>
<td>EASE</td>
<td>Prostate cancer treatment</td>
<td>Identification of participants</td>
<td>Quantitative descriptive</td>
<td>440/178/59</td>
<td>Various mass mailing, media, health service referral and community outreach strategies.</td>
<td>Mass mailing and health service referral strategies were moderately effective. Recruitment uptake was highest in participants identified through health service referral.</td>
<td>Fair</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Author, year</th>
<th>Host RCT</th>
<th>Therapeutic area</th>
<th>Recruitment stage studied</th>
<th>Recruitment study design</th>
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<th>Intervention(s)</th>
<th>Summary of findings</th>
<th>Quality assessment†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kumar et al, 2012</td>
<td>Not specified</td>
<td>Prostate cancer prevention</td>
<td>Identification of participants</td>
<td>Quantitative descriptive</td>
<td>3547/1677/74</td>
<td>Various media, health service referral and community outreach strategies.</td>
<td>Principal investigator referral was the only effective recruitment strategy. TV, newspaper, print and web-based communications and distribution of posters and flyers resulted in very few screenings.</td>
<td>Poor</td>
</tr>
<tr>
<td>Kusek et al, 2002</td>
<td>MTOPS</td>
<td>Benign prostatic hyperplasia treatment</td>
<td>Identification of participants</td>
<td>Quantitative descriptive</td>
<td>4170/NR/2931</td>
<td>Various mass mailing, media, health service referral and community outreach strategies.</td>
<td>Newspaper advertising and stories, and mass mailings were the most effective recruitment strategies.</td>
<td>Fair</td>
</tr>
<tr>
<td>Lee et al, 2011</td>
<td>CAMUS</td>
<td>Benign prostatic hyperplasia treatment</td>
<td>Identification of participants</td>
<td>Quantitative descriptive</td>
<td>1032/NR/369</td>
<td>Various mass mailing, media, health service referral and community outreach strategies.</td>
<td>Newspaper, radio and online advertising, and mass mailing were the most effective recruitment strategies. Emailing was less effective than traditional mailing.</td>
<td>Fair</td>
</tr>
<tr>
<td>Moinpour et al, 2000</td>
<td>PCPT</td>
<td>Prostate cancer prevention</td>
<td>Identification of participants</td>
<td>Before and after</td>
<td>NR/NR/18,822‡</td>
<td>Site-directed minority-targeted recruitment strategies conducted by funded minority recruiter site staff.</td>
<td>Minority-targeted recruitment strategies were not effective at four of the five sites awarded funds for a minority recruiter.</td>
<td>Poor</td>
</tr>
<tr>
<td>Donovan et al, 2002</td>
<td>PROTECT (feasibility)</td>
<td>Prostate cancer treatment</td>
<td>Participant information and consent</td>
<td>Before and after</td>
<td>NR/155/108</td>
<td>Site training and guidance documents to address recruitment issues identified through qualitative research.</td>
<td>Recruitment rates increased after introduction of the recruitment-focused site training and guidance.</td>
<td>Fair</td>
</tr>
<tr>
<td>Donovan et al, 2003</td>
<td>PROTECT (feasibility)</td>
<td>Prostate cancer treatment</td>
<td>Participant information and consent</td>
<td>RCT</td>
<td>NR/167/103</td>
<td>Recruitment visit conducted by nurse vs recruitment visit conducted by urologist.</td>
<td>Recruitment rates in the urologist and the nurse groups were not significantly different. Recruitment by nurse was more cost-effective than recruitment by urologist.</td>
<td>Good</td>
</tr>
<tr>
<td>Donovan et al, 2009</td>
<td>PROTECT</td>
<td>Prostate cancer treatment</td>
<td>Participant information and consent</td>
<td>Before and after</td>
<td>NR/2664/1643‡</td>
<td>Site training and guidance documents to address recruitment issues identified through qualitative research.</td>
<td>Recruitment rates felt slightly after introduction of the recruitment-focused site training and guidance.</td>
<td>Fair</td>
</tr>
</tbody>
</table>
patient databases, commercial mailing lists, volunteer databases and lists of physicians and university employees.

Excluding poor studies, mailing referrals contributed 18%–100% of enrolled participants in the studies that used mailings. Uptake was very low across all studies (0.09%–1.0% of mail recipients went on to be randomised to the host RCT). The direct cost of mailings ranged from $59 to $259 per participant.

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### Table 1 Continued

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Host RCT</th>
<th>Host RCT therapeutic area</th>
<th>Recruitment stage studied</th>
<th>Recruitment study design</th>
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<th>Intervention(s)</th>
<th>Summary of findings</th>
<th>Quality assessment†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eccles et al, 2013</td>
<td>SABRE 1 (feasibility)</td>
<td>Prostate cancer treatment</td>
<td>Participant information and consent</td>
<td>RCT</td>
<td>286/30/4</td>
<td>30 min decision aid video providing trial information vs control (standard information).</td>
<td>Too few participants were recruited to assess effectiveness of the decision aid video. Some indication that the video may have decreased the recruitment rate when compared with control.</td>
<td>Fair</td>
</tr>
<tr>
<td>Wallace et al, 2006</td>
<td>SPIRIT</td>
<td>Prostate cancer treatment</td>
<td>Participant information and consent</td>
<td>Before and after</td>
<td>NR/290/32</td>
<td>Multidisciplinary group information session prior to recruitment vs one-on-one recruitment visit.</td>
<td>Recruitment rates increased after introduction of the multidisciplinary group information sessions.</td>
<td>Fair</td>
</tr>
<tr>
<td>Ford et al, 2004</td>
<td>PLCO/AAMEN project</td>
<td>Prostate, lung and colorectal cancer screening</td>
<td>Identification of participants, assessment of eligibility and patient information and consent</td>
<td>RCT</td>
<td>17 770/12 400/376</td>
<td>Three recruitment approaches of increasing intensity targeted at African-American men, compared with standard recruitment approach.</td>
<td>The most intensive approach to screening, which included face-to-face screening in a church setting, resulted in a higher recruitment rate than control. The improvement was statistically significant but small. Other less intense approaches were no better than control.</td>
<td>Fair</td>
</tr>
<tr>
<td>Lane et al, 2011</td>
<td>PROTECT</td>
<td>Prostate cancer treatment</td>
<td>Assessment of eligibility and participant information and consent</td>
<td>Before and after</td>
<td>NR/2664/1643‡</td>
<td>Peer-conducted site monitoring visits.</td>
<td>Recruitment issues were identified at two out of eight monitored sites. Specific recruitment metrics (consent form return rate, reduction in health-related exclusions) improved at these two sites following monitoring. The impact of the monitoring intervention on overall recruitment was not reported.</td>
<td>Poor</td>
</tr>
</tbody>
</table>

*Refers to number of participants screened (including prescreening), eligible (approached for consent) and randomised to the host RCT as part of the recruitment study.
†Quality rated as good, fair or poor with respect to the quantitative recruitment-related outcomes of interest in this systematic review.
‡Study did not report number of participants included in the recruitment evaluation. Instead total numbers of participants in host RCT are reported.

AAMEN, African-American Men; CAMUS, Complementary and Alternative Medicines Trial for Urological Symptoms; EASE, Eating, Activity and Stress Education; MTOPS, Medical Therapy of Prostatic Symptom; NR, not reported; PLCO, Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; PCPT, Prostate Cancer Prevention Trial; PROTECT, Prostate Testing for Cancer and Treatment; RCT, randomised controlled trial; SABRE, Surgery Against Brachytherapy—a Randomised Evaluation; SELECT, Selenium and Vitamin E Cancer Prevention Trial; SPIRIT, Surgical Prostatectomy versus Interstitial Radiation Intervention Trial; T, Testosterone TV, television.
In one study, postal invitations had a higher uptake than email invitations (0.4% of mail recipients enrolled vs 0.1% of email recipients). However, mail and email lists were drawn from dissimilar populations making a direct, unadjusted comparison problematic.

In one study, mailing women who were past research participants and asking them to invite their spouses resulted in higher recruitment uptake (4.3% vs 1.0% enrolled) and lower cost per participant ($59 per enrolment vs $259 per enrolment) compared with mailing men on a home owners database. However, the home owners mailing list was much larger than the past-participant mailing list (10,000 vs 800 members), and so 95% of participants were recruited through the home owners mailing list despite the lower uptake rate.

Media coverage and advertising
Six studies described a variety of media strategies including news stories on television and in newspapers, advertising on television, radio and in newspapers, listing the study on the clinicaltrials.gov website, other online advertising, and inclusion in military retiree and medical institution newsletters. Two studies reported that media strategies were effective, accounting for 35% and 54% of enrolments. The remaining four studies were excluded for poor quality.

Table 2

<table>
<thead>
<tr>
<th>Description</th>
<th>No of studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapeutic area of host RCT</td>
<td></td>
</tr>
<tr>
<td>Cancer—prostate</td>
<td>11</td>
</tr>
<tr>
<td>Cancer—various</td>
<td>1</td>
</tr>
<tr>
<td>Testosterone</td>
<td>2</td>
</tr>
<tr>
<td>Suicide</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Host RCT type</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>10</td>
</tr>
<tr>
<td>Prevention</td>
<td>5</td>
</tr>
<tr>
<td>Screening</td>
<td>1</td>
</tr>
<tr>
<td>Treatment</td>
<td>10</td>
</tr>
<tr>
<td>Screening</td>
<td>2</td>
</tr>
<tr>
<td>Suicide</td>
<td>1</td>
</tr>
<tr>
<td>Cancer—various</td>
<td>1</td>
</tr>
<tr>
<td>Testosterone</td>
<td>2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recruitment study design</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Quantitative descriptive</td>
<td>10</td>
</tr>
<tr>
<td>Randomised controlled trial</td>
<td>3</td>
</tr>
<tr>
<td>Before and after study</td>
<td>2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No of study participants in recruitment</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0–999</td>
<td>6</td>
</tr>
<tr>
<td>1000–4999</td>
<td>5</td>
</tr>
<tr>
<td>5000–9999</td>
<td>2</td>
</tr>
<tr>
<td>10,000+</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TOTAL recruitment studies included</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RCT, randomised controlled trial.</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Summary of quality assessments—controlled trials*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study</td>
<td>Described as RCT</td>
</tr>
<tr>
<td>---------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Cook et al., 2010</td>
<td>Y</td>
</tr>
<tr>
<td>Donovan et al., 2003</td>
<td>Y</td>
</tr>
<tr>
<td>Eccles et al., 2013</td>
<td>Y</td>
</tr>
<tr>
<td>Ford et al., 2004</td>
<td>Y</td>
</tr>
</tbody>
</table>

†Quality rated as good, fair or poor with respect to the quantitative recruitment-related outcomes of interest in this systematic review.
? not reported/unable to determine; N, no; NA, not applicable; RCT, randomised controlled trial; Y, yes.
Table 4  Summary of quality assessments—descriptive studies*

<table>
<thead>
<tr>
<th>Study</th>
<th>Clear objective</th>
<th>Study pop’n clear</th>
<th>Participants: same time period and pop’n, Criteria: prespecified and uniform</th>
<th>Sample size justification, power, Effect: estimate and variance</th>
<th>Exposure: measure prior to outcome measure</th>
<th>Sufficient time: exposure to outcome</th>
<th>Level of exposure measured</th>
<th>Exposure: clear, valid, reliable and consistent</th>
<th>Exposure: assessment more than once</th>
<th>Outcome: clear, valid, reliable and consistent</th>
<th>Outcome: blinded assessment</th>
<th>Loss to follow-up ≤20%</th>
<th>Confounders: measured and adjusted for</th>
<th>Quality rating—quantitative outcomes†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bhar et al, 2013</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>NA</td>
<td>Y</td>
<td>NA</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>FAIR</td>
</tr>
<tr>
<td>Cauley et al, 2015</td>
<td>Y</td>
<td>Y</td>
<td>?</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>NA</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>POOR</td>
</tr>
<tr>
<td>Chlebowski et al,</td>
<td>Y</td>
<td>Y</td>
<td>?</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>NA</td>
<td>?</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>FAIR</td>
</tr>
<tr>
<td>Heiney et al, 2010</td>
<td>Y</td>
<td>Y</td>
<td>?</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>NA</td>
<td>Y</td>
<td>NA</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>FAIR</td>
</tr>
<tr>
<td>Kumar et al, 2012</td>
<td>Y</td>
<td>Y</td>
<td>?</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>NA</td>
<td>Y</td>
<td>NA</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>FAIR</td>
</tr>
<tr>
<td>Lee et al, 2011</td>
<td>Y</td>
<td>Y</td>
<td>?</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>NA</td>
<td>Y</td>
<td>NA</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>FAIR</td>
</tr>
</tbody>
</table>

†Quality rated as good, fair or poor with respect to the quantitative recruitment-related outcomes of interest in this systematic review.
? = not reported/unable to determine; N = no; NA = not applicable; Y = yes.

Table 5  Summary of quality assessments—before and after studies*

<table>
<thead>
<tr>
<th>Study</th>
<th>Clear objective</th>
<th>Selection criteria: clear and prespecified</th>
<th>Participants representative</th>
<th>All eligible participants enrolled</th>
<th>Sufficient sample size</th>
<th>Intervention clear and consistently</th>
<th>Outcomes: clear, prespecified, valid, reliable and consistently assessed</th>
<th>Blind outcome assessment</th>
<th>Loss to follow-up ≤20%</th>
<th>Loss to follow-up accounted for</th>
<th>Stats methods used. P values reported</th>
<th>Multiple measures of outcome</th>
<th>Group level statistical analysis</th>
<th>Quality rating—quantitative outcomes†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donovan et al, 2002</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>?</td>
<td>Y</td>
<td>Intervention clear and consistently assessed</td>
<td>Blind outcome assessment</td>
<td>Loss to follow-up ≤20%</td>
<td>Loss to follow-up accounted for</td>
<td>Stats methods used. P values reported</td>
<td>Multiple measures of outcome</td>
<td>Group level statistical analysis</td>
<td>Quality rating—quantitative outcomes†</td>
</tr>
<tr>
<td>Donovan et al, 2009</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>?</td>
<td>Y</td>
<td>Intervention clear and consistently assessed</td>
<td>Blind outcome assessment</td>
<td>Loss to follow-up ≤20%</td>
<td>Loss to follow-up accounted for</td>
<td>Stats methods used. P values reported</td>
<td>Multiple measures of outcome</td>
<td>Group level statistical analysis</td>
<td>Quality rating—quantitative outcomes†</td>
</tr>
<tr>
<td>Lane et al, 2011</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>?</td>
<td>?</td>
<td>Y</td>
<td>Intervention clear and consistently assessed</td>
<td>Blind outcome assessment</td>
<td>Loss to follow-up ≤20%</td>
<td>Loss to follow-up accounted for</td>
<td>Stats methods used. P values reported</td>
<td>Multiple measures of outcome</td>
<td>Group level statistical analysis</td>
<td>Quality rating—quantitative outcomes†</td>
</tr>
<tr>
<td>Moinpour et al, 2000</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>?</td>
<td>?</td>
<td>N</td>
<td>Intervention clear and consistently assessed</td>
<td>Blind outcome assessment</td>
<td>Loss to follow-up ≤20%</td>
<td>Loss to follow-up accounted for</td>
<td>Stats methods used. P values reported</td>
<td>Multiple measures of outcome</td>
<td>Group level statistical analysis</td>
<td>Quality rating—quantitative outcomes†</td>
</tr>
<tr>
<td>Wallace et al, 2006</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>?</td>
<td>?</td>
<td>Y</td>
<td>Intervention clear and consistently assessed</td>
<td>Blind outcome assessment</td>
<td>Loss to follow-up ≤20%</td>
<td>Loss to follow-up accounted for</td>
<td>Stats methods used. P values reported</td>
<td>Multiple measures of outcome</td>
<td>Group level statistical analysis</td>
<td>Quality rating—quantitative outcomes†</td>
</tr>
</tbody>
</table>

† Quality rated as good, fair or poor with respect to the quantitative recruitment-related outcomes of interest in this systematic review.
? = not reported/unable to determine; N = no; NA = not applicable; Y = yes.
Table 6  Strategy uptake in included studies

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Intervention/s</th>
<th>Received recruitment intervention, n</th>
<th>Randomised to host RCT, n (%)</th>
<th>Statistical testing</th>
<th>Statistically significant?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recruitment stage: Identification of participants</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bhar <em>et al</em>, 2013[^38]</td>
<td>Referrals from co-investigator’s Veteran’s Affairs mental health clinic</td>
<td>63</td>
<td>24 (38)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Referrals from psychiatric outpatient clinic</td>
<td>18</td>
<td>3 (17)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mass mailing to primary care patients mailing list</td>
<td>869</td>
<td>6 (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Referrals from inpatient psychiatric unit</td>
<td>5</td>
<td>0 (0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Referrals from primary care physicians</td>
<td>0</td>
<td>0 (N/A)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Chlebowski <em>et al</em>, 2010[^40]</td>
<td>Mass mailing to male home owners</td>
<td>60000</td>
<td>600 (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mass mailing to spouses of previous female research participants</td>
<td>800</td>
<td>34 (4)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Heiney <em>et al</em>, 2010[^42]</td>
<td>Referral by physician</td>
<td>24</td>
<td>13 (54)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Referral from previous health research study</td>
<td>206</td>
<td>11 (5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mass mailing to oncology clinic list</td>
<td>1384</td>
<td>15 (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mass mailing to urology clinic list</td>
<td>759</td>
<td>8 (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mass mailing to support services department list</td>
<td>350</td>
<td>2 (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Posters, newspaper articles, other</td>
<td>NR</td>
<td>10 (N/A)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Lee <em>et al</em>, 2011[^45]</td>
<td>Mass mailing by post to former trial participants, health system users and commercial direct mailing lists</td>
<td>34064</td>
<td>143 (0.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Newspaper, radio and online advertising</td>
<td>NR</td>
<td>129 (N/A)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mass mailing by email to university employees, physicians, database of people interested in research</td>
<td>35000</td>
<td>31 (0.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Referral from urology clinic</td>
<td>63</td>
<td>30 (48)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Posters and flyers</td>
<td>NR</td>
<td>8 (N/A)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>NR</td>
<td>28 (N/A)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td><strong>Recruitment stage: Participant information and consent</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>After: Recruitment training and documentation informed by qualitative research</td>
<td>155</td>
<td>108 (70)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Donovan <em>et al</em>, 2003[^49]</td>
<td>Recruitment visit conducted by urologist</td>
<td>75</td>
<td>53 (71)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Recruitment visit conducted by nurse</td>
<td>75</td>
<td>50 (67)</td>
<td>RD=4% (95% CI −10.8% to +18.8%, p=0.60)</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>After: Recruitment training and documentation informed by qualitative research</td>
<td>NR</td>
<td>NR (65)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Before: No site review</td>
<td>Centre A: 24 Centre B: 46</td>
<td>Centre A: 11 (45) Centre B: 23 (50)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>After: Recruitment-focused site review triggered by low performance</td>
<td>Centre A: 14 Centre B: 40</td>
<td>Centre A: 12 (86) Centre B: 31 (78)</td>
<td>Centre A: p=0.020 Centre B: p=0.013</td>
<td>Yes</td>
</tr>
<tr>
<td>Eccles <em>et al</em>, 2013[^44]</td>
<td>Standard study information at recruitment visit</td>
<td>15</td>
<td>3 (20)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Continued
quality or lack of media-related outcome reporting. One study reported that newspapers were the largest source of recruited participants (30%) followed by radio (9%), newsletters (8%) and television (7%). Although five studies mentioned using paid advertising only one poor quality study reported costs with television being the cheapest ($46 per screening), followed by radio advertising ($51 per screening) and print most expensive ($105 per screening). All were more expensive than mass mailing ($38 per screening).

Health service referral
Health service referral was defined as identification of prospective participants by a health service provider. Only strategies which involved the health service provider having performed some initial screening were included. Where mass mail outs were performed using clinic lists without prior clinical screening, these were categorised as mass mailing. Five studies sought referrals from affiliated health services, health service referral was the most effective participant referral strategy contributing 41% and 82% of participants. For the remaining two studies, which sought referrals from health services not linked to the study, health services referrals were comparatively ineffective, contributing only 8% and 10% of participants.

Recruitment uptake from health services referral was generally higher than other strategies but was highly variable, ranging from 0% to 54% of referrals being randomised to the host RCT. Only one study reported cost-effectiveness. Referrals from a variety of health services cost $101 per participant randomised (see table 8 for details). Referral from an affiliated health service was the cheapest referral source ($44 per participant randomised).

Community outreach
Seven studies evaluated community outreach strategies, including posters displayed in community locations and healthcare clinics, and presentations to health service providers and the public. Two studies reported that community outreach activities were ineffective, accounting for only 2% and 4% of participants. The remaining five studies were excluded due to poor quality or failure to report the outcome of community outreach activities.

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Intervention/s</th>
<th>Received recruitment intervention, n</th>
<th>Randomised to host RCT, n (%)</th>
<th>Statistical testing</th>
<th>Statistically significant?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wallace et al, 2006</td>
<td>Before: one-on-one information session</td>
<td>15</td>
<td>1 (7)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>After: Multidisciplinary group information session</td>
<td>263</td>
<td>32 (12)</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

*Strategy uptake defined as the percentage of people receiving the recruitment intervention who went on to be randomised to the host RCT. Studies that did not report the number of participants receiving the recruitment intervention excluded. Poor quality studies excluded. NR, not reported; RCT, randomised controlled trial; N/A, not applicable.

Table 6
Continued
Patient information and consent

Five studies evaluated strategies to improve the patient information and consent process. The strategy uptake reported in each of these studies is shown in table 6. The studies aimed to improve either the content of the information provided to the participant at the recruitment visit or the mechanism by which that information was provided. All studies in this category were hosted within prostate cancer treatment trials, perhaps reflecting the challenges inherent in recruiting participants to prostate cancer trials where treatment options may be diverse, for example, surgery, radiation and watchful waiting.

Two papers evaluated a trial-specific recruitment training intervention delivered to site-based recruitment staff and implemented within the feasibility and main phases of the PROTECT trial. The intervention involved audio-taping recruitment interviews and performing qualitative to investigate how trial information was delivered to participants at the recruitment visit and how this may impact consent rates. Results of this

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Type of intervention</th>
<th>Details</th>
<th>Screened, n</th>
<th>Randomised, n (% of screened)</th>
<th>Contribution, %†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bhar et al., 2013</td>
<td>Health service referral</td>
<td>Co-investigator’s Veteran’s Affairs mental health clinic</td>
<td>45</td>
<td>24 (53)</td>
<td>73</td>
</tr>
<tr>
<td></td>
<td>Mass mailing</td>
<td>Primary care patients mailing list</td>
<td>174</td>
<td>6 (3)</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>Health service referral</td>
<td>Psychiatric outpatient clinic</td>
<td>12</td>
<td>3 (25)</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Health service referral</td>
<td>Inpatient psychiatric unit</td>
<td>2</td>
<td>0 (0)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Health service referral</td>
<td>Primary care physicians</td>
<td>0</td>
<td>0 (0)</td>
<td>0</td>
</tr>
<tr>
<td>Chlebowski et al., 2010</td>
<td>Mass mailing</td>
<td>Male home owners</td>
<td>3961</td>
<td>600 (15)</td>
<td>95</td>
</tr>
<tr>
<td></td>
<td>Mass mailing</td>
<td>Spouses of previous female research participant</td>
<td>61</td>
<td>34 (56)</td>
<td>5</td>
</tr>
<tr>
<td>Heiney et al., 2010</td>
<td>Mass mailing</td>
<td>Oncology clinic list</td>
<td>78</td>
<td>15 (19)</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>Health service referral</td>
<td>Physician</td>
<td>24</td>
<td>13 (54)</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>Health service referral</td>
<td>Previous health research study</td>
<td>161</td>
<td>11 (7)</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>Posters, newspaper articles, other</td>
<td>33</td>
<td>10 (30)</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>Mass mailing</td>
<td>Urology clinic list</td>
<td>52</td>
<td>8 (15)</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>Mass mailing</td>
<td>Support services department list</td>
<td>12</td>
<td>2 (17)</td>
<td>3</td>
</tr>
<tr>
<td>Kusek et al., 2002</td>
<td>Media</td>
<td>Newspaper advertising and new stories</td>
<td>1140</td>
<td>876 (77)</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>Mass mailing</td>
<td>Department of Motor Vehicles, screening lists and patient databases</td>
<td>1022</td>
<td>783 (77)</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>Health service referral</td>
<td>Urology clinic</td>
<td>361</td>
<td>280 (78)</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Media</td>
<td>Radio advertising</td>
<td>326</td>
<td>257 (79)</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Media</td>
<td>Inclusion in newsletters to military retirees and participating medical institutions</td>
<td>325</td>
<td>245 (75)</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Media</td>
<td>Television news stories and public service announcements</td>
<td>223</td>
<td>192 (86)</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>Word of mouth</td>
<td>150</td>
<td>122 (81)</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Community outreach</td>
<td>Poster/display</td>
<td>132</td>
<td>94 (71)</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>Not specified/unknown</td>
<td>461</td>
<td>57 (12)</td>
<td>2</td>
</tr>
<tr>
<td>Lee et al., 2011</td>
<td>Community outreach</td>
<td>Prostate health screening event</td>
<td>30</td>
<td>25 (83)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Mass mailing</td>
<td>Postal invite—former trial participants, health system users and commercial direct mailing lists</td>
<td>608</td>
<td>143 (24)</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>Media</td>
<td>Newspaper, radio and online advertising</td>
<td>273</td>
<td>129 (47)</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>Mass mailing</td>
<td>Email invite - university employees, physicians, database of people who registered interest in research</td>
<td>87</td>
<td>31 (36)</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Health service referral</td>
<td>Urology clinic (chart review)</td>
<td>52</td>
<td>30 (58)</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>Not specified</td>
<td>NR</td>
<td>28 (NR)</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Community outreach</td>
<td>Posters and flyers</td>
<td>12</td>
<td>8 (67)</td>
<td>2</td>
</tr>
</tbody>
</table>

*Poor quality studies excluded.
†Contribution defined as the percentage of all participants randomised to the host randomised controlled trial who were randomised as a result of a particular recruitment strategy.
NR, not reported.
analysis then guided the development of the training intervention. After the implementation of the intervention, the recruitment rate was observed to increase from 30%–40% to 70% during the feasibility stage and to remain between 69% and 65% during the main study. An evaluation of a secondary, intensive training process for underperforming sites found that recruitment rates increased from 45% to 86% (p=0.020) at one site and from 50% to 78% (p=0.013) at another site but numbers at these two sites were small.36 Other participant information and consent interventions were evaluated in one study each. Recruitment by nurses was found to be more cost-effective than recruitment by urologists (£36.40 vs £43.29 per screening) and resulted in similar rates of consent (67% vs 71% p=0.60.)49 Multidisciplinary, group information sessions increased the consent rate from 0% to 16% when compared with a one-on-one recruitment consultation.50 A 30 min decision aid video presented at the recruitment visit may have reduced the consent rate in one study although the study was underpowered.34

**Table 8** Cost of recruitment strategies*

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Costs reported</th>
<th>Recruitment phase</th>
<th>Intervention/s</th>
<th>Randomised, n</th>
<th>Cost</th>
<th>Cost per participant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bhar et al, 2013</td>
<td>Direct cost (stationary, postage, phone calls and catering) and indirect cost (staff time)</td>
<td>Identification of participants</td>
<td>Mass mailing—primary care patients mailing list</td>
<td>6</td>
<td>US$3813</td>
<td>US$636</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Health services referral—co-investigator’s Veteran’s Affairs mental health clinic</td>
<td>24</td>
<td>US$1066</td>
<td>US$44</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Health services referral—psychiatric outpatient clinic</td>
<td>3</td>
<td>US$497</td>
<td>US$166</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Health services referral—primary care physicians</td>
<td>0</td>
<td>US$643</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Health services referral—inpatient psychiatric unit</td>
<td>0</td>
<td>US$519</td>
<td>N/A</td>
</tr>
<tr>
<td>Chlebowski et al, 2010</td>
<td>Mailing cost (not further specified)</td>
<td>Identification of participants</td>
<td>Mass mailing—male home owners</td>
<td>600</td>
<td>US$155596</td>
<td>US$259</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mass mailing—spouses of previous female participant</td>
<td>34</td>
<td>US$2000</td>
<td>US$59</td>
</tr>
<tr>
<td>Donovan et al, 2003</td>
<td>Salary and on-costs for staff time</td>
<td>Participant information and consent</td>
<td>Recruitment visit performed by urologist</td>
<td>53</td>
<td>NR</td>
<td>£43.29</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Recruitment visit performed by nurse</td>
<td>50</td>
<td>NR</td>
<td>£36.40</td>
</tr>
</tbody>
</table>

*Poor quality studies excluded. NR, not reported.

**Table 9** A summary of the contribution of participant identifications strategies to randomised controlled trial recruitment*†

<table>
<thead>
<tr>
<th>Mass mailing</th>
<th>Media coverage and advertising</th>
<th>Health service referrals</th>
<th>Community outreach</th>
<th>Other, unspecified, unknown</th>
<th>Participants enrolled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kusek, 2002</td>
<td>783 (27%)</td>
<td>1570 (54%)</td>
<td>280 (10%)</td>
<td>119 (4%)</td>
<td>179 (6%)</td>
</tr>
<tr>
<td>Chlebowski, 2010</td>
<td>634 (100%)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Lee, 2011</td>
<td>174 (47%)</td>
<td>129 (35%)</td>
<td>30 (8%)</td>
<td>8 (2%)</td>
<td>28 (8%)</td>
</tr>
<tr>
<td>Heiney, 2010</td>
<td>25 (42%)</td>
<td>NR</td>
<td>24 (41%)</td>
<td>NR</td>
<td>–</td>
</tr>
<tr>
<td>Bhar, 2013</td>
<td>6 (18%)</td>
<td>–</td>
<td>27 (82%)</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

*Contribution defined as the number of participants randomised as a result of each strategy (percentage of all participants randomised).
†Poor quality studies excluded.
NR, not reported separately. In total, media and community strategies accounted for 17% of enrolled participants in this study.
Strategies addressing multiple stages of the recruitment process

Two studies evaluated strategies that addressed the recruitment process as a whole (identification of participants, assessment of eligibility, provision of participant information and seeking of consent) rather than one specific stage of recruitment. One study evaluated the impact of peer-conducted site monitoring visits on recruitment. The study reported that of the eight sites visited monitoring identified specific recruitment process issues at two sites. After monitoring, one site altered their process for participant reminders and subsequently consent form return rates increased by 5%. At another site, monitoring uncovered that eligibility criteria were being incorrectly applied and subsequently incorrect exclusion of prospective participants decreased by 5%. While these improvements to site processes are likely to have improved recruitment, the study did not report the impact on overall recruitment.

Another study evaluated four different approaches to recruit African-American men to a cancer screening trial. The study found that the most intensive intervention (mailing invitation endorsed by African-American community leader, phone screening by African-American interviewer and gathering baseline information at a church-based group session with transport provided) increased recruitment uptake from 2.9% to 3.9% compared with control (standard mailed invitation, phone screening by African-American or non-African-American interviewer and collection of baseline forms by mail). While this difference was statistically significant (p<0.01), it was small in absolute magnitude, and the cost of the most intensive intervention is likely to have been high although cost data were not reported. Other approaches that included less intensive combinations of mailing invitation endorsed by an African-American community leader, phone screening by African-American interviewer and gathering baseline information by phone did not result in a statistically significant increase in recruitment uptake compared with control.

DISCUSSION

Principal findings

In this review, we aimed to evaluate recruitment strategies in RCTs of men aged 50 years and older. We found that the best approaches for identifying participants were referral through an affiliated health service provider, media coverage and mass mailings. Community outreach activities and referrals from unaffiliated health service providers were not effective strategies for improving recruitment. Recruitment was improved by trial-specific training informed by qualitative analysis of the recruitment visit and delivered to site-based recruitment staff.

Context within the existing literature

This review included only recruitment evaluations in RCTs of men aged 50 years and over and was dominated by RCTs in prostate cancer. However, our findings were broadly consistent with recruitment studies in both men and women, ranging in age from young adults to the elderly, and across primary care, disease prevention, health screening, and cancer and surgical research. Nonetheless, some previous studies have reported differences in strategy effectiveness based on age and gender. Mass mailing strategies were more effective in men than women, and effectiveness increased with age. By contrast, online advertising strategies were more effective in women than men, and most recruited participants were adolescents and young adults. Community outreach activities appeared to have limited effectiveness in the general population with some suggestion that they were more effective in women than in men. Elsewhere, two reviews reported that community outreach activities might be effective when recruiting hard-to-reach participants such as vulnerable and elderly populations. These reviews reported community outreach activities tailored to the specific target populations. Some tailoring was evident in the studies included in the current review (for example, holding screening sessions at men’s health events but producing brochures in colours expected to appeal to men) but the context and content of community outreach activities were not described in detail. It is unknown whether further tailoring could have improved the effectiveness of community outreach activities in the recruitment of men aged 50 years and over. An upcoming Cochrane review may elucidate how age and gender modify the effect of specific recruitment strategies.

Strengths and limitations

This review is strengthened by the adaption of the SEAR framework to categorise the included studies. Research into recruitment strategies is fragmented, and researchers seeking evidence-based solutions to their recruitment challenges may find the current evidence difficult to digest. Categorising studies according to the stage of the recruitment process rather than categorising by intervention characteristics has a number of advantages. First, it is intuitive to use and understand since it mirrors real-world trial processes. Second, for researchers using the SEAR framework to collect recruitment data and identify recruitment challenges, our review provides a roadmap for navigating the available evidence and selecting the most promising interventions to address these challenges.

By grouping studies according to the SEAR framework, our review uncovered inconsistencies in how strategies to identify prospective participants were evaluated. All studies in this category reported strategy contributions to overall recruitment but only four studies reported strategy uptake and two reported strategy costs. There was a lack of consensus across studies on which of these outcomes was most appropriate and it was unclear how studies decided whether strategies were effective or not. Intuitively, these three possible outcomes (contribution,
uptake and cost) are, individually, insufficient to evaluate overall strategy effectiveness. For example, if a strategy contributed 80% of study participants does this indicate that the strategy was effective or simply that few other strategies were used? Likewise, if a strategy was low cost but resulted in few participants being randomised was it more or less effective than an expensive strategy that delivered large numbers of participants? Greater transparency in how strategies to identify participants are selected and assessed, and the costs involved would assist with the interpretation of study results in this area.

Of the estimated large number of men’s health RCTs conducted worldwide since 2000, only 16 studies of recruitment strategy evaluation were found, and 12 of these studies were related to prostate cancer (four from a single prostate cancer trial). Consequently, this review likely describes only a small fraction of the recruitment practices used to recruit men aged 50 years and older to RCTs and may be subject to publication bias. We included only single-gender, men’s RCTs in order to focus on gender-specific recruitment strategies. Several included studies described recruitment strategies that appeared to be male-focused (identifying participants through veteran’s groups and health services, holding screening sessions at men’s health events, offering screening outside normal working hours and producing brochures in colours expected to appeal to men). However, no study explicitly presented a gender-sensitised approach to recruitment or addressed the literature on men’s health preferences. Since studies evaluating recruitment to RCTs of both men and women were excluded, the results presented in this review are likely to be most relevant to the small but growing number of RCTs in men only. However, our approach to synthesising recruitment evidence and evaluating strategy effectiveness by recruitment stage may be relevant to recruitment to RCTs more broadly.

This review considered only quantitative evidence from recruitment evaluation studies, a common approach in systematic reviews of recruitment strategies. However, qualitative research methods also have the potential to address recruitment challenges and several included studies presented both quantitative and qualitative evidence. Future systematic reviews of recruitment strategies may be strengthened by synthesising all available evidence using a mixed methods approach.

We recommend caution when implementing recruitment strategies based on our findings since generalisability is hampered by weak recruitment study design, and insufficient reporting of the intervention content, context, delivery and cost in many of the included studies. Based on recently proposed criteria, additional evaluations of all potentially effective strategies identified in this review are likely to be of merit.

Implications for research

Our review uncovered areas of uncertainty across all stages of the recruitment process. In particular, further research is needed to assess whether gender-sensitised strategies can enhance recruitment of men aged 50 years and over to RCTs, and to assess the effectiveness of online advertising and promotions to recruit this demographic group. Future research may benefit from being conducted as a prospectively designed Study Within a Trial, following the recent guidance provided by Trial Forge. Researchers are encouraged to reveal how strategy effectiveness was assessed and to report cost outcomes. Since there are many uncertainties in recruitment methods, research should address one or more of the priority recruitment questions recently identified by the Prioritising Recruitment in Randomised Trials study. This will not only improve the impact of individual studies but also deepen the body of recruitment evidence in general.

Acknowledgements We thank Rod Dyson and Sherylin Goldstone for their contributions to this work.

Contributors The review was conceived by KB and GW. KB performed the database searches. KB and GW performed eligibility checking. KB extracted the data from included studies and KB and LA performed the quality assessments. KB wrote the first draft of the manuscript. KB, LA, AK, WH and GW reviewed and refined the manuscript and approved the final manuscript.

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Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Extracted, summary, recruitment data are available on request from the corresponding author (karen.bracken@cts.usyd.edu.au).

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Chapter 3. Recruitment of men to a multi-centre diabetes prevention trial: an evaluation of traditional and online promotional strategies

3.1. Preamble

This chapter is a published manuscript presenting an analysis of the promotional strategies used to identify prospective T4DM study participants. The paper aims to address some of the key limitations in the existing literature identified in Chapter 2, namely: (i) the inadequate reporting of promotion strategy content, implementation and cost, and (ii) the lack of transparency in assessing the effectiveness of promotional strategies.

The supplementary materials associated with this manuscript can be found in Appendix D (recruitment promotional materials) and Appendix E (definition of common Facebook and Google terms).

3.1.1. Publication details


3.1.2. Contribution of authors

KB, GW and WH conceived this promotion evaluation study. KB, WH, AK, AC, DJH, MG, DJ, BS, BBY, WI, CA, RM, KPR and GW conducted and monitored trial recruitment promotions. AC, DH, MG, DJ, BS, BBY, WI, CA, RM and GW recruited participants to the trial at their study sites. KB collected the data. KB and KR performed the data analysis. KB drafted the paper. KB, WH, AK, AC, DJH, MG, DJ, BS, BBY, WI, CA, RM, KPR and GW revised and added further content. All authors read and approved the final manuscript.
Chapter 3. Recruitment promotions

3.2. Published Manuscript
RESEARCH

Recruitment of men to a multi-centre diabetes prevention trial: an evaluation of traditional and online promotional strategies

Karen Bracken 1*, Wendy Hague 1, Anthony Kech 1, Ann Conway 2, David J. Handelsman 2, Mathis Grossmann 3, David Jesudason 4, Bronwyn Stuckey 5, Bu B. Yeap 6, Warrick Inder 7, Carolyn Allan 8, Robert McLachlan 8, Kristy P. Robledo 1 and Gary Wittert 9

Abstract

Background: Effective interventions are required to prevent the current rapid increase in the prevalence of Type 2 diabetes. Clinical trials of large-scale interventions to prevent Type 2 diabetes are essential but recruitment is challenging and expensive, and there are limited data regarding the most cost-effective and efficient approaches to recruitment. This paper aims to evaluate the cost and effectiveness of a range of promotional strategies used to recruit men to a large Type 2 diabetes prevention trial.

Methods: An observational study was conducted nested within the Testosterone for the Prevention of Type 2 Diabetes (T4DM) study, a large, multi-centre randomised controlled trial (RCT) of testosterone treatment for the prevention of Type 2 diabetes in men aged 50–74 years at high risk of developing diabetes. Study participation was promoted via mainstream media—television, newspaper and radio; direct marketing using mass mail-outs, publicly displayed posters and attendance at local events; digital platforms, including Facebook and Google; and online promotions by community organisations and businesses. For each strategy, the resulting number of participants and the direct cost involved were recorded. The staff effort required for each strategy was estimated based on feedback from staff.

Results: Of 19,022 men screened for the study, 1007 (5%) were enrolled. The most effective recruitment strategies were targeted radio advertising (accounting for 42% of participants), television news coverage (20%) and mass mail-outs (17%). Other strategies, including radio news, publicly displayed posters, attendance at local events, newspaper advertising, online promotions and Google and Facebook advertising, each accounted for no more than 4% of enrolled participants. Recruitment promotions cost an average of AU$594 per randomised participant. The most cost-effective paid strategy was mass mail-outs by a government health agency (AU$745 per participant). Other paid strategies were more expensive: mail-out by general practitioners (GPs) (AU$1104 per participant), radio advertising (AU$1081) and newspaper advertising (AU$1941).

Conclusion: Radio advertising, television news coverage and mass mail-outs by a government health agency were the most effective recruitment strategies. Close monitoring of recruitment outcomes and ongoing enhancement of recruitment activities played a central role in recruitment to this RCT.

(Continued on next page)
Background

Worldwide, an estimated 1 in 11 adults has diabetes, and Type 2 diabetes accounts for 90% of these cases [1]. Research to identify effective interventions to prevent diabetes is urgently needed to address this global problem. However, recruitment to disease prevention trials, including diabetes prevention trials, can be challenging. Firstly, since participants in disease prevention trials tend to be healthy and asymptomatic, clinicians may not be able to identify eligible patients through their clinics [2]. Secondly, potential participants may not perceive benefit in participating in disease prevention research, particularly if they do not believe that they are at risk of the disease [3, 4]. Lack of perceived benefit may contribute to lower rates of consent, requiring larger numbers of people to be screened [5]. Thirdly, screening numbers must be large in prevention trials if a modest effect size is hypothesised to ensure adequate power.

To overcome the challenge of recruiting sufficient numbers of participants, previous diabetes prevention trials have reported promoting study participation through: media coverage [6–9], advertising [7–11], mass mailings [7, 9, 12], referrals from physicians or clinics [6, 7, 9, 10, 12], community-based initiatives [6, 7, 10, 12, 13] and public screening events [7–9, 12]. Evaluations of these recruitment strategies have also been reported in other research areas, including lifestyle improvement interventions [14], smoking cessation [15] and treatment of benign prostatic hyperplasia [16, 17]. While the existing literature provides useful recruitment guidance, papers have often lacked sufficient detail on how strategies were implemented and delivered, and how much they cost [18], making replication difficult [19]. Evaluations of approaches to promote randomised controlled trial (RCT) participation to members of the public is an area of research need, identified as one of the top ten areas for recruitment methodology research in a recent priority-setting study [20].

Recently, online recruitment through Facebook and Google advertising has been reported to be both affordable and effective in recruiting participants to survey research [21] and trials of short duration involving web-based interventions [22, 23]. Online advertising has some advantages over more traditional promotional strategies as it is faster to implement, easier to monitor, has lower start-up costs and can potentially reach larger numbers of people quickly [24]. However, to date, most evaluations of online strategies to recruit to RCTs have focussed on recruiting younger people [24–26]. Furthermore, evidence on the effectiveness of online strategies in the recruitment of men is mixed. Two studies found online promotions less effective in recruiting men compared to women [27, 28], but one found no significant difference in gender balance between online and traditional approaches [24]. More evidence is needed to assess whether online recruitment strategies are effective in recruiting middle-aged and older men to RCTs [29].

The aim of this study was to describe and evaluate the strategies used to promote recruitment to the T4DM diabetes prevention RCT.

Methods

Setting

This observational study of recruitment strategies was set within the Testosterone for the Prevention of Type 2 Diabetes (T4DM) trial (ACTRN12612000287831). The design of the T4DM trial has been published separately [30]. Briefly, T4DM is a large, multi-centre, phase-III, double-blind, placebo-controlled, 2-year trial of testosterone therapy combined with a lifestyle intervention (‘Weight Watchers®’) compared to the lifestyle intervention alone for the prevention of Type 2 diabetes. The trial is running through six centres in Australian capital cities and recruitment occurred from January 2013 to February 2017. The trial enrolled men aged 50–74 years who were overweight or obese (≥ 95 cm waist circumference), had pre-diabetes or newly diagnosed Type 2 diabetes, and testosterone level ≤ 14.0 nmol/L. The trial is ongoing and follow-up is due to be completed in May 2019.

The T4DM trial design presented a number of recruitment challenges. Firstly, very few participants could be referred to the study by investigators at the participating centres since prospective participants were unlikely to be under the care of an endocrinologist. We therefore planned to seek prospective participants directly from the community, predicting that only one in four men screened in this non-targeted way would be eligible based on the entry criteria of elevated blood glucose and low serum testosterone. Secondly, we predicted that the placebo-controlled and injectable nature of the study treatment, as well as its 2-year duration, might limit the number of men willing to participate. Taking these two factors into account, we estimated that approximately

Trial registration: ANZCTR, ID: ACTRN12612000287831. Registered on 12 March 2012.

Keywords: Participant recruitment, Recruitment strategies, Men’s health, Randomised controlled trials, Diabetes prevention, Advertising, Social media.
20,000 men would need to be screened in order to reach the final recruitment target of 1000 participants.

**Screening and enrolment process**

Men who heard about the study through the promotional strategies to be described in this paper were invited to complete a pre-screening questionnaire online (on the T4DM study website, www.diabetesprevention.org.au), or over the telephone (by calling the central coordinating centre). Men who were eligible on the pre-screening questionnaire were emailed or posted a pre-screening patient information and consent form, instructions and a request form to attend for screening blood tests to be conducted at one of a large number of contracted pathology collection centres from one national commercial pathology provider company. Participants who were eligible on the screening blood tests were then contacted by their preferred centre to arrange a screening clinic visit. Eligible and consenting participants were enrolled and randomised at the clinic.

**Recruitment oversight and planning**

During the recruitment phase, the Steering Committee met monthly by telephone to oversee the recruitment plan and monitor the ongoing performance of recruitment strategies. The Human Review Ethics Committees approved the study’s recruitment strategies and promotional material. Where promotional activities involved real-time communication with the public; for example, through Facebook posts, the approach to be taken with these communications, and the subject matter to be covered, received ethical review and approval.

Development of the recruitment plan involved four key considerations based on marketing principles [31]: selection of the target audience, definition of the call to action, design of the promotional material and selection of promotional strategies to be used (Table 1).

**Recruitment strategies**

Recruitment strategies were coordinated centrally by the study project manager (KB). In general, nationwide strategies were implemented by staff at the central coordinating centre, while local and community strategies were implemented by site study nurses and investigators. Each strategy is described in turn below. Strategy descriptions were guided by the Template for Intervention Description and Replication (TIDieR) Checklist, which lists the items to be reported when describing interventions to support replication [19].

**Radio advertising**

Radio advertising involved 30-second paid advertisements on 20 different radio stations (nine talkback stations and 11 music stations). Three different scripts were recorded over the course of the study in order to keep the message fresh (see Additional file 1). Advertisements ran from January 2014 to July 2016, but were not run continuously on all stations over this period. Instead, advertisements ran in campaigns of 3–4 weeks’ duration, with stations running between one and seven campaigns over the course of study recruitment. In total 68 campaigns were run, 45 on talkback stations and 23 on music stations, and advertisements were played in a total of 7110 paid spots.

In addition to paid spots, stations offered bonus filler spots free of charge. In some cases these were more frequent than the paid spots and so the total number of times that study radio advertisements were run is likely to be in the range of 10,000–15,000 times.

In Australia, radio stations are generally broadcast within a single state so advertisements were booked separately for each of the five states where the study sites were located. Radio stations were selected based on advertising costs and listener demographics. To inform selection of advertising times, we sourced listener

---

**Table 1 Recruitment plan formulation**

<table>
<thead>
<tr>
<th>Planning considerations</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target audience</td>
<td>Men aged 50–74 years who were overweight or obese and living in a capital city with a participating study centre. No further restrictions were placed as other eligibility criteria were to be assessed during the screening process</td>
</tr>
<tr>
<td>Call to action</td>
<td>Prospective participants were invited to visit study website or call a central information line to learn more about the study and complete the pre-screening questionnaire</td>
</tr>
<tr>
<td>Content of promotional material</td>
<td>Content decisions were guided by qualitative research in men’s health communication preferences [32], pro-bono advice from marketing professionals, and pre-testing and ongoing feedback from study participants</td>
</tr>
<tr>
<td>Communication style:</td>
<td>• Frank, humorous and empathetic message [32]</td>
</tr>
<tr>
<td></td>
<td>• Simple, informal and easy-to-remember language</td>
</tr>
<tr>
<td>Key components of the message:</td>
<td>1. Identification of the problem: men aged 50–74 years and overweight/obese are at risk of diabetes, weight gain and urinary and sexual problems</td>
</tr>
<tr>
<td></td>
<td>2. Positioning of the study as a solution: the Testosterone for the Prevention of Type 2 Diabetes (T4DM) study can support men to lose excess weight and address related health issues</td>
</tr>
<tr>
<td></td>
<td>3. Call to action: invitation to join the study and instructions on how to join</td>
</tr>
<tr>
<td>Promotional strategies/platforms</td>
<td>Promising promotional strategies were identified by review of the published literature, discussion with the study’s industry partners, brainstorming by the Steering Committee, suggestions from study participants and pro-bono advice from marketing professionals</td>
</tr>
<tr>
<td></td>
<td>Strategies were first tested for a short period of time, and if they appeared effective and affordable, were adopted on an ongoing basis.</td>
</tr>
</tbody>
</table>
demographics (including age and gender) by time of day for each radio station. Generally, men aged 50 to 74 years were most likely to listen in the early mornings and late afternoons on weekdays, although these were also the most expensive times to advertise. A single campaign was booked on selected stations and the number of participants screened and enrolled, as well as the cost per participant screened and enrolled, were measured. Campaigns on stations with a cost of less than AUS$50 per participant screened were generally repeated. Modifications were made to the time of day that advertising was played based on the performance of previous campaigns and on advice from radio station advertising personnel.

**Mail-outs**

Mass mail-outs involved posting a study invitation package to men on the Medicare database by the Australian Government Department of Human Services (DHS). The Medicare database, the infrastructure underpinning the national health scheme, includes Australian residents who are eligible for public healthcare, generally those who are Australian or New Zealand citizens, or have permanent Australian residency status. Mailings were conducted in July 2016 (40,000 invitations sent), September 2016 (60,000 invitations sent) and November 2016 (30,000 invitations sent), with 130,000 men in total being mailed once each. Mailing recipients were randomly selected from the Medicare database based on being male, aged 50–74 years and living within close proximity of one of the study sites (the initial mailing included a sample of men living within a 20-km radius of a study site and the subsequent mailings were further restricted to men living within 5–10 km of a study site). Men who had been prescribed testosterone or anti-diabetic therapies within the previous 12 months were excluded from the mailing list by linking to the Pharmaceutical Benefits Scheme database. The invitation package consisted of a cover letter from the DHS, an invitation letter from the study Chair and a study postcard (see Additional file 1). The mailing was conducted by a third party mailing house contracted by the DHS. The contact details of mailing recipients were kept confidential and were not shared with the study coordinating centre.

In addition, a one-time mail-out by a single network of general practices (GPs) to a targeted group of their patients was conducted from February to March 2013 in one city. Though the number of letters sent in this GP mail-out was not recorded it is estimated to be less than 500 letters.

It is possible but unlikely that men who received a letter in the GP mail-out in early 2013 also later received a letter from the DHS in 2016. The responses to the small GP mail-out and the later and much larger DHS mail-out were recorded and reported separately.

**Television, radio and newspaper news coverage**

In the period January 2013 to June 2016, approximately 15 press releases and approaches to media were made. The study chose not to engage a public relations firm due to cost concerns. Instead, press releases were facilitated by site investigators and prepared by University and Hospital media offices and were distributed to local, state and national television, radio and newspaper news organisations. Press releases highlighted newsworthy aspects of the study and provided quotes from study investigators and study participants. Media office contact details were provided so that journalists could arrange interviews with investigators and participants. Over the recruitment period, nine newspaper stories, eight television stories and seven radio news stories were broadcast.

**Facebook promotions and advertising**

The study Facebook page was set up by the central coordinating centre in May 2013. Over the period May 2013 to December 2016, 94 stories were posted to the study Facebook page. Stories covered a mixture of topics including information about the study and how to join, links to news stories about the study, men’s health information and general interest stories. In addition, 23 advertising campaigns and paid boosted posts were run intermittently in the period October 2013 to December 2016 (see Additional file 2 for definitions of common Facebook advertising terms). Advertisements focussed on inviting men to join the study. By contrast, boosted stories tended to promote news stories relating to the T4DM study. Advertisements and paid boosted stories targeted men aged 50 years or older living in a capital city with a T4DM study site. Examples of advertisements and posts can be found in Additional file 1. The Facebook Ads Manager application allowed advertising performance to be monitored in real time by reporting the number of impressions, number of clicks, cost per click and cost per 1000 impressions of each campaign. While paid campaigns were running, the coordinating centre reviewed performance statistics daily and increased or decreased the advertising spend according to the success of the advertisement. Comments from participants and from the public were used to refine Facebook page content over time.

Indirect Facebook promotions were also used. When participants completed the online screening questionnaire they were invited to share information about the study on their Facebook page. Local organisations and businesses, such as sporting clubs, social clubs and healthcare providers, were also approached to share information about the study on their own Facebook pages.
We were unable to determine how many people and organisations shared information about the study on their Facebook pages.

**Google advertising**

Paid Google advertising was set up by the central coordinating centre using the Google AdWords application (see Additional file 2 for definitions of common Google advertising terms). The purpose of these advertisements was to display a link to the study website at the top of the Google search results screen when members of the public googled terms which indicated that they might be interested in joining the study. We identified four possible Google search themes: diabetes prevention, low testosterone, weight loss and nocturia (night-time urination). However, after further investigation the low-testosterone theme was rejected due to Google advertising rules and the weight-loss theme was rejected due to the high levels of competition and hence high cost. For the two remaining themes (diabetes prevention and nocturia), Google AdWords provided a list of the most commonly used related search terms, known as keywords, which we used to build our advertising campaigns (see Additional file 1). Advertising ran from July 2013 to October 2014 and October to December 2015. All advertisements were targeted to users within Australia only.

Later in the recruitment period, additional Google advertisements were run to ensure that people who searched for the T4DM study name were able to locate the website easily. Since the purpose of these advertisements was to facilitate screening of potential participants who already knew about the study rather than to promote the study to the public, these advertisements and their associated costs have not been included in this paper.

**Newspaper advertising**

In December 2013, one paid advertisement was placed in a Sunday newspaper with a circulation of 250,000 in one capital city. If effective, we planned to roll out newspaper advertising to other cities.

**Community outreach activities**

Throughout the recruitment period, site staff, and to a lesser extent, central coordinating centre staff, conducted a range of community outreach activities. These included: (1) displaying posters in local businesses, organisations, libraries and hospitals; (2) attendance at local community and health service events and (3) approaching local businesses and organisations to promote the study to their customers, members and employees. Organisations who agreed to support the study included men’s community and recreational groups, private school old boys’ associations, private health insurance companies, trade unions, government workplaces, diabetes groups and Weight Watchers®. These organisations supported the study through a variety of means including placing information about the study in their print newsletters, email newsletters, on their websites, on Facebook pages and on notice boards. The majority of community outreach activities occurred in the first year of study recruitment (2013), but continued sporadically throughout recruitment.

In addition to these unpaid promotions, one paid promotion through a professional football club based near one study site was trialled for 1 week in June 2016. The study was featured in the club’s weekly email newsletter to its 9300 members as well as in banner and gutter ads on the club’s website.

**Healthcare provider referrals and promotions**

Throughout the recruitment period we approached local general practitioners (GPs) and pathology collection centres to support study recruitment. The central coordinating centre wrote to 1024 GPs in the areas surrounding study sites to ask them to refer suitable patients to the study and to display a study poster in their waiting room areas. Site staff also attended local GP meetings to inform them about the study. We asked pathology companies to display posters in their waiting rooms and to print information about the study on the bottom of the reports of men who might be eligible for the study based on their blood test results.

**Recruitment strategy monitoring and enhancement**

The recruitment management process involved repeated cycles of strategy implementation, monitoring and enhancement. The number of participants enrolled as a result of each strategy, the direct costs and the staff effort involved were monitored in real time and reported to the Steering Committee on a monthly basis. The Committee identified the number of participants enrolled as the primary means for assessing strategy effectiveness but also considered cost-effectiveness, staff effort, potential to reach large numbers of men or to be targeted to men who were most likely to be eligible.

**Outcomes and data analysis**

**Strategy attributes**

Attributes which were thought to impact recruitment results were described for each strategy: content format (text, image, audio, audio-visual), content length (short, medium, long), approach to prospective participants (direct, indirect), level of targeting (ability to reach members of the public who were most likely to be eligible for the study in terms of age, location and health), potential reach (the number of people who would see
the strategy), frequency of exposure, and whether or not the strategy included an online component.

**Strategy exposure and contribution**
Where possible, we recorded the number of people exposed to each strategy. In addition, all men completing the pre-screening questionnaire were asked to report how they heard about the study. This information was linked to the participant's screening and enrolment status by a unique participant identifier to estimate the contribution of the strategy (the percentage of all screened and randomised participants contributed by each strategy) and to estimate how many participants heard about the study through online and traditional sources.

**Strategy cost**
The direct cost of implementing each recruitment strategy was recorded. The direct cost did not include staffing costs or the cost of conducting screening and enrolment activities. Costs were recorded in Australian dollars and were adjusted for inflation using the Australian Consumer Price Index [33]. All costs in this paper are expressed in June 2018 terms.

We determined that measuring the indirect cost of each strategy would not be feasible. Instead, we collected detailed feedback from recruitment staff (at the central coordinating centre and at study sites) in order to estimate the staff effort involved in implementing each strategy (categorised as low, moderate or high per participant enrolled).

**Overall strategy appraisal**
For each strategy, the number of participants randomised, the direct cost per participant, and the staff effort per participant were estimated and each scored 0 (lowest) to 3 (highest). Since the number of participants randomised was identified as the most important outcome, this was the primary means of assessing the effectiveness of each strategy (highly effective, effective, moderately effective, limited effectiveness, ineffective). However, the direct cost per enrolment, level of staff effort required per enrolment, and the strategy's attributes were also considered to come to a final subjective appraisal of each strategy.

**Statistical methods**
Data analysis was conducted in SAS v 9.4 (Cary, NC, USA). Simple descriptive statistics were used to describe the number of participants screened and randomised. Differences between groups in enrolment rates and in the proportion aged 60 years or older were tested using chi-square analyses with a significance level of 5%.

**Results**

**Overall study recruitment**
During the recruitment period (January 2013 to February 2017) 19,022 men were screened and 1007 were randomised to the T4DM trial. The number of men screened per month fluctuated over the recruitment period (Fig. 1), most likely influenced by the mix of promotional activities occurring at the time. Spikes in the number of men screened were observed when the trial was featured in media news stories and when radio advertising campaigns and mass mail-outs were being conducted.

**Evaluation of promotional activities**

**Number of participants recruited**
Table 2 shows the number of men screened and randomised as a result of each promotional activity. Almost 80% of participants heard of the study through one of three methods; radio advertising (42% of participants), television news coverage (20%) or mass mail-outs (17%). No other single strategy contributed more than 4% of all enrolments. Excluding strategies that resulted in fewer than ten randomisations, the randomisation rate (percentage of screened participants who went on to be randomised) did not differ between strategies ($p = 0.31$). The average randomisation rate was 5%.

The response rate to the mass mail-out by the DHS was 2.5% (3211 men screened from 130,000 letters sent); 173 of these men went on to be randomised (0.1% of all men mailed). It was not possible to calculate the response rate for other recruitment strategies; for example, radio advertising and news stories, since the denominator number of men exposed to these strategies was unknown.

**Recruitment cost**
A total of AU$598,633 was spent on promotional activities at an average cost of AU$31 per participant screened and AU$594 per participant randomised. The total direct cost and cost per participant for each strategy are shown in Table 3. The cost of individual strategies ranged from no cost (free media news coverage and word of mouth) to AU$312 per screened participant for online promotion of the study by a football club. Of the paid strategies, mass mail-out by the DHS was the most cost-effective (AU$40 per screening and AU$745 per randomisation).

**Staff time and effort**
The task of organising, conducting and monitoring promotional activities took an estimated average of 20 person-hours per week over the 4-year recruitment period. The work was divided between seven study team members (one project manager at the central
coordinating centre and six site-based study nurses) and fluctuated throughout the recruitment period. The staff effort required for each strategy, proportional to the number of participants enrolled, is estimated in Table 4. In general, paid strategies, such as advertising and mass mail-outs, required the least staff effort, while low-cost and unpaid strategies, such as community activities, required the most staff effort.

**Overall strategy appraisal**

Table 4 describes each strategy’s attributes, its ratings for the three key outcomes (number of participants enrolled, direct cost and staff effort), and a subjective appraisal of the advantages and disadvantages of the strategy. While radio advertising, television news coverage and mass mail-outs were identified as the most effective recruitment strategies, each of these strategies had at least one disadvantage in terms of cost, frequency or format.

**Response to online recruitment strategies**

Eight hundred and thirty-one people liked the study Facebook page, but engagement with content posted on the Facebook page was generally low. Unpaid posts usually received less than five likes (mostly from study staff) and few, if any, comments. Facebook-paid advertisements and boosted posts cost AU$10,029 and received 2,473,966 impressions, resulting in 21,477 clicks or other engagements. The average cost per click was AU$0.47 and the average cost per 1000 impressions was AU$4.05.

The results of the Google advertising campaigns are shown in Table 5. AU$1931 was spent on Google advertising to promote study participation, resulting in advertisements being displayed 57,202 times and clicked on 5939 times. The average click-through rate was 10% and the average cost per click was AU$0.33. We did not record how many of the people who clicked on an advertisement went on to be screened and randomised to the T4DM study.

In total, 1433 participants (8%) of participants reported hearing about the study online. However, this is likely to be an underestimation since some sources had online and offline components; for example, organisations promoted the study by publicly displaying posters and posting information on their websites, and it was, therefore, not always possible to determine whether a participant’s
### Table 2: How screened and randomised participants reported hearing about the study

<table>
<thead>
<tr>
<th>Description of associated recruitment promotions</th>
<th># Screened</th>
<th># Randomised (%)</th>
<th>Contribution (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radio advertising 7110 × 30-s paid advertisement placements across 20 radio stations</td>
<td>7667</td>
<td>418 (5%)</td>
<td>42%</td>
</tr>
<tr>
<td>TV news 8 television news stories (6 national and 2 in single cities)</td>
<td>4127</td>
<td>202 (5%)</td>
<td>20%</td>
</tr>
<tr>
<td>Mail-out by DHS 130,000 invitation letters posted to government mailing list</td>
<td>3211</td>
<td>173 (5%)</td>
<td>17%</td>
</tr>
<tr>
<td>Community promotions Posters, community events, promotion on other organisations’ websites, newsletters and Facebook pages</td>
<td>998</td>
<td>43 (4%)</td>
<td>4%</td>
</tr>
<tr>
<td>Word of mouth (not otherwise specified) N/A</td>
<td>491</td>
<td>34 (7%)</td>
<td>3%</td>
</tr>
<tr>
<td>Newspaper news 9 newspaper stories (3 major newspapers, 3 local newspapers, 2 online news sites, 1 professional magazine)</td>
<td>622</td>
<td>31 (5%)</td>
<td>3%</td>
</tr>
<tr>
<td>Healthcare provider 1024 GP clinics mailed, attendance at GP events, distribution of posters to pathology collection centres, GP’s, clinics and hospitals</td>
<td>450</td>
<td>29 (6%)</td>
<td>3%</td>
</tr>
<tr>
<td>Facebook 94 unpaid Facebook posts, 23 paid Facebook advertisements and boosted posts, requests to participants and organisations to share study on Facebook</td>
<td>369</td>
<td>16 (4%)</td>
<td>2%</td>
</tr>
<tr>
<td>Other internet Three Google AdWords campaigns, study website, links on other websites</td>
<td>410</td>
<td>15 (4%)</td>
<td>1%</td>
</tr>
<tr>
<td>Radio news 7 radio news stories (all in single cities)</td>
<td>182</td>
<td>10 (5%)</td>
<td>1%</td>
</tr>
<tr>
<td>Mail-out by GP Invitations mailed from GP clinic near to one study site. Number of invitations sent not known</td>
<td>47</td>
<td>1 (2%)</td>
<td>0%</td>
</tr>
<tr>
<td>Newspaper advertising 1 advertisement in a Sunday paper in 1 city</td>
<td>33</td>
<td>1 (3%)</td>
<td>0%</td>
</tr>
<tr>
<td>Football club promotion Email newsletter and 1 week of website advertising at one football club near to 1 study site</td>
<td>5</td>
<td>0 (0%)</td>
<td>0%</td>
</tr>
<tr>
<td>Not specified N/A</td>
<td>410</td>
<td>34 (8%)</td>
<td>3%</td>
</tr>
<tr>
<td>Total</td>
<td>19,022</td>
<td>1007 (5%)</td>
<td>100%</td>
</tr>
</tbody>
</table>

**Notes:**
- DHS Department of Human Services, GP general practitioner, N/A not applicable
- 1Where a participant reported hearing about the study from multiple sources only the primary source is shown
- 2Unless otherwise specified, strategies were implemented across all study sites
- 3Percentage of screened participants who went on to be randomised to the study
- 4Contribution defined as the percentage of all participants randomised who were randomised from a particular source

### Table 3: Direct cost of recruitment strategies

<table>
<thead>
<tr>
<th>Recruitment strategy</th>
<th>Total direct cost</th>
<th>Cost per screening</th>
<th>Cost per randomisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radio advertising</td>
<td>$451,705</td>
<td>$59</td>
<td>$1081</td>
</tr>
<tr>
<td>Mail-out by DHS</td>
<td>$128,968</td>
<td>$40</td>
<td>$745</td>
</tr>
<tr>
<td>Community promotions</td>
<td>$122(^{3})</td>
<td>N/A(^{4})</td>
<td>N/A(^{4})</td>
</tr>
<tr>
<td>Healthcare provider</td>
<td>$1272(^{3})</td>
<td>N/A(^{4})</td>
<td>N/A(^{4})</td>
</tr>
<tr>
<td>Facebook</td>
<td>$10,029</td>
<td>N/A(^{4})</td>
<td>N/A(^{4})</td>
</tr>
<tr>
<td>Google advertising</td>
<td>$1931</td>
<td>N/A(^{4})</td>
<td>N/A(^{4})</td>
</tr>
<tr>
<td>Mail-out by GP</td>
<td>$1104</td>
<td>$23</td>
<td>$1104</td>
</tr>
<tr>
<td>Newspaper advertising</td>
<td>$1941</td>
<td>$59</td>
<td>$1941</td>
</tr>
<tr>
<td>Football club promotion</td>
<td>$1561</td>
<td>$312</td>
<td>N/A(^{5})</td>
</tr>
<tr>
<td>Total</td>
<td>$598,633</td>
<td>$31</td>
<td>$594</td>
</tr>
</tbody>
</table>

**Notes:**
- DHS Department of Human Services, GP general practitioner, N/A not applicable
- 1All costs are expressed in Australian dollars. Costs have been adjusted for inflation and are expressed in June 2018 prices
- 2Excluding strategies that did not involve any direct cost (TV, radio and newspaper news coverage, word of mouth)
- 3Cost of printing and posting posters. Community promotions and contact with healthcare providers was predominantly free of direct cost
- 4Where it was not possible to differentiate participants enrolled through paid and unpaid activities; for example, paid Facebook advertising vs unpaid sharing of Facebook posts, a cost per screening and randomisation is not reported
- 5No participants were randomised as a result of this strategy. The cost per randomisation could not be calculated
### Table 4 Promotional strategy attributes, outcomes and appraisal of effectiveness

<table>
<thead>
<tr>
<th>Promotion</th>
<th>Attributes</th>
<th>Assessment of outcomes</th>
<th>Appraisal of effectiveness³</th>
</tr>
</thead>
<tbody>
<tr>
<td>TV news and current affair coverage</td>
<td>Audio-visual, medium</td>
<td>+++ + Yes +++</td>
<td>Highly effective</td>
</tr>
<tr>
<td>Mass mail-out by DHS</td>
<td>Text + image, long</td>
<td>+++ ++ +++ + No +++</td>
<td>Highly effective</td>
</tr>
<tr>
<td>Radio advertising</td>
<td>Audio, short</td>
<td>+ +++ +++ No +++</td>
<td>Highly effective</td>
</tr>
<tr>
<td>Newsletter mentions: businesses and community organisations</td>
<td>Text (+ image), usually short</td>
<td>+ + ++ + Yes ++</td>
<td>Effective</td>
</tr>
<tr>
<td>Word of mouth</td>
<td>UNK + UNK + UNK UNK ++</td>
<td>Effective</td>
<td>Advantages: no cost, trusted source Disadvantages: usually incidental</td>
</tr>
<tr>
<td>Newspaper articles: print and online</td>
<td>Text (+ image), medium</td>
<td>+++ + Yes ++</td>
<td>Effective</td>
</tr>
<tr>
<td>Publicly displayed posters</td>
<td>Text + image, medium</td>
<td>+ + ++ No ++</td>
<td>Effective</td>
</tr>
<tr>
<td>Online promotion: businesses and community organisations</td>
<td>Text (+ image), short</td>
<td>+ ++ + Yes +</td>
<td>Moderately effective</td>
</tr>
<tr>
<td>Radio news coverage/interviews</td>
<td>Audio, medium</td>
<td>+++ + No +</td>
<td>Moderately effective</td>
</tr>
<tr>
<td>Referral by GP</td>
<td>Face-to-face</td>
<td>+++ +++ + + No +</td>
<td>Limited effectiveness</td>
</tr>
<tr>
<td>Direct approach/invitation from study centre</td>
<td>Text, long</td>
<td>++ +++ + + No +</td>
<td>Limited effectiveness</td>
</tr>
<tr>
<td>Referral by pathology service (printed on bottom of path results)</td>
<td>Text, short</td>
<td>++ +++ + + No +</td>
<td>Limited effectiveness</td>
</tr>
<tr>
<td>Organic Google</td>
<td>Text, short</td>
<td>++ ++ UNK Yes +</td>
<td>Limited effectiveness</td>
</tr>
</tbody>
</table>
information source was online or offline. In younger participants (aged < 60 years) 7% reported using an online source compared to 8% in older participants (aged ≥ 60 years). The proportion of participants hearing about the study online did not differ by age (p < 0.28).

Discussion

The three most effective recruitment strategies were: (1) repeated bursts of high-frequency, targeted radio advertising; (2) infrequent but high-reach television news reports; and (3) direct, mass-mailed invitations from a credible government health agency. Other promotional strategies, including newspaper and radio news coverage, newspaper advertising, publicly displayed posters, attendance at local community events, mentions in email and posted newsletters, and promoting the study online through Facebook, Google and other websites, collectively accounted for less than 20% of all randomisations. These findings are broadly consistent with those reported by other contemporary RCTs recruiting men aged over 50 years [16, 17, 34]. While previous studies reported that community outreach activities, such as displaying posters in the local community and attending community events, were ineffective [16, 17, 34], we achieved moderate success by expanding our community outreach activities to encompass online promotion through organisations’ email newsletters, websites and Facebook pages. While the numbers of resulting participants were small, the fact that these online approaches involved no direct cost and little staff effort made them a worthwhile component of the overall recruitment strategy mix. Unlike previous studies [16, 35, 36], we found that newspaper advertising was not an effective strategy and so this strategy was abandoned after the

Table 4 Promotional strategy attributes, outcomes and appraisal of effectiveness (Continued)

<table>
<thead>
<tr>
<th>Promotion</th>
<th>Attributes</th>
<th>Assessment of outcomes</th>
<th>Appraisal of effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Format†,</td>
<td>Direct‡,</td>
<td>Targeted§,</td>
</tr>
<tr>
<td></td>
<td>length¶</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paid Google search</td>
<td>Text, short</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Facebook-paid ad</td>
<td>Text + image (+ audio-visual), short</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Community events: presentation/stand</td>
<td>Mixed</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Newspaper advertisement: print</td>
<td>Text + image, short</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Mass mail-out by GP</td>
<td>Text, long</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Unpaid post on study Facebook page</td>
<td>Text + image, short</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

†Format categorised as text, image, audio, audio-visual, face-to-face or mixed
‡Length categorised as short, medium or long
§+++ = to a great extent, ++ = somewhat, + = a little, [blank] = not at all, UNK = unknown
¶+ – – = high, – = moderate, – = low, [blank] = none
*Qualitative judgement of the effectiveness (in terms of the estimated number of participants enrolled), advantages and disadvantages of each strategy

Online newspaper advertising is a possible recruitment strategy but was not used in this study.
Our efforts to recruit participants using Facebook and Google advertising achieved disappointing results. Like others [24, 28, 38], we found such online advertising fast and flexible to implement, and easy to monitor in real time. However, unlike studies recruiting predominantly younger people [21, 25] and women [27, 28], our Facebook advertising campaigns resulted in few enrolments. While large numbers of men aged over 50 years use Facebook [39], their engagement with the study content on Facebook was low. This was likely to have constrained the reach and impact of the study’s Facebook promotions. It was unclear whether this lack of engagement was due to a deficiency in the content we posted or due to men in this age group’s social media habits more generally [38]. Future research could address this uncertainty by using the randomised split-testing capabilities built into the Facebook advertising interface to evaluate men’s responses to variations in content messaging and images [25, 28]. We also observed a disappointing response to our Google advertising campaign. We hypothesise that this failure was due to the nature of the study question focussing on diabetes prevention. Prospective participants may not have been aware that they were at an increased risk of developing diabetes. We presume they were, therefore, unlikely to search in Google for terms relating to diabetes prevention and pre-diabetes, limiting the reach of our Google advertisement. By contrast, studies that were able to define study-specific search terms, for example, relating to cessation of smokeless tobacco [22] or depression [23], reported that Google advertising was an effective and affordable recruitment strategy.

Limitations and areas for future research
Despite being rigorously conducted, the analyses presented in this paper are based on observational data. The results may be confounded by differences in the timing and target location of recruitment strategies, which we were not able control for in the analyses. Furthermore, the individual promotional strategies, by their nature, involved differences in the form, length and style of content. It is possible that differences in the observed responses to strategies were due, in some part, to these content differences rather than the promotional strategies themselves. The results observed in this study may not be generalisable to other RCTs due to the possible impact of differences in disease area, target population, study design and location.

Another limitation of this study was the difficulty in accurately measuring the contribution of each strategy to enrolment. This difficulty was two-fold. Firstly, some participants supplied insufficient information to pinpoint a specific recruitment strategy. For example, if the source of information was reported as ‘GP’ then it was unclear whether the participant was referred to the study by their GP, or whether they saw a study recruitment poster in the GP’s waiting room. Since we knew where and when particular strategies were being conducted, we cross-referenced the participant’s location and date of screening to resolve these uncertainties wherever

Table 5 Results of Google advertising campaigns

<table>
<thead>
<tr>
<th>Campaign</th>
<th>Date range</th>
<th>Maximum cost per click bid</th>
<th># Clicks</th>
<th># Impressions</th>
<th>Click-through rate</th>
<th>Total cost</th>
<th>Average cost per click</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes prevention: Campaign 1</td>
<td>Jul 13—Oct 14</td>
<td>Auto*: $1.01</td>
<td>4940</td>
<td>46,325</td>
<td>10.66%</td>
<td>$1040</td>
<td>$0.21</td>
</tr>
<tr>
<td>Diabetes prevention: Campaign 2</td>
<td>Oct 15</td>
<td>$2.00</td>
<td>684</td>
<td>4971</td>
<td>13.76%</td>
<td>$356</td>
<td>$0.52</td>
</tr>
<tr>
<td>Nocturia campaign</td>
<td>Oct 15—Dec 15</td>
<td>$3.00</td>
<td>315</td>
<td>5906</td>
<td>5.33%</td>
<td>$535</td>
<td>$1.70</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>5939</td>
<td>57,202</td>
<td>10%</td>
<td>$1931</td>
<td>$0.33</td>
</tr>
</tbody>
</table>

*An amount set by the advertiser as the maximum amount they are willing to pay per click. The actual amount paid may be less than this depending on how much other advertisers have bid

2Number of times a user clicked on the link within an advertisement

3The number of times that an advertisement was shown on screen

4The number of times an ad was clicked on, divided by the total number of times the ad was shown

5All costs are expressed in Australian dollars. Costs have been adjusted for inflation and are expressed in June 2018 prices

6The maximum bid for this campaign was set automatically by Google AdWords to optimise results
possible. Secondly, for practical reasons we coded only a single recruitment source for each participant. However, it was evident from the optional, free-text responses provided by some participants, as well as from speaking directly to study participants, that some participants heard about the study through multiple sources. In such cases, the marginal contribution of these multiple strategies could not be measured, possibly influencing the estimates of effectiveness. To address these challenges, future studies could adapt digital marketing techniques, such as custom Universal Resource Locator (URL) tracking and Google Analytics goals, to more accurately track the sources of participant recruitment. Future researchers could also conduct participant interviews early in the recruitment phase to understand the media habits and preferences of the target population and the possible impact of multiple promotional sources. Such marketing activities may require specialised skills and additional resources. Trial recruitment managers face the challenge of straddling the divide between the methodological rigour of clinical trial research and the ‘move fast and break things’ culture of digital marketing [40]. The best approach to combining these divergent paradigms is still to be determined, particularly given the ethical standards and oversight required in RCT recruitment [38].

A trial-and-error approach to optimising recruitment promotions is likely to increase recruitment costs and result in recruitment delays, yet, in the past, trial recruitment managers had little other choice due to the lack of reliable evidence. This observational evaluation presents an approach for selecting, implementing, monitoring and enhancing recruitment promotional activities. We hope that future trials can adapt and improve on this approach to meet their recruitment targets.

Conclusion
The most effective strategies to recruit men aged 50–74 years to the T4DM diabetes prevention RCT were repeated bursts of high-frequency radio advertisements supported by occasional television news coverage and mass mail-outs by a government health agency. Close monitoring of recruitment outcomes and ongoing enhancement of recruitment activities played an important role in overcoming the recruitment challenges in this RCT. This paper provides future researchers with estimates of the effectiveness of a range of traditional and online promotional strategies as well as presenting an approach to collecting and analysing promotional strategy recruitment metrics.

Additional files

Additional file 1: Examples of various promotional materials used throughout the T4DM diabetes prevention study. (PDF 2004 kb)

Additional file 2: Definitions of common Facebook and Google terms. (PDF 325 kb)

Abbreviations
DHS: Department of Human Services; GP: General practitioner/general practice; RCT: Randomised controlled trial; T4DM: Testosterone for the Prevention of Type 2 Diabetes study; TIDIEr: Template for Intervention Description and Replication Checklist; URL: Universal Resource Locator

Acknowledgements
We thank: The coordinating centre team: Caitlin Van Holst Pellekaan and Sandra Healey (NHMRC Clinical Trials Centre). The T4DM study nurses: Glenda Fraser (ANZAC Research Institute and Concord Hospital), Jenny Healy (Austin Hospital), Helen Daniels and Chyn Soh ( Fremantle Hospital and Fiona Stanley Hospital), Jody Sawyer (Princess Alexandra Hospital), Rosemary Cox and Fiona Cossey (The Queen Elizabeth Hospital), Lee Mahoney (The Kogah Institute for Medical Research). Sherilyn Goldstone (NHMRC Clinical Trials Centre) for her assistance with the preparation of this manuscript. The T4DM study participants.

Authors’ contributions
AC, DH, MG, DJ, BS, BBY, CA, RM, AK and GW (with others) designed and secured funding for the T4DM study. KB, GW and WH conceived this promotion evaluation study. KB, WH, AK, AC, DJH, MG, DJ, BS, BBY, WI, CA, RM, KPR and GW conducted and monitored trial recruitment promotions. AC, DH, MG, DJ, BS, BBY, WI, CA, RM and GW recruited participants to the trial at their study sites. KB collected the data. KB and KR performed the data analysis. KB drafted the paper. KB, WH, AK, AC, DJH, MG, DJ, BS, BBY, WI, CA, RM, KPR and GW revised and added further content. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate
The following Human Review Ethics Committees approved the study’s recruitment strategies and also, where applicable, reviewed and approved promotional material: Sydney Local Health District HREC – CRGH, Central Adelaide Local Health Network Human Research Ethics Committee, South Metropolitan Health Service Human Research Ethics Committee, Bellberry Human Research Ethics Committee.

Consent for publication
Not applicable.

Competing interests
GW has received research funding from Bayer, Lilly, Lawley Pharmaceuticals and Weight Watchers®, and speaker honoraria from Bayer, Lilly and Besins Healthcare. CA has received honoraria from Besins Healthcare and is an advisory board member for Ferring. MG has received research funding from Bayer, Novartis, Weight Watchers®, Lilly, and speaker’s honoraria from Besins Healthcare and Otsuka. DJH has received institutional grants for investigator-initiated studies of testosterone pharmacology (Lawley, Besins Healthcare) but no personal income and has provided expert testimony to anti-doping and professional standards tribunals and testosterone litigation. BBY has received speaker honoraria and conference support from Bayer, Lilly and Besins Healthcare, research support from Bayer, Lilly and Lawley Pharmaceuticals, and has been a member of advisory committees for Lilly and Besins Healthcare. All other authors declare no relevant conflicts of interest.
References


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Chapter 4. A high-volume, low-cost approach to participant screening and enrolment: Experiences from the T4DM diabetes prevention trial

4.1. Preamble

The manuscript presented in this chapter has been accepted by *Clinical trials* and is currently in press. It presents an evaluation of the centralised, semi-automated screening and enrolment process implemented in the T4DM study. This screening approach is proposed as an alternative to the costly and time-consuming site-based screening processes reported in previous diabetes prevention trials.

The supplementary materials associated with this manuscript can be found in Appendix F (screenshots from the T4DM study website).

4.1.1. Contribution of authors

GW, WH and AK conceived the screening process. KB specified, implemented and managed the screening process. KB collected the data. KB and KR analysed the data. KB, GW, WH and KR interpreted the data. KB wrote the first draft of the manuscript. KB, GW, CA, AC, MD, VG, MG, WH, DJH, WI, AJ, AK, RM, KR, BS and BBY revised and approved the manuscript.

4.2. Manuscript
Chapter 4. Screening and enrolment process

A high-volume, low-cost approach to participant screening and enrolment: Experiences from the T4DM diabetes prevention trial


* Corresponding author

Abstract

**Background/aims:** Participant recruitment to diabetes prevention randomised controlled trials (RCTs) is challenging and expensive. The T4DM study, a multicentre, Australia-based, Phase IIIb RCT of testosterone to prevent Type 2 diabetes in men aged 50 – 74 years, faced the challenge of screening a large number of prospective participants at a small number of sites, with few staff, and a limited budget for screening activities. This paper evaluates a high-volume, low-cost, semi-automated approach to screen and enrol T4DM study participants.

**Methods:** We developed a sequential multi-step screening process: i) web-based pre-screening, ii) laboratory screening through a network of third-party pathology centres, and iii) final on-site screening, using online data collection, computer-driven eligibility checking, and automated, email-based communication with prospective participants. Phone and mail-based data collection and communication options were available to participants at their request. The screening process was administered by the central coordinating centre through a central data management system.

**Results:** Screening activities required staffing of approximately 1.6 full time equivalents (FTEs) over four years. Of 19,022 participants pre-screened, 13,108 attended a third-party pathology collection centre for laboratory screening, 1217 received final, on-site screening, and 1007 were randomised. Ninety-five percent of participants opted for online pre-screening over phone-based pre-screening.
Chapter 4. Screening and enrolment process

Screening costs, including both direct and staffing costs, were AUD$1,420,909 in total (AUD$75 per subject screened and AUD$1411 per randomised participant).

**Conclusions:** A multi-step, semi-automated screening process with web-based pre-screening facilitated low-cost, high-volume participant enrolment to this large, multicentre RCT. Centralisation and automation of screening activities resulted in substantial savings compared to previous, similar studies. Our screening approach could be adapted to other RCT settings to minimise the cost of screening large numbers of participants.
Chapter 4. Screening and enrolment process

Introduction

Participant recruitment is a crucial and challenging component of randomised controlled trial (RCT) conduct, and strategies to address recruitment obstacles and to improve the efficiency of recruitment processes are needed. Trials in diabetes prevention may face particular recruitment challenges. They commonly seek to enrol an enriched participant population - those at highest risk of developing diabetes due to pre-diabetic status and/or being overweight or obese. While identifying overweight or obese participants is relatively straightforward, distinguishing those with pre-diabetes is problematic as the pre-diabetic population is largely asymptomatic and undiagnosed. Thus, identifying sufficient pre-diabetic participants through clinician referral is rarely feasible. More often, diabetes prevention RCTs have invited the community-dwelling population to participate through promotional strategies such as mass mailings, mass media coverage and advertising. This recruitment approach has high rates of screening failure, with only 2 – 21% of screened subjects enrolled in previous RCTs. To reduce unnecessary testing of large numbers of ineligible participants, diabetes prevention RCTs have adopted a multi-step screening approach with less expensive and less invasive screening tests carried out first, and more expensive and invasive assessments performed only in those most likely to meet eligibility for enrolment. Although multi-step screening minimises invasive and expensive testing, it involves additional cost and time commitment by both participants and trial staff, particularly if participants are required to return to the study site for multiple screening assessments prior to enrolment. This has been mitigated by phone- or mail-based pre-screening in some RCTs. Centralisation of screening data collection and processing has also been adopted to reduce the administrative burden on site staff, and to increase screening efficiency.

Because the yield from screening in diabetes prevention RCTs is low, methods to minimise both costs and time commitment by participants and study personnel are needed. Digital technologies may offer avenues for cheaper and more efficient screening processes. Web-based pre-screening may lessen participant and site staff burden by replacing clinic- and phone-based screening visits. Furthermore, collection of web-based screening data may facilitate automated eligibility checking, further reducing site workload. Online screening in RCTs of online and behavioural interventions has delivered
Chapter 4. Screening and enrolment process

substantial time and resource savings. Anecdotal evidence suggests that web-based screening has
been implemented in diabetes prevention RCTs including those involving pharmacotherapy
interventions, yet published evaluations are lacking in this setting.

The T4DM study

The T4DM study is a soon to be completed, Phase IIIB, multicentre, randomised, placebo-controlled
trial of testosterone for the prevention of Type 2 diabetes, or the reversal of newly diagnosed diabetes,
and the study protocol has been published. Eligible participants were overweight or obese men aged
50 – 74 years, with pre-diabetes or newly diagnosed diabetes, and serum testosterone ≤14 mmol/L.

Participants received a minimum of two (up to four) years of treatment with intramuscular
testosterone injections or matched placebo, combined with a lifestyle intervention (Weight
Watchers®). The trial is managed by a central coordinating centre at the NHMRC Clinical Trials
Centre, University of Sydney, and is conducted through six endocrinologist-led, tertiary hospital-
based sites in Australian capital cities. The initial recruitment target was 1500 participants, later
reduced to 1000 participants through modifications to the study design. Study power was maintained
by the introduction of a continuous primary endpoint. The duration of recruitment was increased from
two to four years as early recruitment to the study was slower than expected.

The T4DM study team faced several obstacles to recruitment. First, as in previous trials, sufficient
numbers of pre-diabetic participants could not be referred from investigators’ clinics, and so
prospective overweight or obese, 50 – 74 year old male participants were sought directly from the
community using a range of promotional activities. The T4DM study had the additional challenge of
seeking participants who were not only pre-diabetic but also had lowered serum total testosterone.
Based on analyses from our prior cohort studies, we anticipated that about 40 – 50% of the men
aged 50 – 74 years with pre-diabetes would have a total testosterone ≤14 nmol/L. We therefore
expected a high proportion of screened participants to be ineligible on laboratory tests for pre-diabetes
and lowered testosterone combined. Additionally, high rates of participant drop-out during the
screening process have been reported in previous disease prevention RCTs, perhaps due to lack of
perceived personal benefit of trial participation in apparently healthy volunteers. Accounting for
Chapter 4. Screening and enrolment process

both ineligible participants and screening drop-out, we planned to screen 20,000 men in order to meet the recruitment target of 1000 participants.

The T4DM study thus faced the challenge of screening a large number of prospective participants at a small number of sites, with few staff, and a limited budget for screening activities. This paper describes and provides an evaluative summary of the development, implementation and management of a high-volume, low-cost, semi-automated approach to screen and enrol participants to the T4DM study.

Methods

Screening and enrolment process

T4DM study participants were screened using a three-step process: (i) online pre-screening, (ii) laboratory screening, and (iii) on-site clinic screening (Figure 4.1). Screening assessments were ordered sequentially to minimise the screening burden on participants and to reduce cost and resource requirements.
Chapter 4. Screening and enrolment process

Step 1 Online pre-screening. Prospective participants were invited to visit the study website (www.diabetesprevention.org.au) through a range of promotional and advertising activities including television, radio and newspaper news coverage; direct, mass mailed invitations by a government health agency; radio and newspaper advertisements; publicly displayed posters and attendance at community events; promotions through community groups and businesses; and online promotions and advertising. An evaluation of these promotional activities has been published separately. The website presented general information about Type 2 diabetes, described the design of the T4DM study and the study’s eligibility criteria, and provided access to the web-based pre-screening questionnaire (see Appendix F). The website was designed to be easy to read, intuitive to navigate and to appeal to men in terms of look, feel and choice of language. The initial concept for the website was reviewed by approximately 10 members of a men’s health consumer group. Based on their feedback, the website’s design, navigation, and content were drafted. Next, the website was piloted by three men from the community and a further three men working at an affiliated University but not directly associated with trial coordination. Their feedback was incorporated into the website prior to launch. Ongoing updates and enhancements to the website were made based on feedback from study participants and on pro bono advice received from a public relations and digital marketing company. The website was initially developed with the help of a web developer and graphic designer, and ongoing content and design updates were performed by the study project manager (KB) at the coordinating centre using an open-source website content management application (Umbraco v 4.7.0, Odense, Denmark).

The pre-screening questionnaire was a bespoke, web-based application (Java v1.7, Oracle Corporation, Redwood Shores, USA) embedded within the study website. It comprised 20 yes/no and multiple-choice questions relating to: willingness to comply with study requirements, basic medical history, medication use, waist circumference, and plans for future fatherhood. It was intended to be quick and easy to complete, and to collect information that was likely to be known to the participant without the need for clinical judgement. We aimed to exclude as many ineligible participants as possible during this step, prior to any invasive screening assessments. Participants’ contact details were collected so that they could be contacted for further screening.
Online self-screening was the preferred pre-screening method to permit screening 24 hours per day, 7 days per week, and to accommodate fluctuating and unpredictable screening volumes without the need to adjust staffing levels centrally or at sites. We expected that the higher set-up cost associated with building a user-friendly, web-based questionnaire would be offset by lower ongoing costs of administering the questionnaire compared to phone-based screening. Nonetheless, participants could opt to complete the questionnaire over the phone instead of online, by calling a central information phone line. The central information phone line was located at the central coordinating centre and was staffed by members of the study coordinating team during business hours (8.00am – 4.30pm, Monday to Friday).

Eligibility on the pre-screening questionnaire was determined by a computer-driven algorithm and participants were immediately informed if they were eligible. Eligible participants received an instantaneous, automated email that included instructions for attending laboratory screening, a screening information and consent form, and a pre-filled pathology request form. Participants could also request to receive a copy of these documents by mail.

**Step 2. Laboratory screening.** Laboratory screening was performed through a national network of third-party pathology centres with 1300 locations in states with a study site. Participants’ eligibility was assessed based on glucose tolerance, testosterone and other laboratory assays by the routine methods of that pathology corporate network. Participants attending their chosen collection centre had their signed screening consent form collected and sufficient venous blood drawn to perform all required screening blood tests, including fasting and 2-hour samples for a 75g oral glucose tolerance test (OGTT). Although participants attended the collection centre only once, assays were conducted sequentially based on pre-defined rules, known as reflexing. Full blood count, 2-hour glucose levels on OGTT and HbA1c were assayed for all participants. If these measures were within the eligible ranges, serum testosterone was then promptly assayed using the stored sample. If testosterone was within the eligible range, the remaining screening assays were run, again using the stored sample. This approach saved the cost of performing unnecessary assays on ineligible participants while requiring only a single participant visit to the pathology collection centre. The advantages of blood
Chapter 4. Screening and enrolment process

collection by the third-party pathology company over collection at the study site or hospital pathology service were expected to be: standardisation of sample analysis across study sites, convenience for participants of a choice of multiple collection centre locations and longer opening hours, and reduced staffing requirements at study sites. Collection of screening blood samples by site staff would have been particularly resource-intensive for this study given the nature of the 2-hour OGTT.

Blood test results were downloaded from the pathology company’s website and matched to the participant’s record in the central data system in a validated, automated, real-time process. Participant eligibility was determined by a computer-driven algorithm. All participants, irrespective of eligibility, received blood test results directly from the pathology company by mail, and an automated email from the central coordinating centre confirming their eligibility or not. The contact details of eligible participants were automatically transferred to their selected study site to arrange on-site screening. In addition, abnormal pathology results were automatically flagged and transferred to study site staff for phone follow-up. Pre-screened participants who did not respond to the lab screening invitation were sent a series of reminders by email, short message service (SMS), phone or mail.

Step 3. On-site screening. At the clinic visit, written informed consent for trial participation was sought, final screening and baseline assessments were performed, and the participant’s eligibility was confirmed by a study investigator, prior to enrolment. Enrolment and random treatment allocation were performed using an interactive web response system (IWRS) incorporated into the central data system and, in most cases, the enrolled participant immediately received the first treatment injection.

Central data management system

The screening and enrolment processes were facilitated by the central data system (Flexetrias v5.9.4, Sydney, Australia). Bespoke, add-on modules were developed to support the online pre-screening questionnaire and laboratory data management interface. All data systems accessed by study participants and study site staff were web-based and therefore did not require any local software installation.
Chapter 4. Screening and enrolment process

Data collection

Participant enrolment data. The central data system recorded participant demographics, screening data, contact details, and screening and enrolment status. Since all data were housed within a single repository, participant enrolment metrics could be easily monitored in real-time using the system’s reporting function. Potential roadblocks were identified using reports reviewed weekly by the central coordinating staff and monthly by the study Steering Committee. Feedback received from participants by email, phone, and in-person at clinic screening, was collated and frequently reviewed by the project manager to identify and implement enhancements to the screening systems and processes. Website activity, including the number of visitors, their characteristics, and website behaviour, was tracked using the web service, Google Analytics (https://analytics.google.com).

Cost data. Screening and enrolment costs were coded to the relevant component of the screening process and tracked in the coordinating centre accounting system. Where a cost related to both screening and general study activities, the proportion relating to screening activities was estimated. Staff time spent on specific screening and enrolment activities was estimated each quarter and tracked. Staff time reported in this paper relates to screening and enrolment activities only. It does not include time spent promoting the study which has been published separately. Differences in cost compared to previous studies were based on published estimates of staff time required for screening in similar studies and were calculated using the standardised hourly rate for clinical trials coordinators and clinical trial managers including overhead costs. Costs reported in this paper are expressed in Australian dollars and have been adjusted for inflation using the Australian Consumer Price Index.

All costs in this paper are expressed in June 2018 terms.

Statistical methods

Data analyses were conducted in SAS v 9.4 (Cary, USA). Descriptive statistics were used to describe the participants completing each stage of the screening and enrolment process. Participants were classified as completing the pre-screening questionnaire online or over the phone, and differences between these groups in enrolment rates and in the proportion of participants aged 60 years or older were performed using Chi-square tests with a significance level of 5%.
Chapter 4. Screening and enrolment process

**Ethical review**

The details of the T4DM screening process and participant-facing written recruitment documents were reviewed and approved by each ethics committees overseeing the T4DM study: Sydney Local Health District HREC – CRGH, Central Adelaide Local Health Network Human Research Ethics Committee, South Metropolitan Health Service Human Research Ethics Committee, and Bellberry Human Research Ethics Committee.

**Results**

From January 2013 – February 2017, 19,022 participants were screened, and 1007 were enrolled (Figure 4.2).
Chapter 4. Screening and enrolment process

Pre-screening questionnaire completed (n=19,022)

Excluded on pre-screening questionnaire\(^1\) (n=5814)  
970 previous diabetes diagnosis  
1081 history of cancer  
2074 contraindicated medications  
580 waist circumference too small  
1209 other exclusion

Eligible for lab screening (n=13,108)

Did not attend lab screening (n=2195)

Declined lab screening (n=2383)

Attended lab screening (n=8530)

Excluded at lab screening\(^1\) (n=7313)  
6221 normal blood glucose  
546 testosterone too high  
546 other exclusion on blood tests

Eligible for clinic screening (n=1217)

Declined clinic screening/enrolment (n=108)

Excluded at clinic screening\(^1\) (n=102)  
22 contraindicated medications  
11 previous diabetes diagnosis/metformin use  
12 prostate-related exclusion  
9 cardiovascular exclusion  
9 off-study T treatment commenced/indicated  
39 Other exclusion

Randomised (n=1007)

\(^1\) Screening stopped if any ineligibility criterion was met. Men were counted only once according to the first exclusion criterion met. Therefore numbers of men with each exclusion criterion are likely to be underestimated.

Figure 4.2: Participant screening and enrolment flow
Chapter 4. Screening and enrolment process

Costs and resource use

After establishment of the data systems, screening and enrolment activities took an average of 1.6 full time equivalent (FTE) staff per year. Screening and enrolment activities were performed by three coordinating centre staff (one project manager, one data manager and one clinical trial assistant) and six study nurses (one at each of the study sites). Staff members’ residual time was spent on non-screening related activities. Screening, enrolment and randomisation activities took an estimated 11 hours of staff time per successfully randomised participant (3 hours of central coordinating staff time and 8 hours of site nurse time). The total cost of the screening and enrolment process including direct and staffing costs was AUD$1,420,909 (Table 4.1). This cost translated to AUD$75 per participant screened and $1411 per participant randomised.

Table 4.1: Cost of screening and enrolling trial participants

<table>
<thead>
<tr>
<th>Screening component</th>
<th>Description of costs</th>
<th>Cost (AUD$)¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study website</td>
<td>Website (design, implementation and management)</td>
<td>$34,076</td>
</tr>
<tr>
<td></td>
<td>Website hosting (4 years)</td>
<td>$15,253</td>
</tr>
<tr>
<td></td>
<td>Paid search promotions (Google AdWords)</td>
<td>$10,200</td>
</tr>
<tr>
<td>Pre-screening</td>
<td>Questionnaire application (design, implementation, maintenance, integration with other data systems)</td>
<td>$33,707</td>
</tr>
<tr>
<td></td>
<td>Central information phone line — staffing and call costs</td>
<td>$112,084</td>
</tr>
<tr>
<td>Laboratory screening</td>
<td>Laboratory management system (design, implementation, maintenance, integration with other data systems — screening component only)</td>
<td>$34,792</td>
</tr>
<tr>
<td></td>
<td>Postage of lab screening forms to participants (on request only)</td>
<td>$1387</td>
</tr>
<tr>
<td></td>
<td>Central information line (responding to participant inquiries regarding laboratory screening) — staffing and call costs</td>
<td>$28,021</td>
</tr>
<tr>
<td></td>
<td>Pathology assays (by contracted pathology company)</td>
<td>$461,686</td>
</tr>
<tr>
<td></td>
<td>Processing of laboratory screening results by coordinating centre staff</td>
<td>$68,977</td>
</tr>
<tr>
<td></td>
<td>Laboratory screening reminders — staffing, mail, phone call and messaging costs</td>
<td>$59,224</td>
</tr>
<tr>
<td>On-site screening</td>
<td>Implementation of IWRS (screening and enrolment component only)</td>
<td>$1992</td>
</tr>
<tr>
<td></td>
<td>Site costs</td>
<td>$559,510</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td></td>
<td><strong>$1,420,909</strong></td>
</tr>
</tbody>
</table>

IWRS: Interactive Web Response System

¹All costs are in Australian dollars. Costs are adjusted for inflation and expressed in June 2018 prices.
Chapter 4. Screening and enrolment process

Screening process evaluation

Web-based self-screening was chosen over phone-based pre-screening by almost all participants (95% and 5% respectively). The proportion of participants completing the pre-screening online was slightly higher in men aged less than 60 years (96%) than in men 60 years and older (93%) (p<0.0001). However, there was no difference in enrolment rates according to whether pre-screening was conducted online or over the phone (p=0.36) and 5% (1007/19,022) of screened participants went on to be randomised.

Pre-screening volumes fluctuated dramatically over the recruitment period. At the peak, 500 men were screened in a single hour and 1,403 in a single day, following a trial press release that attracted nationwide television news coverage. The ten busiest screening days accounted for 21% (3,979/19,022) of all screenings. In total, the study website received 123,589 visits from 96,770 unique visitors. The majority of participants (60%) accessed online pre-screening outside normal business hours.

Laboratory screening cost AUD$654,087 in total. Assay-related costs alone accounted for AUD$530,663, with a saving of $455,779 (46%) achieved through reflex rules that limited further, unnecessary assaying of samples from ineligible participants. This was despite external system issues resulting in only 19% of tests being automatically ordered and the remainder requiring daily, manual ordering at an unplanned staffing cost of approximately AUD$50,000 over the course of recruitment. Alternatively, if, instead of a single collection centre visit, participants had been required to return for additional blood collections following each assay, at least an additional 3496 participant screening visits would have been required, resulting in inconvenience to participants, risk of participant drop-out and additional collection costs.

Automation of eligibility checks and participant communications up to the point of final screening minimised the workload for site-based staff (and its associated cost). Site staff effort was focused on those men most likely to be enrolled into the study. Only 6% (1217/19,022) of prospective participants were screened at a study site, and 83% (1007/1217) of these participants went on to be randomised into the study.
Chapter 4. Screening and enrolment process

Discussion

The T4DM study incorporated centralised, online and automated elements in the screening and enrolment process to support high-volume screening at relatively low cost and with few staff. Web-based pre-screening was a key component of the success of the process. Promotion of study participation through national television news coverage resulted in fluctuating, high volumes of screening enquiries. Staffing a phone line to accommodate this volume of enquiries would have been challenging from a staff availability and training perspective, particularly since mass media coverage was often secured with little notice. Even if many more staff had been employed, the inevitable long wait times in peak demand periods may have adversely impacted recruitment. Furthermore, the majority of participants accessed online pre-screening outside normal business hours and this demand would have been expensive and impractical to accommodate through phone-based pre-screening.

Although cost is a key consideration in recruitment and screening conduct, it is rarely reported. Only three previous diabetes prevention RCTs reported the staff resource requirements for screening, with estimates per randomised participant of 69 hours (calculated based on reported 1.8 FTEs staff over 25 months), 91 hours and 98 hours (although these estimates also included the time spent by site staff on promotional activities). The screening resource requirement for the T4DM study was markedly lower than these previous studies (11 hours per randomised participant). Even after accounting for the cost of designing, implementing and managing centralised screening systems (AUD$130,020), an estimated saving of between AUD$5,443,347 (compared to 69 hours per participant) and AUD$8,230,030 (compared to 98 hours per participant) in staff resource costs was achieved through our semi-automated and centralised screening approach. A further AUD$455,779 was saved through the sequential, reflex approach to assaying of laboratory screening samples, giving a likely total saving of at least AUD$5,899,126 compared to previous RCTs. T4DM study screening and enrolment activities cost AUD$75 per participant screened and AUD$1411 per participant randomised including both direct and staffing costs. One other diabetes prevention RCT reported a direct screening cost of $2727 (adjusted to June 2018 Australian dollar terms) per participant but this estimate included the cost of trial promotional activities and did not include staffing costs of 98
Chapter 4. Screening and enrolment process

hours per participant. Comparison of screening costs between trials can be problematic due to different approaches to measuring cost and resource use, as well as the impact that eligibility criteria, trial design and location are likely to have on cost. Thus, our estimates of cost savings should be extrapolated with caution. To compare the cost-effectiveness of different screening approaches more robustly, we could have directly measured and compared the costs of our screening approach and a traditional approach, for example using a cluster-randomised or before-and-after study design. However, conducting such an experiment would have been complex, costly and impractical, and could have compromised the aims of the main T4DM study.

Close monitoring of the screening process to identify and address possible roadblocks has been recognised as a key trial management activity in several large and successful RCTs\textsuperscript{60, 76, 86} and centralised screening data collection can facilitate this process\textsuperscript{60, 76}. The T4DM study coordinating centre collected detailed, real-time screening metrics, as well as participant feedback, to enhance screening processes over the course of recruitment. Enhancements included changes to the wording of participant communications to improve readability, addition of more information to the study website, improvements to navigation in the web-based pre-screening questionnaire and the addition of screening reminders for participants who did not promptly attend for laboratory screening assessments\textsuperscript{82}. Perhaps as a result, the proportion of screened participants who went on to be randomised was increased from 3% in the first recruitment year to 5% overall. Despite restricting participation based on testosterone levels as well as glucose tolerance and recruiting only men, the T4DM study achieved a similar or higher enrolment rate than several previous large-scale diabetes prevention RCTs\textsuperscript{51-53}.

Men have been historically under-represented in diabetes prevention\textsuperscript{51, 56, 57} and weight-loss\textsuperscript{7} RCTs and have been characterised as under-users of health services more generally\textsuperscript{87}. However, it is now recognised that men will engage with health services that are tailored to their preferences\textsuperscript{88, 89}. To address men’s preferences, services can offer anonymity, confidentiality, convenience and after-hours access\textsuperscript{10}. Men may prefer to avoid demands that conflict with work times, to do their own health research and to monitor their own health before determining whether or not they need to seek help.
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from a health service provider\textsuperscript{11}. We hypothesised that an automated, web-based approach to pre-screening would address these preferences. Web-based pre-screening offered participants the convenience of 24/7 access to trial information, and the opportunity to assess their own initial eligibility before contacting trial personnel or proceeding to laboratory- and clinic-based screening. Indeed, 95\% of T4DM participants selected web-based pre-screening over the phone-based alternative. More broadly, both men and women are increasingly turning to the internet for health services and health information\textsuperscript{90} and web-based screening has been shown to be effective in RCTs of online or behavioural interventions\textsuperscript{77, 78}. Therefore, although our evaluation was set within a men’s diabetes prevention RCT, we believe that our automated, web-based pre-screening approach could also be effective and affordable to recruit other participant demographic groups. This approach may be particularly effective in RCTs seeking to screen a large number of participants or where a high screen failure rate is expected and further evaluations in other settings are thus needed.

Conclusion

A multi-step, semi-automated process with web-based pre-screening facilitated low-cost, high-volume participant enrolment to this large, multicentre diabetes prevention RCT. Screening activities cost AUD$1,420,909. Savings achieved by automating and centralising the early stages of screening are conservatively estimated at AUD$5,899,126. Our approach to screening could be adapted to a range of RCT settings and is likely to be particularly effective in RCTs which seek to screen large numbers of participants or have high rates of screening failure.
Chapter 5. Telephone call reminders did not increase screening uptake more than SMS reminders: a recruitment study within a trial

5.1. Preamble

A key component of the screening and enrolment process described in Chapter 4 was the collection of detailed recruitment data. These data were analysed to identify roadblocks in the recruitment process. One such roadblock was the substantial proportion of prospective participants who did not proceed to attend further screening assessments after completing the pre-screening questionnaire. A randomised evaluation of screening reminder interventions was conducted to determine how best to address this roadblock. This chapter presents a published evaluation of the effectiveness and cost of telephone call reminders versus SMS reminders in increasing screening uptake. The evaluation was conducted using the ‘Study Within A Trial’ (SWAT) methodology.

5.1.1. Publication details


5.1.2. Contribution of authors

K.B., G.W., W.H., A.Ke., and A.Ki. designed the evaluation presented in this article. K.B. and K.P.R. carried out the evaluation and collected the data. K.B., K.P.R., and A.Ki. performed the statistical analyses. K.B. wrote the first draft of the article. All authors revised and approved the article.

5.2. Published Manuscript
Telephone call reminders did not increase screening uptake more than SMS reminders: a recruitment study within a trial


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Abstract

Objectives: The aim of the study was to compare the response rates and costs of phone call vs. short message service (SMS) screening reminders to prospective randomized controlled trial (RCT) participants.

Study Design and Setting: This study was a randomized evaluation within a large Australian diabetes prevention RCT. Participants were men aged 50–74 years, overweight or obese, without a previous type 2 diabetes diagnosis. Those eligible on a prescreening questionnaire who did not attend a further screening assessment within 4 weeks were randomized to receive an SMS or phone call reminder (N = 709). The primary outcome was attendance for further screening assessment within 8 weeks of prescreening.

Results: Attendance was 18% (62/354) in the SMS reminder group, and 23% (80/355) in the phone reminder group, with no statistically significant difference in response according to reminder type (relative risk = 1.29, 95% confidence interval [CI]: 0.96–1.73, P = 0.09). The lower confidence limits for response to SMS (95% CI: 14–22%) and phone reminders (95% CI: 18–27%) did not include the 8-week attendance rate before this evaluation, 12%. Phone reminders cost substantially more than SMS reminders (AUD$6.21 vs. AUD$0.53 per reminder).

Conclusion: SMS reminders were as adequate a method as phone reminders to boost RCT screening uptake and were considerably more affordable. © 2019 Elsevier Inc. All rights reserved.

Keywords: Participant recruitment; Recruitment strategies; Randomized controlled trials; Telephone reminders; Text message reminders; Study within a trial

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1. Introduction

Recruitment of participants to randomized controlled trials (RCTs) is challenging, and an estimated 50% of trials fail to reach their recruitment targets [1,2]. Disease prevention RCTs face additional recruitment challenges compared with those for disease treatment, reporting higher attrition of volunteers at each stage of recruitment [3]. Several explanations for this observation have been proposed. First, disease prevention RCTs commonly seek to enroll healthy individuals who may perceive their risk of disease to be low, reducing their motivation to participate in clinical research [4,5]. Second, participants in disease prevention RCTs must usually be identified directly from the general public rather than through clinician referral [6,7]. Lack of involvement in recruitment by a potential volunteer’s personal clinician may leave an individual unsure about the suitability of the trial for them [8] or misunderstanding the trial processes [4], reducing interest in participation.

In RCTs where attrition during early recruitment and initial screening phases is important, interventions to address participant uncertainty and low motivation may boost recruitment, saving time and money. In studies evaluating the use of participant reminders [9–11], phone calls increased RCT enrollment among individuals who failed to respond to an initial mailed invitation compared with no reminder [10] and to a mailed reminder [11]. Also, a series of four short message service (SMS) reminders increased enrollment (compared with no reminder) among participants who did not respond after initial screening [12]. Elsewhere, health services research shows strong evidence that SMS reminders are as effective as phone call reminders for improving attendance at clinic appointments [13–15]. However, to our knowledge, no randomized evaluation has been published comparing SMS and phone reminders to improve recruitment to RCTs [16]. Unlike an SMS, a phone call reminder provides the opportunity to build rapport and to clarify specific uncertainties, arguably more important for participants interested in joining a disease prevention RCT than for patients due to attend a pre-booked clinic appointment for disease management. By contrast, SMS reminders have the advantage of being cheaper [13], less intrusive, and providing written information that participants can refer to later.

Men are underrepresented in disease prevention and health promotion RCTs [7,17] despite experiencing higher rates of avoidable mortality than women [18]. In the past, men have been mischaracterized as disinterested in health promotion and disease prevention, but there is growing recognition that men care about their health and engage with health services if they are tailored to their needs [19,20]. Men may prefer to monitor their own health and gather information independently before making the decision to engage with professional health services [21]. We hypothesized that SMS reminders may address this preference for independent decision-making in our male participants.

This study within a trial (SWAT) aimed to compare, in randomized fashion, the efficacy and cost-effectiveness of phone call and SMS reminders in improving attendance for screening assessments for a large multicenter diabetes prevention RCT (registered as SWAT 88 on the SWAT repository).

2. Methods

2.1. Setting

This reminder study was conducted in the context of the Testosterone for Diabetes Mellitus (T4DM) trial. The design of the T4DM study is published elsewhere [22], but briefly, T4DM is a Phase III, multicenter, double-blind, placebo-controlled trial of testosterone for the prevention of diabetes or reversal of newly diagnosed diabetes (trial registration ACTRN12612000287831). The trial is run through six Australian hospital-based centers and is coordinated by a central university-based coordinating center. Eligible T4DM participants were men aged 50–74 years, obese or...
overweight, with prediabetes or newly diagnosed type 2 diabetes, and a serum testosterone ≤14 mmol/L. The trial used a three-step semiautomated approach to participant screening (Fig. 1). Men from the general population were invited to complete a prescreening questionnaire (Step 1), either online or over the phone. Those who were eligible were then invited by e-mail or mail to attend one of 1,300 contracted pathology collection centers for laboratory screening tests (Step 2), and if eligible, for final screening and study enrollment at the nearest study center (Step 3).

2.2. Rationale for the reminder study

Of participants who were eligible on the prescreening questionnaire before the commencement of this reminder study, approximately 50% attended laboratory screening within 4 weeks of prescreening. Nonattenders received up to 10 screening reminders per year, including an automated e-mail reminder at 4 weeks after prescreening, quarterly e-mail and SMS reminders, and approximately annual phone call and postal reminders. Despite these reminders, only 12% of nonresponders at 4 weeks proceeded to attend by 8 weeks, and a further 8% proceeded to attend after 8 weeks. In total, 40% of all potentially eligible participants did not proceed past prescreening, representing a substantial missed recruitment opportunity. This reminder study was conceived to evaluate the impact on laboratory screening rates of phone call or SMS reminders at 4 weeks after prescreening.

2.3. Design of the reminder study

The reminder study was a parallel-group RCT. Individual participants were randomized in a 1:1 ratio to receive either an SMS or phone call reminder 4 weeks after completing the T4DM prescreening questionnaire if they had not attended laboratory screening within 4 weeks of prescreening. Participants were excluded if they had declined laboratory screening. All participants had previously consented to receive reminders as part of the standard prescreening consent process; therefore, further consent to randomization was deemed unnecessary.

2.4. Interventions

2.4.1. SMS screening reminder

SMS reminders were sent by the central coordinating center within 1 to 2 days of randomization using an online bulk SMS service. The SMS reminder message (see text below) was designed to provide key enrollment information as well as including a peripheral cue based on the concept of social proof [23] (looking to the actions of others for reassurance in situations of uncertainty) to encourage action by the study participants.

---

Fig. 1. Testosterone for Diabetes Mellitus study screening process and reminder study design.
SMS reminder text

It’s not too late to join the T4DM study. [Number] men around Australia are already taking part. Why not book your blood tests today?
Text FORMS if you need another copy of your blood test forms. Text DECLINE to opt out.
More info: askt4dm@ctc.usyd.edu.au or 1300865436.

2.4.2 Phone screening reminder

Phone reminders were conducted by two staff at the central coordinating center. Calls were made within 4 days of randomization with one further attempt made if the first call was not answered. If the participant could not be reached on the second attempt, a voicemail message was left, if possible. Staff members were provided with a reminder call script, which included the following discussion points:

- Reminding the participant that they had registered for the T4DM study
- Asking if they were still interested in joining the study
- Explaining that the next step was to attend for their laboratory screening tests and explaining what this involved
- Asking if they needed to have another copy of their laboratory screening forms sent to them
- Asking if they had any other questions about laboratory screening or joining the T4DM study in general
- Giving the participant the opportunity to decline further study screening and enrollment

2.5 Ethics

The use of phone and SMS screening reminders was approved by each ethics committee overseeing the main T4DM study: Sydney Local Health District HREC—CRGH, the Human Research Ethics Committee (TQEH/LMH/MH), the South Metropolitan Health Service Human Research Ethics Committee, and Bellberry Human Research Ethics Committee.

2.6 Outcomes

The primary study endpoint was attendance for laboratory screening within 8 weeks of prescreening completion (i.e., within 4 weeks of receiving the phone or SMS reminder). Attendance at the collection center was determined using assay results uploaded electronically, in real time, by the contracted pathology company and imported into the main study’s clinical data management database using a validated process.

The secondary endpoint was the cost of performing the reminders. Total cost was made up of direct and indirect (staffing) costs. The direct cost of SMS reminders was measured by referring to invoices and billing information from the bulk SMS service. The direct cost of phone reminders was estimated based on the flag fall and per minute costs of calling a mobile number from the coordinating center. This information was combined with the average call duration to calculate an average phone call cost. The time taken to conduct SMS and phone reminder calls was estimated by maintaining a log of the time spent on reminders over two 1-week periods, one at the beginning of the reminder study, and one at the end. Time tracking included not only the time to make or send the reminder but also the time to reply to participant questions either by phone or SMS. This information was combined with the hourly staffing cost to calculate the indirect (staffing) cost. All costs are quoted in Australian dollars.

2.7 Sample size

Based on prior experience, a response rate of 17% in the SMS reminder arm was assumed. To achieve 80% power, with a two-sided significance level of 5%, 540 participants would be required to detect a 10% higher response rate in the phone reminder compared with the SMS arm (27%). If the response rate in the SMS arm were only 14%, 540 patients would have more than 95% power to detect an increase in response to 27% in the phone arm. Ten percent was chosen as the likely minimum effect that would be considered operationally meaningful.

2.8 Randomization

Confirmation of eligibility and randomization was performed weekly by a central, automated computer system. After confirmation of eligibility, men were randomized by minimization and stratified by center, age group (50–59, 60–64, 65–69, 70–74 years), and participant’s screening questionnaire completion method (online or phone).

2.9 Statistical methods

All analyses were performed according to the intention to treat principle. Baseline characteristics were summarized using counts and percentages for categorical variables, and mean and standard deviation for continuous variables. Intervention groups were compared using a chi-square test. Relative risks (RRs) and 95% confidence interval (CI) were used to summarize this effect. P values for interaction terms were obtained from logistic regression. Subgroup analyses for age (50–64 and 65–74 years), how men heard about the study (mail, radio, other), and prescreening questionnaire completion mode (online vs. phone) were prespecified in the protocol. However, as 98% of men completed their screening questionnaire online and only 2% by phone, this subgroup analysis was not undertaken. Cost-effectiveness was estimated by calculating incremental cost-effectiveness ratios (ICERs). No adjustments were made for multiple comparisons. Analyses were performed using SAS v 9.4 (Cary, NC).
3. Results

The T4DM study was open to recruitment from January 2013 to February 2017. In that time, 19,022 participants were screened, and 1,007 were randomized. The reminder study opened to recruitment in June 2016 and closed in October 2016, the week that the calculated sample size was attained. During that period, 2,315 participants were screened to the main study, and 709 of them were eligible for the reminder study (having neither attended nor declined laboratory screening within 4 weeks of completing the screening questionnaire). All 709 eligible participants were randomized, with 354 men allocated to SMS reminders, and 355 men to phone call reminders (Fig. 2). Of the 709 men who participated in the reminder study, 142 (20%) attended for laboratory screening within 8 weeks, and 28 (4%) went on to be enrolled in the main T4DM study. Enrollment was ceased the week that the calculated sample size was reached. Characteristics of the men participating in the screening reminder study are shown in Table 1, with the two intervention arms well-balanced.

3.1. Reminder delivery

Of participants randomized to receive an SMS reminder, 312 of 354 (88%) were sent the reminder, with the remaining 25 participants not sent a reminder due to having attended laboratory screening before the reminder could be sent, having provided an invalid mobile phone number or having only provided a landline number (Fig. 2). By comparison, of the participants randomized to receive a phone reminder, staff spoke to 237 of 355 (67%) and left a voicemail for an additional 38 (11%). The remaining 99 participants did not receive a phone reminder due to having attended laboratory screening before the reminder phone call could be made, having provided an invalid phone number, or having not picked up the phone reminder calls and having no facility to leave a voicemail message. All participants were followed for response and included in the analysis, regardless of whether the allocated intervention was delivered or not.

3.2. Response to the reminder

There was no statistically significant difference in response to phone vs. SMS reminders (23% vs. 18%, respectively, RR = 1.29, 95% CI: 0.96–1.73, \( P = 0.09 \); Table 2). The difference in response was not affected by how men heard about the study (\( P = 0.13 \); data not shown). However, in older men (aged 65–74 years), compared with younger men (aged 50–64 years), there was a trend for greater uptake in the phone compared with the SMS arm (39% vs. 15%, RR = 2.26, 95% CI: 1.12–4.56; \( P \) for age interaction = 0.07). This difference could not be explained by higher success rates in reaching men by phone in the older group. In fact, a higher proportion of younger men were contactable by phone, with staff successfully speaking to 68% of men aged 50–64 years and 59% of men aged 65–74 years.

![Fig. 2. Reminder study CONSORT diagram.](image-url)
3.3. Cost of reminders

The cost of phone call reminders ($6.21 per reminder) was more than 10 times that of SMS reminders ($0.53 per reminder), with most of the additional cost due to the additional staff time required to make the phone calls (Table 3). Staff spent approximately 4 minutes on each phone call reminder made. By comparison, the staff time per SMS reminder was negligible. It took a total of 3 minutes to send an entire batch of SMS reminders, irrespective of the number of reminders included.

The ICER of phone call reminders compared with SMS was AU$112.05, meaning that if reminders were made by phone, an additional AU$112.05 would be spent for each additional participant who attended laboratory screening. However, in men aged 65–74 years, the ICER for phone calls compared with SMS reminders was consequently lower (AU$31.45 compared with the overall ICER of AU$112.05).

4. Discussion

4.1. Summary of findings

In this randomized evaluation of screening reminders, there was no statistically significant difference in response to phone call and SMS reminders (RR = 1.29, 95% CI: 0.96–1.73, \( P = 0.09 \)). However, the overall attendance rate in those who received a phone or SMS reminder was 20% at 8 weeks, compared with the previously observed attendance rate of 12% in the main study. As in similar studies [13,14], we found that phone reminders were substantially more expensive to perform than SMS reminders (AU$6.21 vs. AU$0.53 per reminder). We hypothesize that the personal nature of phone reminders may have been more important to participants aged 65 years, as in that subgroup, we observed a higher response rate to phone reminders (33% compared with 15% to SMS reminders), and the ICER for phone calls compared with SMS reminders was consequently lower (AU$31.45 compared with the overall ICER of AU$112.05).

4.2. Implications for future practice

SMS messages are an effective communication tool in various healthcare settings including reminders for clinic appointments [13,24], repeat testing after mass screening [25,26], and adherence to treatment regimens [27,28]. Still, published accounts of using SMS reminders to boost recruitment to RCTs remain scarce. Our results provide evidence that SMS reminders may be an appropriate lower cost, but similarly effective, alternative to phone reminders in the RCT recruitment setting. SMS reminders may be particularly worthwhile when phone reminders are not feasible due to the large numbers of reminders to be made or the limited trial budget available for reminder activities.

4.3. Limitations and areas for future research

The overall response rate to reminders in our study (20% by 8 weeks) was higher than that has been reported in previous reminder studies (13% [11], 12% [10], 8% [9], and 3.5% [12]). A possible explanation for the higher rate may be that the recipients of reminders in our study had

Table 1. Characteristics of all reminder study participants (N = 709)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>SMS reminder at 4 wk, (n = 354)</th>
<th>Phone reminder at 4 wk, (n = 355)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD, y</td>
<td>58.5 ± 6.0 y</td>
<td>58.1 ± 6.0 y</td>
</tr>
<tr>
<td>Center</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Center 1</td>
<td>89 (25%)</td>
<td>90 (25%)</td>
</tr>
<tr>
<td>Center 2</td>
<td>74 (21%)</td>
<td>76 (21%)</td>
</tr>
<tr>
<td>Center 3</td>
<td>69 (19%)</td>
<td>66 (19%)</td>
</tr>
<tr>
<td>Center 4</td>
<td>57 (16%)</td>
<td>54 (15%)</td>
</tr>
<tr>
<td>Center 5</td>
<td>38 (11%)</td>
<td>42 (12%)</td>
</tr>
<tr>
<td>Center 6</td>
<td>27 (8%)</td>
<td>27 (8%)</td>
</tr>
<tr>
<td>Prescreening completion method</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Online</td>
<td>350 (99%)</td>
<td>348 (98%)</td>
</tr>
<tr>
<td>Information line (phone)</td>
<td>4 (1%)</td>
<td>7 (2%)</td>
</tr>
<tr>
<td>How they heard about the study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mail-out</td>
<td>197 (56%)</td>
<td>195 (55%)</td>
</tr>
<tr>
<td>Radio</td>
<td>123 (35%)</td>
<td>121 (34%)</td>
</tr>
<tr>
<td>Other/not specified</td>
<td>34 (10%)</td>
<td>39 (11%)</td>
</tr>
</tbody>
</table>

Abbreviations: SD, standard deviation; SMS, short message service.

Table 2. Response to reminder delivered 4 weeks after completing prescreening^a^

<table>
<thead>
<tr>
<th>Recruitment outcome</th>
<th>SMS reminder (n = 354)</th>
<th>Phone reminder (n = 355)</th>
<th>RR (95% CI)</th>
<th>P value</th>
<th>Interaction P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attended laboratory</td>
<td>62 (18%)</td>
<td>80 (23%)</td>
<td>1.29 (0.96–1.73)</td>
<td>0.09</td>
<td></td>
</tr>
<tr>
<td>Attended laboratory by age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50–64 y</td>
<td>53/292 (18%)</td>
<td>60/294 (20%)</td>
<td>1.12 (0.81–1.57)</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td>65–74 y</td>
<td>9/62 (15%)</td>
<td>20/61 (33%)</td>
<td>2.26 (1.12–4.56)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Randomized to T4DM trial^b^</td>
<td>6 (2%)</td>
<td>9 (3%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; RR, relative risk; T4DM, Testosterone for Diabetes Mellitus.

^a^ Response defined as attendance for laboratory screening tests by 8 wk after completing prescreening.

^b^ Participants who attended laboratory screening within 8 wk after completing prescreening and went on to be randomized to the main T4DM trial at any time following laboratory screening. The study was not powered for this outcome; therefore, statistical testing is not presented.
already completed a prescreening questionnaire, selecting for willingness to participate in the trial. In addition, the responses to phone and SMS reminders were evaluated in the context of our existing screening processes, including email and SMS communications with participants after prescreening (Fig. 1), and these communications may have increased the observed response rate. These factors may impact the generalizability of our results. For example, it remains possible that phone reminders remain superior to SMS reminders in situations where participants are yet to respond to the initial invitation to participate in the trial and where no prior communications have been sent to participants. Furthermore, the T4DM study recruited only men aged 50–74 years. Our findings suggest that older participants may prefer phone reminders, and this has implications for RCTs recruiting participants who are older or younger than those included in our study. We hypothesize that SMS reminders may have been particularly appealing to our all-male participant cohort because they supported men to make an independent decision about trial participation. Reminder preferences in women may therefore differ and would merit investigation.

In a nonrandomized comparison, we found that attendance following either SMS reminder (18%, 95% CI: 14–22%) or phone reminder (23%, 95% CI: 18–27%) was higher than the previously observed attendance rate at 8 weeks of 12%. We elected not to include a “standard care” arm (neither phone call nor SMS reminder) in this randomized evaluation due to concerns that it might hamper the main study, particularly given the existing evidence on the effectiveness of screening reminders [9–11]. Future studies, if conducted earlier in their host trial’s recruitment phase, could include a “standard care” or no reminder arm. This would allow calculation of a reminder cost per randomized participant to guide decisions about whether reminders (either phone or SMS) are more or less cost-effective than other strategies designed to boost recruitment, for example, mass mail outs or advertising to invite more people to participate in the study.

In addition to the analyses reported here, we conducted an exploratory evaluation of subsequent reminders conducted more than 8 weeks after prescreening. These data are not shown here but suggested that a subsequent phone reminder to men who did not respond to an initial SMS reminder was almost three times more effective than a further SMS reminder (13% and 5%, respectively). Thus, further investigation of the impact of subsequent reminders may be of merit.

We reported higher reminder delivery in the SMS group (88% delivered) compared with the phone group (67% delivered, 78% if voicemail messages are also included). However, this apparent difference in intervention delivery fidelity is likely to be an artifact of how delivery was measured in each group. For phone reminders, we recorded whether the participant was spoken to on the phone or if a voicemail message was left. For SMS reminders, we could record only whether the SMS message was sent without bouncing back. We could not determine whether the participant received and read the SMS reminder. Thus, the actual delivery rates in each arm may be more similar than our estimates suggest. Furthermore, any difference in reminder delivery fidelity between the arms would likely also occur if these reminders were incorporated into practice.

The SMS reminder message in this evaluation included key information about trial participation and informed the participant that large numbers of men had already joined the trial, a peripheral cue to action based on the concept of social proof. This approach is underpinned by the Elaboration Likelihood Model of persuasion [23], which states that persuasion to action can occur through either a central (cognition-based) or peripheral (cue-based) route, with the peripheral route requiring less motivation and effort to process. Elsewhere, messages of scarcity (communicating that limited numbers of places are available) [9] and quotes from participants [12] were effective in boosting RCT recruitment using SMS reminders. Future research could extend these findings by evaluating manipulations in the content of SMS reminders using a theory-based approach [29,30]. It is possible that by optimizing the content of SMS reminder messages, response rates can be further improved.

5. Conclusion

Compared with SMS reminders, phone call reminders were more costly and did not significantly increase the screening uptake rate of nonresponders in this large multicenter RCT. There was some suggestion that phone call reminders were more effective than SMS reminders in men aged 65 years. SMS reminders were substantially cheaper and quicker to perform than phone call reminders, making them a promising approach for boosting recruitment in RCTs with limited budgets.

Acknowledgments

The authors thank the coordinating center team: Caitlin Van Holst Pellekaan and Sandra Healey (NHMRC Clinical Trials Center); the T4DM study nurses: Glenda Fraser (ANZAC Research Institute and Concord Hospital), Jenny Healy (Austin Hospital), Helen Daniels and Chyn Soh (Fremantle Hospital and Fiona Stanley Hospital), Jody Sawyer (Princess Alexandra Hospital), Rosemary Cox and Fiona

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Table 3. Cost of performing SMS and phone reminders

<table>
<thead>
<tr>
<th>Cost component</th>
<th>SMS</th>
<th>Phone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct cost per reminder</td>
<td>$0.18</td>
<td>$0.54</td>
</tr>
<tr>
<td>Cost of staff time per reminder</td>
<td>$0.35</td>
<td>$5.67</td>
</tr>
<tr>
<td>Total cost per reminder</td>
<td>$0.53</td>
<td>$6.21</td>
</tr>
</tbody>
</table>

* All costs are quoted in Australian dollars.
Cossey (The Queen Elizabeth Hospital), Lee Mahoney (The Keogh Institute for Medical Research); Sherilyn Goldstone for her assistance with the preparation of this article; and the T4DM study participants.

References


Chapter 6. Conclusions

This research addressed a clear gap in the literature on clinical trial recruitment. I aimed to identify and evaluate strategies to recruit men to clinical trials. To achieve this aim, I performed a systematic review of recruitment strategies in trials of men aged 50 years and older. I then conducted a program of recruitment evaluations set within a large trial, the T4DM diabetes prevention study. In this chapter, I present my key findings, discuss implications for recruitment practice and outline opportunities for future research.

6.1. Summary of key findings

In Chapter 2, I presented a systematic review including 16 previous studies of recruitment strategies in trials of men aged 50 years and older. Nine of the 16 studies were set within prostate cancer trials, with the remainder in benign prostatic hyperplasia, testosterone supplementation, suicide prevention and other cancer trials. Of the included studies, nine evaluated strategies to identify prospective participants; the remainder addressed further steps in the recruitment pathway, including assessment of eligibility, provision of participant information and seeking of consent. The most effective strategies for identifying prospective participants were referral through an affiliated health service, media coverage and mass mailings. Recruitment was also improved by site-based training designed to address trial-specific recruitment challenges. Only one of the 16 studies was of good quality, with the remaining 15 of fair or poor quality as assessed using tools developed by the National Heart, Lung and Blood Institute. The most common source of potential bias was inadequate reporting of the recruitment interventions, how they were delivered and how much they cost. None of the included studies presented strategies to recruit men to diabetes treatment or diabetes prevention trials.

In Chapter 3, I evaluated the range of promotional strategies used to identify prospective participants to the T4DM trial. I found that repeated, high-frequency bursts of paid radio advertising; infrequent but high-reach television news coverage; and direct, mass mailed invitations from a government health agency were the most effective strategies. Promotions through community groups and local businesses, online advertising, referral by general practitioner, free of charge news coverage in
Chapter 6. Conclusions

newspapers and on radio stations, and paid newspaper advertising were also implemented but were less effective. Men were not offered any monetary incentives to participate in the trial.

In Chapter 4, I presented a centralised, semi-automated approach to screening and enrolling participants to the T4DM trial. This approach delivered high-volume, low-cost participant recruitment. Efficiencies were achieved by offering participants an online, self-administered pre-screening questionnaire; conducting laboratory eligibility screening through a network of third-party pathology laboratories and automating participant email communications. The T4DM screening and enrolment process achieved substantial cost savings when compared to other similar diabetes prevention trials. Savings were estimated at between 76% and 112% of the entire T4DM trial budget. Thus, the T4DM study would certainly not have been feasible without the cost savings achieved through this high-volume, low-cost screening process.

The T4DM screening and enrolment process was closely monitored using centrally collected metrics to identify and address roadblocks. One such roadblock was the failure of almost half of the participants to attend for further screening assessments in a timely manner after completing the pre-screening questionnaire. In Chapter 5, I compared two interventions to encourage these participants to attend for further screening assessments: SMS and telephone call reminders. I found no significant difference in screening uptake between these two types of reminders, although SMS reminders cost substantially less than telephone call reminders. Either type of reminder increased screening uptake compared to neither reminder. SMS reminders were thus an adequate and affordable strategy for increasing screening uptake.

On average, 5% of screened men went on to be randomised into the trial and this proportion did not differ across promotional strategies. Men aged ≤ 59 years were less likely than older men to attend for lab screening after completing the pre-screening questionnaire (analyses not shown). I was unable to assess the representativeness of the recruited sample for other characteristics such as waist circumference, weight or educational status as these characteristics were collected at the clinic-based screening visit and were therefore unknown in men who were found to be ineligible or who declined participation prior to this point.
6.2. Implications for recruitment practice

6.2.1. Estimates of the cost and effectiveness of recruitment strategies

This thesis presents estimates of the cost and effectiveness of recruitment strategies including: a range of recruitment promotion activities, a centralised, semi-automated process for screening and enrolling participants and the sending of two different types of participant screening reminders. Future trials may find the cost estimates presented in this research particularly useful since previous recruitment studies have rarely reported recruitment costs\(^\text{34, 42}\). This lack of published cost evidence has made it difficult to estimate and justify the costs of recruitment in study budgets and grant applications. My research addresses this gap. Nevertheless, care should be exercised when seeking to generalise my research findings. The findings were derived from a specific participant population: relatively healthy, predominantly city-dwelling Australian men aged 50–74 years being invited to participate in a diabetes prevention trial. Thus, my findings are likely to be most relevant to trials seeking to enrol a similar participant population.

Recently, researchers have proposed a set of criteria to determine whether further replication of existing trial methodology research findings are justified\(^\text{91}\). Based on these criteria, replication of my evaluations is likely to be of merit to increase GRADE certainty and to broaden the context of the findings. It is too early to say with certainty that the strategies that I assessed as being effective in the T4DM trial would be effective more broadly. Nonetheless, my research provides a program of promising recruitment innovations for trialists to adopt and adapt.

6.2.2. Recruitment methods

Given the diversity of participant populations and trial settings, it is unlikely that there will ever be sufficient high-certainty evidence to guide recruitment in all trials, or even in most trials. It is more likely that trialists will need to consider the available evidence, even though esoteric, and seek to generalise this evidence to their own trials. In this context, the accurate and transparent reporting of recruitment methods is a crucial element in producing useful recruitment research. If recruitment
Chapter 6. Conclusions

research is to guide future practice then good-quality reporting of recruitment methods is as important, if not more important, than the reporting of recruitment outcomes.

Methods for implementing recruitment strategies

It is widely acknowledged that the current quality of intervention reporting in recruitment research is poor33, 34, 36, 43. In the systematic review presented in Chapter 2, I found that inadequate reporting of recruitment strategy procedures, how they were delivered and how much they cost was a source of bias in most included studies. To address this gap, I have provided detailed reporting of all evaluated recruitment methods, including their rationale, design, content, implementation, location, duration, frequency and cost. This approach is intended to assist trialists to interpret my findings, assess their generalisability and replicate them in future trials. The methods described in this thesis are likely to be relevant to a broad range of trials not limited to men aged over 50 years, particularly those trials seeking to promote participation directly to the public, and those seeking a low-cost approach to screening large numbers of participants.

Methods for assessing recruitment strategy effectiveness

Even as the recruitment evidence base expands, trialists should continue to pilot recruitment strategies within their own trials before settling on a recruitment plan4. For trials using advertising and media coverage to boost recruitment, piloting will be particularly important due to the constantly evolving nature of the marketing sector. By the time recruitment promotion findings are published, the relevance of the findings to future research will already have been reduced by publication delay92. Accordingly, trialists should be encouraged to design an initial recruitment plan based on the available evidence and to enhance this plan over the course of recruitment by assessing the effectiveness of strategies within their specific setting.

In my systematic review, I observed that previous recruitment promotion evaluations did not clearly report how they had assessed promotion effectiveness. Studies most commonly reported the number of participants recruited as a result of a promotional strategy as a surrogate outcome for strategy effectiveness. However, this outcome is not a sufficient indicator of strategy success; a strategy might
Chapter 6. Conclusions

contribute a large proportion of recruited participants simply because few other strategies were implemented. Furthermore, this outcome gives no indication of cost effectiveness, though cost is likely to be a key driver in the selection of promotional strategies. I addressed this gap in Chapter 3 where I proposed a novel approach for judging the effectiveness of recruitment promotions by qualitatively assessing the promotion’s attributes (format, length, directness, targeting, reach, frequency) and recruitment outcomes (contribution, direct cost, staff effort). This approach would be straightforward for future trials to adapt and need not be limited to specific trial settings or participant populations since the importance of each of the factors to be considered may be modified to suit the trial setting. For example, for trials with small recruitment budgets cost may be the primary factor for assessing promotional activities, while for other trials the number of participants recruited may be the key consideration. To my knowledge, this approach has not been presented in previous research. Replication in a range of trial settings is likely to be of merit.

6.2.3. Adapting recruitment strategies to address men’s needs

In the past, men have been characterised as disinterested in their health and unwilling to attend healthcare services63. However, this has been refuted by more recent research that has demonstrated that men do care about their health and will access healthcare services that address their needs and preferences10, 64. Several previous large diabetes prevention trials conducted in the United States and Europe failed to achieve gender balance51, 54, 57; men were underrepresented despite being at higher risk of developing diabetes47. The T4DM recruitment plan incorporated evidence from the literature on men’s health preferences and help-seeking behaviours to tailor recruitment strategies to men’s needs8, 9, 11, 12. Advertising material used humour to engage men and delivered a frank message about men’s possible risk of diabetes and related health problems. The study website provided men with the opportunity to complete pre-screening independently at a time convenient to them. Likewise, collection of blood for laboratory screening through a network of third-party pathology collection centres enabled men to attend a location near work or home, and to attend on the weekend if preferred. Regular screening reminders were incorporated into the screening process, designed to
Chapter 6. Conclusions

maintain men’s awareness of the study while allowing men to proceed with trial participation at a time they judged to be appropriate. SMS screening reminder messages were implemented as this direct but impersonal approach was expected to appeal to men. This research demonstrates the feasibility of adapting recruitment strategies to address previously documented men’s healthcare needs and preferences. This approach would be straightforward to adapt in future men’s health trials and, more broadly, in any trials seeking to enrol men.

6.3. Opportunities for future research

6.3.1. Gender-sensitised strategies to recruit men to trials

As discussed, the T4DM recruitment plan sought to address men’s needs and preferences. The results observed during T4DM trial recruitment accord with the broader literature on men’s health research\(^8\), \(^9\), \(^12\), \(^13\), \(^64\). Large numbers of men were recruited through the frank and humorous radio advertisements. Additionally, most men (95%) opted to self-administer the pre-screening questionnaire online rather than complete it over the phone with a member of the study team, and 60% of pre-screening questionnaires were completed outside normal business hours. Telephone call reminders, providing the opportunity for personal interaction with study staff, were no more effective in increasing screening uptake than impersonal but direct SMS reminders. However, while these recruitment strategies were designed to address men’s preferences, and resulted in the successful recruitment of 1007 participants, I was not able to assess whether these approaches were more, or less, effective than non-gender-sensitised approaches. Further qualitative research to explore participant satisfaction with recruitment by interviewing men about their motivations for joining the T4DM study, and their experiences with the recruitment process is currently underway but is outside the scope of this thesis. Future studies could compare gender-sensitised recruitment approaches to standard approaches, using a cluster randomised design, to assess the effect of gender-sensitisation on recruitment numbers.

If effective in recruitment, similarly gender-sensitised approaches could be extended to other aspects of trial conduct. For example, follow-up communications could be designed to address men’s preferred communication style and study clinics could be offered on weekends. However, given the
likely costs and practical challenges of weekend study clinics, it would be important to assess the effect of this strategy on participant retention and satisfaction before advocating for such a strategy to be broadly implemented.

6.3.2. Marketing and trial recruitment

Marketing theory has been successfully incorporated into recruitment planning and monitoring in a number of trials\textsuperscript{93-95}, including the T4DM trial (Chapter 3). However, this remains an emergent area of research. More sophisticated marketing research methods could inform the choice of study promotion, and the fine-tuning of promotional material content.

Like T4DM, previous recruitment studies have relied on trial-and-error to identify channels for trial promotion\textsuperscript{92, 96}. This is a pragmatic approach, given the lack of good quality evidence to inform choice of promotions. Future research could incorporate feedback from participants and the public, elicited through market research methods, into the initial recruitment promotion plan. Better knowledge of the media habits and healthcare decision-making processes of the target demographic group may assist future trialists to build a prospective, evidence-based trial-specific recruitment promotion plan.

Future research could also evaluate methods to enhance the content of promotional material. A small number of studies have evaluated manipulations to the content of participant communications and promotions with promising results\textsuperscript{97, 98}. Yet most recruitment evaluations to date have focused on the choice of promotional channels rather than the content of the promotions\textsuperscript{42}. In hindsight, there were opportunities to conduct content evaluations within the T4DM setting but they were foregone due to lack of time and expertise in marketing techniques. For example, during the initial mass mailing of trial invitations, men could have been randomised to receive different versions of the invitation, with further mailings adopting the most effective invitation version. Manipulations of the invitation could have been based on the amount of detail included, the sending of a reminder letter following the initial invitation\textsuperscript{99}, or on the incorporation of cues informed by behaviour change theory\textsuperscript{100}. Likewise, the A/B testing functionality provided by Google Analytics, Google Adwords and other online advertising platforms could have been used to conduct simple, randomised experiments of different content on the
Chapter 6. Conclusions

T4DM study website and in online advertising\textsuperscript{92}. In A/B testing, the researcher sets up two or more versions of a website or advertisement (version A and version B). The platform then randomises users to receive the different versions and evaluates the response. Outside of medical research, marginal enhancements to online content through this method have delivered substantial improvements in user engagement\textsuperscript{101}. Given the large numbers of men receiving mass mailed invitations and/or visiting the study website, evaluations would have had good power to identify the best content quickly. This evidence could have informed further recruitment activities on the T4DM study as well as on future trials. Lack of marketing expertise was a barrier to conducting these evaluations in the T4DM study and so future researchers may find that conducting interdisciplinary research, in partnership with marketing professionals, will assist them to select and execute promotion evaluations well.

In addition to requiring marketing expertise, online recruitment promotion presents trialists with ethical challenges. Although online marketing is not inherently unethical\textsuperscript{92}, the current clinical trial ethical review process is largely incompatible with the adaptive nature of online marketing and the opportunities it provides for real-time interactions with the public. This complication may dissuade trialists from making the most of online recruitment opportunities. In Chapter 3, I described my approach to ensuring ethical oversight of T4DM recruitment activities within the context of digital and social media marketing. I found that the guidelines and procedures for ethical submission and review were silent on social media promotion of trials. It was unclear whether online interactions with the public were analogous with printed promotional material (requiring ethical review of content) or face-to-face interactions with the public, for example at public screening events (presented for ethical review as part of the trial’s processes but not requiring ethical review of the ‘content’ of verbal interactions). I worked closely with the trial’s lead human research ethics committee to apply the existing processes and guidelines to the range of T4DM trial promotions, including Facebook posts, study website updates, and email and SMS screening reminders. Further research, incorporating input from ethicists, trialists and marketers, is needed to ensure that procedures for ethical oversight of trial recruitment materials keep pace with technological advances while also continuing to protect the rights and safety of trial participants and the general public.
6.3.3. Selecting promising recruitment strategies for future evaluations

As I have demonstrated, although recruitment was identified as the most important area for methodology research, the existing evidence to guide recruitment is limited and often esoteric. As a first step to strengthening the evidence base, the James Lind Alliance has published the Top 10 questions in recruitment research\(^\text{102}\), identified through the Prioritising Recruitment in Randomised Trials (PRioRiTy) priority-setting partnership (Figure 6.1). Given the lack of high-quality evidence across all areas of the recruitment process, this list may guide trialists to select the most salient recruitment questions to address in their recruitment research. The research presented in this thesis addresses several of the Top 10 priority recruitment uncertainties (including Questions 4, 9 and 10) and is therefore well-aligned with the international recruitment research agenda.

In addition to addressing a priority recruitment question, future research should also be designed with reference to existing and on-going recruitment evaluations. Replication of existing recruitment findings, like the ones presented in this thesis, is a crucial step in reducing recruitment uncertainty\(^\text{34}\).\(^\text{91}\). Trialists can refer to the SWAT store, a repository of existing recruitment research protocols, to identify promising interventions to evaluate within their own trials\(^\text{103}\). The protocol for the screening reminder evaluation presented in Chapter 5 is listed on the SWAT store to facilitate replication of my findings in future trials.
Figure 6.1 Top 10 uncertainties in recruitment methodology research (Source: The PRoRiTy study, https://priorityresearch.ie/, 2018. Reproduced with permission.)
Future recruitment research should also seek to maximise value. Recruitment methodology research seeks to reduce waste in clinical trial conduct, yet conducting this research also involves cost and the potential for waste, however minimal. Trialists should only embark on recruitment methodology research if the value of the information to be gained is expected to outweigh the cost of conducting the research. In the past, trials have monitored recruitment at a macro level, focusing solely on the number of randomised participants without further consideration of the complexity of the recruitment process. This ‘black box’ approach to recruitment management may lead to the evaluation of recruitment strategies that fail to address the underlying causes of recruitment failure. My thesis demonstrates a data-driven approach to pinpointing the components of the recruitment pathway where recruitment methodology research is most likely to add value. I collected and analysed granular screening and enrolment metrics in real-time, as presented in Chapter 4. More recently, the Screened, Eligible, Approached, Randomised (SEAR) framework has been proposed as a generalisable approach for collecting and monitoring recruitment data. However, this framework has yet to be evaluated. Future research could replicate the centralised screening data collection processes presented in Chapter 4 to evaluate the SEAR framework. The detailed recruitment information collected through this process could then be used to select the most promising recruitment strategies for evaluation in future research.

6.4. Conclusion

Men have higher rates of avoidable mortality than women and also experience higher rates of chronic diseases including coronary heart disease and Type 2 diabetes. It is therefore crucial that interventions to prevent these diseases are evaluated men. However, recent disease prevention and lifestyle intervention trials have failed to recruit adequate numbers of male participants. Prior to my research, there was limited evidence on how best to engage men in clinical trials. More broadly, the majority of trials experience slow or inadequate recruitment. Efforts by trialists to implement evidence-based strategies to address poor recruitment have been stymied by the lack of high-quality evidence. Instead, trialists have often relied on trial and error, resulting in wasted time and resources.
Chapter 6. Conclusions

I set out to identify and evaluate strategies to recruit men to clinical trials, based on experiences from the T4DM diabetes prevention trial. I have designed, implemented, and evaluated a program of recruitment strategies designed to target men aged over 50 years. My research provides estimates of the cost and effectiveness of strategies to identify, screen and enrol trial participants. Furthermore, my research presents a targeted and adaptive approach to recruitment planning, informed by detailed, centrally collected screening and enrolment metrics.

It is widely acknowledged that recruitment intervention methods have been poorly reported in previous research. Throughout this thesis, I have provided detailed reporting of the methods associated with each recruitment intervention to assist trialists to interpret my findings and to foster their replication in future trials. My methods are likely to be generalisable to a broad range of trials not limited to those recruiting men aged over 50 years. My research addresses the need for well-conducted and transparently reported recruitment methodology research. I hope that my published findings will assist trialists to develop evidence-based recruitment plans in future trials, and will pave the way for future research in this area.
References


References


References


References


References


Appendices

Appendix A: The T4DM study design paper
CLINICAL TRIAL DESIGN

Testosterone therapy to prevent type 2 diabetes mellitus in at-risk men (T4DM): Design and implementation of a double-blind randomized controlled trial

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Funding information
National Health and Medical Research Council (NHMRC) Project Grant 1030123, Bayer, Lilly, University of Adelaide. Weight Watchers provided enrolment to their programme for trial participants without cost.

Background: Low circulating testosterone is associated with an increased risk of developing type 2 diabetes (T2DM) in overweight men with impaired glucose tolerance (IGT).

Aims: To determine in a multi-centre, double-blinded placebo-controlled randomized trial whether testosterone treatment combined with lifestyle intervention (Weight Watchers) relative to lifestyle intervention alone reduces T2DM incidence and improves glucose tolerance at 2 years.

Study population: Overweight or obese men aged 50-74 years with a serum testosterone of ≤ 14 nmol/L and IGT or newly diagnosed T2DM established by an oral glucose tolerance test (OGTT).

Setting, drug and protocol: Six Australian capital city-based tertiary care centres. Participants were randomized 1:1 and injected with testosterone undecanoate (1000 mg/4 mL) or vehicle (4 mL castor oil), at baseline, 6 weeks and 3-monthly thereafter.

Primary endpoints: (a) Proportion of participants with 2-hour OGTT ≥ 11.1 mmol/L at 2 years, and (b) a difference at 2 years ≥ 0.6 mmol/L in the mean 2-hour OGTT glucose between treatments.

Secondary endpoints: Fasting insulin, HbA1c, body composition, maximal handgrip strength; sexual function and lower urinary tract symptoms; serum sex steroids and sex hormone binding globulin; mood and psychosocial function; adherence to lifestyle intervention; and healthcare utilization and costs.

Safety: Overseen by an Independent Data Safety Monitoring Committee. Haematocrit, lipids and prostate-specific antigen (PSA) are assessed 6-monthly and information relating to hematological, urological and cardiovascular adverse events from each clinic visit.

Sub-studies: (a) Changes in bone density and micro-architecture, (b) motivation and behaviour, (c) telomere length, (d) extended treatment up to 4 years, and (e) hypothalamo-pituitary testicular axis recovery at treatment end.

KEYWORDS
body composition, cardiovascular, motivation, obesity, prevention, testosterone, type 2 diabetes mellitus
1 | INTRODUCTION

Obesity is a well-established reversible cause of lowered serum testosterone concentration (T) in men.1–3 A high proportion of men with type 2 diabetes (T2DM) have low T that is inversely associated with obesity, insulin resistance and glycaemia.4,5 In men with T2DM and metabolic syndrome (MetS) mean T is 2.6 nmol/L lower than in controls.5–7 Low T is also associated with an increased risk of incident T2DM in men.5,8,9 A systematic review with meta-analysis showed that men with T > 15.5 nmol/L have a 42% reduced risk of T2DM versus men with T ≤ 15.5 nmol/L.6 There are plausible mechanisms by which obesity-associated reduction in T may induce dysglycaemia. Reducing T to castrate levels in men with prostate cancer increases risk of insulin resistance10,11 and T2DM.12 T effects on insulin sensitivity may be mediated by changes in body composition.13 Direct effects of T are enhanced catecholamine-induced lipolysis14 and reduced lipoprotein lipase activity and triglyceride uptake in human abdominal adipose tissue.15 Moreover, T levels correlate positively with mitochondrial indices of insulin sensitivity in human skeletal muscle16 and modulate pathways regulating skeletal muscle glucose metabolism in mice.17

In an uncontrolled observational study, 6 years of T treatment in men with T2DM resulted in significant and sustained improvements in body weight, glycaemia and overall cardiovascular risk.18 A systematic review of placebo-controlled randomized trials found that T therapy did not lower HbA1c in men with established T2DM, although insulin resistance may have improved, at least over the short term, in men with T2DM and/or MetS.19 The limited efficacy of T treatment in men with established T2DM, in contrast to men with MetS, suggests that T treatment may be of most benefit to prevent progression to T2DM and, in established T2DM, benefit may be limited to the earliest stages.

There is international consensus supporting lifestyle intervention in T2DM prevention and management,20 and such interventions can increase circulating T. The benefits of T therapy, particularly body weight loss,21 may be greatest when combined with lifestyle interventions.22 Whether this is a direct T effect on glucose metabolism, an indirect effect via improved body composition or motivation for lifestyle change,23 remains undetermined. However, there is no large-scale trial assessing T treatment as an adjunct to lifestyle intervention for preventing T2DM in men. Hence, we are undertaking a randomized, double-blind, placebo-controlled trial to determine whether T treatment combined with lifestyle intervention reduces the risk of T2DM at 2 years versus lifestyle intervention alone in ~1000 high-risk men.

2 | TRIAL DESIGN, ORGANIZATION, MONITORING AND REPORTING

2.1 | Overall organization

The trial (ACTRN12612000287831) is funded by the Australian National Health and Medical Research Council (NHMRC) (Project Grant 1030123), Bayer, Eli Lilly and the University of Adelaide, with in-kind support from Weight Watchers (WW) and participating research centres.

A Steering Committee of the grant holders, chaired by the Principal Investigator (PI) (G.W.), maintains academic oversight. Day-to-day trial co-ordination, risk-based monitoring and data management are handled by the NHMRC Clinical Trials Centre (CTC, University of Sydney) in collaboration with the PI.

An Independent Data Safety Monitoring Committee (IDSMC) oversees participant safety. All participating sites received approval from the relevant human research ethics committees (HREC) before commencing recruitment.

The trial was registered in March 2012 and trial initiation was January 2013. The last patient enrolled in February 2017. All visits will complete by May 2019.

2.2 | Study design

This is a 2-year, Phase IIIb, multi-centre, double-blind, randomized, placebo-controlled trial with equal allocation between two treatment arms (Figure 1). There are six Australian capital city-based tertiary care centres: Concord Repatriation General Hospital, Sydney; Queen Elizabeth Hospital, Adelaide; Austin Hospital, Melbourne; Princess Alexandra Hospital, Brisbane; and in Perth, the Keogh Institute for Medical Research and Fremantle Hospital, which relocated to the Fiona Stanley Hospital about halfway through enrolment.

2.3 | Participants

2.3.1 | Inclusion criteria

Participants need to meet all inclusion criteria (Table 1). To maximize the probability of having undiagnosed or developing T2DM at the end of the 2-year study we recruited men aged 50–74 years, with abdominal obesity (waist circumference ≥ 95 cm) and the absence of exclusion criteria, for initial screening laboratory investigations. If the 2-hour plasma glucose was ≥ 7.8 and ≤ 15 mmol/L in response to a 75 g oral glucose tolerance test (OGTT), and serum T was ≤ 14 nmol/L, then men were enrolled. If the serum T was < 8 nmol/L then endocrine review was undertaken to exclude significant hypothalamic-pituitary-testicular (HPT) axis pathology.

We initially enrolled men with T < 11 nmol/L.5 However, the inverse relationship of insulin resistance with T in men with T2DM does not have a clear breakpoint and remains present with normal range T.4 We settled on a T cut-off of 14 nmol/L at which incident T2DM began to increase in an analysis of longitudinal data from the Florey Adelaide Male Ageing Study (FAMAS),5 and 15.5 mmol/L in the prospectively followed cohorts in the meta-analysis of Ding et al. (2006).6 This is reflected in the Study Protocol V1.5, approved by the lead HREC on 20 April 2013.

2.3.2 | Exclusion criteria

Exclusion criteria (Table 1) included previously diagnosed T2DM or use of any oral or injectable antidiabetic pharmacotherapy. We initially excluded men newly diagnosed with T2DM by the OGTT. However, given the arbitrary nature of the 2-hour OGTT cut-off for diagnosing
Eligible participants
- Men aged 50–74 years
- Prediabetic or newly diagnosed diabetic
- Serum T ≤ 14 nmol/L
- Waist circumference ≥ 95 cm.

Stratification:
- Centre
- Age group 50–59 years, 60–74 years
- Waist circumference (cm)
  95–100;
  101–115;
  > 115.
- 2-h glucose on OGTT (mmol/L)
  7.8–9.5;
  9.6–11.0;
  11.1–15.0.
- Currently smoking-yes, no.
- First-degree family history of T2D-yes, no.

FIGURE 1 T4DM study design

TABLE 1 Eligibility criteria

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men aged ≥50 and ≤ 74 y</td>
<td>Significant hypothalamic-pituitary-gonadal (HPG) pathology</td>
</tr>
<tr>
<td>Waist circumference ≥ 95 cm</td>
<td>Testosterone treatment in the past 12 mo, or history of anabolic steroid use at any time</td>
</tr>
<tr>
<td>Serum testosterone ≤ 14 nmol/L</td>
<td>Medications affecting testosterone or SHBG in the previous month, or conditions indicating potential future use of such medications</td>
</tr>
<tr>
<td>2-h plasma glucose ≥ 7.8 and ≤ 15 mmol/L on 75 g OGTT</td>
<td>Previously diagnosed T2DM, use of medication to lower blood glucose</td>
</tr>
<tr>
<td>Willing to participate in a lifestyle programme coordinated by Weight Watchers</td>
<td>2-h glucose &gt; 15 mmol/L on OGTT, or symptoms of hyperglycaemia at any level</td>
</tr>
<tr>
<td>Able and willing to meet all protocol-required procedures and visits</td>
<td>Treatment with antiobesity drugs or any investigational medication within 6 mo prior to informed consent, previous or planned bariatric surgery</td>
</tr>
<tr>
<td>Able to read and understand the Participant Information and Consent Form and provide informed consent to participate</td>
<td>Major cardiovascular event in previous 6 mo or active cardiovascular disease, including cardiac failure with NYHA classification ≥2, angina or arrhythmias</td>
</tr>
</tbody>
</table>

T2DM, and because the objective was to remediate glucose tolerance, we amended the protocol (V2.0, approved by the HREC on 19 March 2014) to increase the 2-hour glucose for exclusion to >15 mmol/L. This was a level below which we reasoned that more aggressive management than provided in the trial could be safely delayed. Current or planned treatment of obesity within 6 months precluded participation.

We excluded men treated with T any time in the preceding 12 months, or with established HPT axis pathology where treatment with T was, or was probable to be, required. We also excluded men who used any medication affecting T production (e.g., opioids, gonadotropin-releasing hormone [GnRH] analogues) or action (e.g., spironolactone, finasteride, dutasteride), or production of sex hormone binding globulin (SHBG) (growth hormone, antiepileptics and thyroxine [unless on stable dose thyroxine for >3 months]) or with an underlying condition probable to require such treatments within 2 years.

We took a conservative approach to the presence of cardiovascular disease, requiring no events or significant symptoms in the preceding 6 months, no cerebrovascular disease (transient ischaemic attack [TIA] or stroke) in the preceding 3 years, and blood pressure (systolic/diastolic) ≤ 140/≤90 mm Hg at screening. Because of the association of T treatment with thrombosis and increased red cell mass, we excluded men with a significant personal or first-degree family history of thrombosis and those with haematocrit >50%. Given T administration by deep intramuscular injection, we excluded men taking anticoagulants other than low dose aspirin (<150 mg) and/or clopidogrel.

Other exclusions are: ongoing major depression or other significant psychiatric disorder, known infection with human immunodeficiency or hepatitis virus, malignancy current or past (other than non-melanomatous skin cancer), abnormal liver (alanine transaminase [ALT], aspartate aminotransferase [AST], gamma-glutamyl transferase [GGT], bilirubin ≥ 3 times upper limit of normal) or renal dysfunction (estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m²).

If there was a score > 19 on the International Prostate Symptom Score (IPSS) (Questions 1–7), indicating severe voiding (lower urinary tract) symptoms (LUTS), entry was conditional on urological review excluding significant pathology. Despite the cautions of some clinical
guidelines, a recent systematic review concludes there is scant evidence that T treatment is contraindicated in men with severe LUTS. A history of prostate cancer precluded enrolment.

All trial participants who consumed >2 standard drinks of alcohol a day were counselled to reduce their intake. Those men considered by the site investigator at the time of screening to have problem drinking were excluded. Men using recreational drugs, or with major non-malignant disease requiring medical intervention and/or probably lead to serious illness or death within 2 years, were excluded.

### 2.3.3 | Participant recruitment

Strategies to recruit participants included mass media coverage, radio advertising, articles in health insurance company newsletters, direct approaches to general practitioners, online marketing and staged mail-outs by the Australian Department of Human Services (DHS) to men in the target age group. Prospective participants were directed to a study-specific website (www.diabetesprevention.org.au) or centralized phone line to obtain information.

### 2.3.4 | Screening

After providing consent for screening, initial eligibility was established by questionnaire responses. Eligible men had a consent form and laboratory request forms mailed or made available online ahead of presenting to the clinic the morning after an overnight fast. The clinics were members of a network of collection centres from a single national pathology service provider (Sonic Healthcare Ltd, Sydney). Consent forms were checked and filed. Following a baseline blood draw a further sample was taken 2 hour after 75 g oral glucose. The baseline full blood count (FBE), HbA1c by HPLC (Biorad D-100) and baseline and 2-hour glucose were assayed. If men were eligible based on haematocrit and 2-hour glucose, then serum T was assayed. If this was >14 nmol/L (Electrochemiluminescence Immunoassay, T II, Roche Diagnostics, GmbH, Mannheim, Germany), the remaining assays needed to confirm eligibility were run. All screening test results were electronically transferred from the pathology service to the central data management system. Participants were notified as to their eligibility or not. Site staff were notified electronically, and the study nurse called eligible participants to schedule an appointment for the remaining screening and enrolment processes (Table 2).

### 2.3.5 | Enrolment and randomization

At the initial appointment, written consent for enrolment into the study was obtained, a standardized medical assessment performed, and the participant’s eligibility verified by a site investigator. Eligible men were randomized in a concealed allocation via a centralized, web-based randomization system using the method of minimization in a 1:1 ratio to the intervention and placebo arms (Flexetrials v5.9.4, Sydney, Australia). Randomization was stratified by centre, age group (50-59, 60-74 years), waist circumference (95-100, 101-115, >115 cm), 2-hour glucose on OGTT (7.8-9.5, 9.6-11.0, 11.1-15.0 mmol/L), currently smoking (yes, no) and first-degree family history of T2DM (yes, no).

Baseline questionnaires were completed. Body weight, un-shod and in light clothing, and waist circumference in a horizontal plane midway between the iliac crest and ribs and read in the mid-axillary line during expiration, were measured. Peak handgrip muscle strength of each hand (mean of three measures on each occasion) was assessed using either a Jamar (Patterson Medical, Warrenville, Illinois) or Smedley (Stoelting Co., Wood Dale, Illinois) hand dynamometer. Venous blood was drawn for the central laboratory, participants were enrolled in WW and the first study injection administered. Predeparture, participants were provided with an appointment for a dual energy X-ray absorptiometry (DXA) scan to assess regional and whole-body bone mineral density, muscle and fat mass. DXA scanners are Hologic and Hologic Discovery A (Hologic Inc., Marlborough, Massachusetts) and GE Lunar Prodigy, GE Lunar Prodigy Advance and GE Lunar iDXA (GE Healthcare Lunar, Madison, Wisconsin). Wherever possible, DXA scans for each participant use the same machine.

### 2.3.6 | On study

Participants attend study visits at 6 weeks and 3 months, and 3-monthly thereafter for further injections, clinical review, blood collection and questionnaire completion. They also separately attend for a further DXA scan at 2 years. Study procedures and schedule of assessments are summarized in Table 2. Study sites are masked to all safety laboratory investigations unless there is a prespecified flag (Table 3).

### 2.4 | Treatment

Injectable T undecanoate (Reandron, Bayer) (1000 mg/4 mL) in a 4 mL castor oil vehicle or 4 mL vehicle alone in identical ampoules (Bayer), was administered to participants by slow deep intramuscular injection in the upper outer gluteal region by clinic nurses at randomization, 6 weeks (±1 week), and 3-monthly (±2 weeks) thereafter. Adherence to the treatment schedule was monitored in the central data management system. This schedule maintains physiological circulating T concentrations and obviates the need for monitoring adherence and drug exposure. Serum from all visits is stored frozen (−80°C) and sex steroids measured (as described below) in batches as participants complete the trial. Masking is maintained, and no dosage adjustment made during treatment. T undecanoate is registered in Australia for treatment of male hypogonadism (ARTG 106946).

### 2.5 | Lifestyle intervention

Collaboration with WW facilitates the standardization of, and ease of access to, a lifestyle intervention that is acceptable to men and effective for T2DM prevention, including in an Australian context.

At enrolment, a temporary membership card, programme information, and a telephone number for the WW call centre were provided. Participants were encouraged to attend weekly WW meetings. An interactive website provides diet and activity guidelines, and self-monitoring tools that allow men to log food, physical activity and weigh-in details. Men are encouraged to achieve a 5% reduction in body weight each year and to monitor and record their own body weight weekly because frequent self-weighing is helpful for body weight loss. Adherence with the overall lifestyle programme is
monitored via website log-ins and activity, meeting attendance and information collected at 3-monthly clinic visits.

2.6 Outcome measures

2.6.1 Primary endpoints and power calculation

Rationale for two endpoints

The initial decision was to enrol obese men with prediabetes (2-hour glucose ≤ 11 mmol/L on the OGTT) and examine reduction in progression to T2DM at 2 years based on a repeat OGTT. However, 12 months into the 4-year recruitment period we amended the protocol and obtained ethics approval to include men with a 2-hour glucose of up to 15 mmol/L. The cut-offs used to define T2DM on the OGTT are somewhat arbitrary and poorly reproducible. Furthermore, T2DM of recent onset is reversible with body weight loss, and improvements in, and even normalization of, glycaemia has been reported in observational studies of T treatment. Accordingly, we originally defined the primary outcome as the proportion of patients with OGTT ≥ 11.1 mmol/L at 2 years, accepting some loss of precision by using a categorical variable for a continuous measurement. For example, a 2-hour glucose of 9 mmol/L at baseline and 10 mmol/L at 2 years represents a poor outcome compared with a 2-hour glucose of 10 mmol/L at baseline and 8 mmol/L at 2 years, but both would have been classed as the same outcome according to our initially planned endpoint (percentage non-diabetic).

Hence, to reduce the reliance on the categorical endpoint of percentage non-diabetic, we introduced a continuous variable as a second primary endpoint and will assess the mean change in OGTT between the treatments at 2 years. The primary outcome of the trial will be considered positive if either of the 2 co-primary endpoints is met (Table 4).

Power calculation

Based on our 5-year follow-up of the FAMAS cohort, the estimated 2-year incidence rate of T2DM for men aged ≥50 years with a T ≤ 14 mmol/L and prediabetes is 23% (unpublished data). This rate was adjusted by 30% to account for lifestyle intervention benefits, and improvements in, and even normalization of, glycaemia has been reported in observational studies of T treatment. Accordingly, we originally defined the primary outcome as the proportion of patients with OGTT ≥ 11.1 mmol/L at 2 years, accepting some loss of precision by using a categorical variable for a continuous measurement. For example, a 2-hour glucose of 9 mmol/L at baseline and 10 mmol/L at 2 years represents a poor outcome compared with a 2-hour glucose of 10 mmol/L at baseline and 8 mmol/L at 2 years, but both would have been classed as the same outcome according to our initially planned endpoint (percentage non-diabetic).

Hence, to reduce the reliance on the categorical endpoint of percentage non-diabetic, we introduced a continuous variable as a second primary endpoint and will assess the mean change in OGTT between the treatments at 2 years. The primary outcome of the trial will be considered positive if either of the 2 co-primary endpoints is met (Table 4).

### Table 2 Schedule of assessments

<table>
<thead>
<tr>
<th>Study visit</th>
<th>Screen, enrol and baseline</th>
<th>On study</th>
<th>12-weekly for 2-4 y (except 2-year visit)</th>
<th>2 y</th>
<th>End of study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Informed consent</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eligibility screen</td>
<td>X</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Medical history, physical exam, digital rectal examination (DRE)</td>
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<td>X</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Demographics</td>
<td>X</td>
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<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Height</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BP, pulse, weight, waist circumference</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Handgrip assessment</td>
<td></td>
<td>Every second visit</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dual energy X-Ray absorptiometry (DEXA) scan</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Questionnaires: Physical activity (Active Australia), Macarthur Scale of Subjective Social Status, Quality of Life (SF-12), Personal Mastery Scale (Pearlin), 13-item Sense of Coherence Questionnaire, IIEF 15, IPSS, PSQI</td>
<td></td>
<td>Every second visit</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CES-D depression questionnaire</td>
<td>X</td>
<td></td>
<td>At 1 y</td>
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<td></td>
</tr>
<tr>
<td>Adverse events, concomitant medications</td>
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<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Weight Watchers compliance</td>
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<td>X</td>
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</tr>
<tr>
<td>OGTT</td>
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<td>Screening blood tests</td>
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</tr>
<tr>
<td>FPG</td>
<td>X</td>
<td></td>
<td>Every second visit</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>HbA1c</td>
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<td></td>
<td>X</td>
<td>X</td>
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<tr>
<td>Safety monitoring blood tests</td>
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<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Blood collection for central lab</td>
<td>X</td>
<td></td>
<td>Weeks 18 and 66 only</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

### Table 3 Prespecified reasons for early discontinuation of study treatment

- Alanine transferase (ALT) measurement >3-fold the upper limit of normal (ULN)
- Haematocrit level ≥ 54%
- PSA > age-specific ULN
- Development of contraindications to testosterone
- Allergic or severe adverse reaction to any component of the investigational product
- The participant needs to take concomitant drugs that interfere with the investigational product
- The participant is no longer able to participate for other medical reasons
- The participant withdraws consent
- At the discretion of the investigator
TABLE 4  Study endpoints

Co-primary endpoints
- 2-h glucose in the diabetic range (≥11.1 mmol/L on 75 g OGTT) at 2 y
- Change in 2-h glucose at 2 y from baseline

Secondary endpoints
- Normalized blood glucose (2-h glucose <7.8 mmol/L)
- Initiation of anti-diabetic pharmacotherapy
- Glucose metabolism: FPG, insulin and HbA1c
- Anthropometrics: body weight, waist circumference
- Body composition: using Dual energy X-Ray absorptiometry (DEXA) measurements for whole-body and regional fat and lean mass
- Muscle strength: peak handgrip
- Sex steroid hormone profile: testosterone, dihydroT (DHT), estrone (E1), estradiol (E2) and SHBG
- Sexual function and lower urinary tract symptoms (LUTS)
- Biomarkers for metabolic function: lipids (total cholesterol, LDL, trigs, HDL)
- Psychosocial function
- Compliance with lifestyle intervention programme
- Healthcare expenditure

the control group to 9.0% in the T-group). This sample size will have ≥88% power to detect a difference in the reduction of OGTT from baseline to 2 years between groups of 0.6 mmol/L based on a standard deviation of 2.4 mmol/L. Because the anticipated correlation between the 2 endpoints is 0.75, the significance levels for the individual endpoints were adjusted using numerical methods in the ACCoRD (Analysis of Censored and Correlated Data) software package v8.5.3 (Eastwood, Australia). The overall study will have >80% power to detect the stated differences with a significance level of 3.5% for the endpoint of OGTT ≥11.1 mmol/L and 2.5% for the endpoint of change in OGTT of at least 0.6 mmol/L. This level of significance will have an overall (family-wise) significance level of 5%. This sample size allows for non-compliance of 5% and attrition of 15%.

2.6.2  |  Subgroup analysis of primary endpoints

A subgroup analysis will determine whether T2DM incidence and the degree of change of OGTT from baseline to 2 years among those receiving T relative to placebo varied according to whether the participant was prediabetic or newly diagnosed T2DM at baseline (baseline OGTT ≤11.1 mmol/L or ≥ 11.1 mmol/L).

2.6.3  |  Secondary endpoints

Secondary endpoints (Table 4) and the reason for their inclusion are now described:

  Additional markers of glycaemic status: The percentage of men with normal glucose (2-hour glucose <7.8 mmol/L) at 2 years; the initiation of anti-diabetic pharmacotherapy established by participant report and Pharmaceutical Benefits Scheme records, and measurement of fasting plasma glucose (FPG) and HbA1c.

  Mechanism/s of effect of testosterone may relate to either or both of: (a) improved body composition reflected by a decrease in total and or abdominal fat mass and increase in lean mass (DXA) and muscle strength (handgrip dynamometry) at 2 years, and in insulin sensitivity by the measurement of FPG and insulin and assessment of insulin resistance (IR) via the homeostasis model assessment of IR (HOMA-IR), (b) enhanced adherence to the WW programme as reflected by attendance at groups, use of the online programme, or both, and its relationship to body weight loss, and (c) increase in physical activity as assessed by the Active Australia questionnaire.

  Treatment-specific benefits: may be attributable either to T, improvement in health behaviours and body weight loss, or an interaction between T and the latter factors. These outcomes include: erectile function, sexual desire and LUTS as assessed by the International Index of Erectile Function (IIEF-5), Sexual Desire Inventory and IPSS, respectively, as used in the Men in Australia Inflammation Lifestyle, Environment and Stress (MAlLES) study.

  Treatment impact on psychosocial factors: (a) health-related quality of life (HRQoL) assessed by the Short-Form Health Survey (SF-12) testing the hypotheses that HRQoL will improve over time and be greater at study completion for men receiving T versus placebo, (b) psychosocial function and motivation for lifestyle change assessed by the MacArthur Scale of Subjective Social Status, Pearson’s Personal Mastery Scale, and Sense of Coherence, addressing the following hypotheses: subjective social status, mastery, and sense of coherence will improve over time in men and be greater at study end for men receiving T versus placebo.

  To determine whether psychosocial measures mediate the impact of T on glycaemic status: hypotheses being tested are that improvements in subjective social status, mastery, and sense of coherence will partially or fully mediate (account for, in the causal pathway) the impact of T on glycaemia.

  To determine whether the relationship between T and glycaemic status varies by socio-demographic measures: this framing acknowledges that T will not influence sociodemographic status but that such measures could modify T impact on glycaemia; it also explicitly explores moderation rather than simply statistically controlling for sociodemographic measures (including highest education, household income [adjusted for employment status], occupation, and marital or cohabitation status) as covariates. The hypothesis is that greater education, greater household income, higher status occupation, or being married or cohabitating, will strengthen the relationship between T and glycaemic status and, conversely, lesser values for these measures will be associated with a lesser strength of the relationship between T and glycaemic status.

  Association of outcomes with baseline and change in sex steroid concentrations: circulating T, dihydroT (DHT), oestradiol (E2) and oestrone (E1) will be measured by stable isotope dilution liquid chromatography-tandem mass spectrometry (LC-MS/MS; API-5000) at baseline, 18, 66, and 102 weeks. Serum SHBG, follicle stimulating hormone (FSH) and luteinizing hormone (LH) will be measured by automated electrochemiluminescence immunoassay.

  Treatment impact on health care expenditure: will be based on costs of prescribed pharmaceuticals from the pharmaceutical benefits scheme (PBS), costs of hospitalizations from the database of Australian Refined Diagnostic Related Groups (AR-DRGs) and costs of GP visits from the database of the Medical Benefits Schedule (MBS). The theoretical cost of the T and lifestyle programme will also be estimated at every third follow-up. An economic evaluation will be undertaken...
between groups for incremental costs of the intervention per unit of health service resource used. Based on trial data, a cost-effectiveness analysis will be undertaken to determine the incremental cost-effectiveness ratio (ICER) of T therapy. The ICER is simply the net cost (cost of intervention minus cost savings from illness prevention) divided by the net change in health outcome. The trial-based ICER will be expressed as net cost per incident T2DM prevented. Using epidemiological and cost data regarding T2DM, modeling will then estimate ICERs in terms of net cost per death prevented, life year gained, and quality-adjusted life year (QALY) gained.

Biobanking: aliquots of whole blood, plasma and serum from each participant are stored for future assays, including genomics, covered by the initial consent.

2.7 | Safety

Table 3 summarizes the prespecified safety reasons for study drug discontinuation. A haematocrit $\geq 54\%$ requires a confirmatory test without fasting within 2 weeks before withdrawal. If a significant increase in haematocrit occurs with symptoms (e.g. new onset or worsened ischaemic symptoms [TIA or angina]) then venesection may be offered in addition to drug withdrawal. If PSA levels increase above the age-specific normal range, the test will be repeated, ensuring factors that may lead to a false positive are eliminated, for instance, infection or bicycling, following which there is referral to a urologist whose decision it would be to either monitor or biopsy. Withdrawal will be based on the urologist’s advice.

The IDSMC, comprising a cardiologist, endocrinologist, pharmacist and biostatistician, meets every 6 months. The IDSMC functions independently of the T4DM trial conduct and is responsible for monitoring participant safety, trial conduct and emerging results. To date, the trial has been permitted to proceed as per protocol.

2.8 | Sub-studies

Three sub-studies aim to determine the effects of T treatment on:
(a) bone micro-architecture (high resolution peripheral quantitative computed tomography [HR-pQCT], Austin Health only) and density (DXA) (T4Bone), (b) motivation and behaviour (T4M&B), and (c) telomere length (T4Telomeres). Two additional sub-studies determine effects of extended treatment with T for up to 4 years (T4DM run-on), and rate of HPT axis recovery at the end of treatment (T4DM run-off), respectively.

2.9 | Statistical methods

Treatment effects on primary and secondary endpoints will be analysed according to a modified intention-to-treat principle. Baseline characteristics will be summarized using N and % for categorical variables, and medians and interquartile ranges for skewed continuous variables. The primary analysis will be an unadjusted analysis of the proportion of participants with T2DM at 2 years and treatment comparisons will utilize the chi-squared test. For the mean change in glucose level from baseline, a 2-sample t-test will be used. These analyses will be unadjusted. As these two endpoints are correlated, a significance level of 0.035 will be used for the 2-hour glucose $\geq 11.1$ mmol/L and 0.025 for the mean change in glucose. Where appropriate, secondary analyses adjusted for covariates will be conducted using appropriate regression methods (i.e. Cox regression, logistic regression, generalized estimating equations [GEE]). Baseline T by LC-MS/MS ($<8, 8-11$ and $11.1+$ nmol/L) and stratification variables of centre, age group (50-59 and 60-74 years), waist circumference (95-100, 100-115, $>115$ cm), 2-hour glucose (7.8-9.5, 9.5-11, 11-15 mmol/L), current smoking and first-degree family history of T2DM will be adjusted for. Additional baseline factors as potential covariates are body weight, serum testosterone and use of selective serotonin reuptake inhibitors (SSRIs). A missing data analysis will use logistic regression to explore associations of baseline OGTT results and whether an OGTT at 2 years was obtained. Secondary outcomes will be analysed using chi-squared or t-tests where appropriate, and for repeated measures with binary outcomes, a GEE (exchangeable correlation structure) and a log link function will be used. For subgroup analyses of prediabetic and newly diagnosed T2DM, an interaction term between this and treatment will be fitted in a GEE model and the relative risk and associated 95% confidence interval will be reported for each level of the subgroup. The nominal p-value for significance for secondary endpoints is 5% and all comparisons will be 2-sided. The statistical analysis plan will be agreed upon and database locked before unmasking of treatment allocation.

ACKNOWLEDGMENTS

Sonic Healthcare, Australia.

Nurses: Glenda Fraser (ANZAC Research Institute and Concord Hospital), Jenny Healy (Austin Hospital), Helen Daniels and Chyn Soh (Fremantle Hospital and Fiona Stanley Hospital), Jody Sawyer (Princess Alexandra Hospital), Rosemary Cox and Fiona Cossey (The Queen Elizabeth Hospital), and Lee Mahoney (The Keogh Institute for Medical Research).

National Health and Medical Research Council (NHMRC) Clinical Trials Centre: Simone Marschner, Dr. Andrzej Januszewski, Caitlin Van Holst Pellekaan and Sandra Healey.

CONFLICTS OF INTEREST

G.W. has received research funding from Bayer, Lilly, Lawley Pharmaceuticals and Weight Watchers, and speaker honoraria from Bayer, Lilly and Besins Health Care. C.A. has received honoraria from Besins Health Care and is an advisory board member for Ferring. M.G. has received research funding from Bayer, Novartis, Weight Watchers, Lilly and speaker’s honoraria from Besins Healthcare and Onsuka. D.J.H. has received institutional grants for investigator-initiated studies of testosterone pharmacology (Lawley, Besins Healthcare) but no personal income and has provided expert testimony to antidoping and professional standards tribunals and testosterone litigation. B.B.Y. has received speaker honoraria and conference support from Bayer, Lilly and Besins Healthcare, research support from Bayer, Lilly and Lawley Pharmaceuticals, and has been a member of advisory committees for Lilly and Besins. E.A., K.B., A.C., M.D., W.H., V.G., W.I., A.J., R.M., A.K., K.R. and B.S. declare no relevant conflicts of interest.
REFERENCES


Appendix B: Chapter 2, supplementary file 1
(systematic review database search strategies)

Searches undertaken 28-30 August 2017 and updated 1 December 2017

Database(s): Ovid MEDLINE(R) 1946 to November Week 4 2017
Search Strategy:
1 Patient Selection/ (62722)
2 (recruit* or enrol*).ti. (29374)
3 1 or 2 (89212)
4 (male or men or men's or mens or man).tw. (1328352)
5 3 and 4 (4910)
6 randomized controlled trial.pt. (505126)
7 controlled clinical trial.pt. (100403)
8 randomized.ab. (391531)
9 placebo.ab. (189148)
10 clinical trials as topic.sh. (197003)
11 randomly.ab. (266025)
12 trial.ti. (175432)
13 or/6-12 (1131407)
14 exp animals/ not humans.sh. (4742733)
15 13 not 14 (1035827)
16 5 and 15 (881)
17 limit 16 to (english language and yr="2000 - 2017") (717)

Database(s): Embase Classic 1947 to 1973, Embase 1974 to 2017 November 29
Search Strategy:
1 patient selection/ (82554)
2 (recruit* or enrol*).ti. (37067)
3 1 or 2 (118188)
4 male/ (7776297)
5 (male or men or men's or mens or man).tw. (2046754)
6 4 or 5 (8236464)
7 Randomized Controlled Trial/ (485342)
8 rct.tw. (26750)
9 7 or 8 (502579)
10 3 and 6 and 9 (2490)
11 limit 10 to (human and english language and exclude medline journals and yr="2000 -Current") (112)

Database: CINAHL
Search strategy:
S1 ((MH "Research Subject Recruitment") OR (TI recruit*) OR (TI enrol*))
S2 ((MH "Male") OR (MH "Men") OR (TI (men OR male* OR man OR mens OR men's))
S3 (MH "Clinical Trials+")
S4 S1 and S2 and S3
S5 S4 Limiters - English Language; Published Date: 20000101-20171231; Exclude MEDLINE records (108)

Database: ORRCA
Appendix B: Systematic review database search strategies

Search strategy:

Inclusion:
  • Gender = Male only

Exclusion:
  • Aged <18 years
  • Published before 2000
  • Study outcome “Reason for participant refusal” only
Appendix C: Chapter 2, supplementary file 2
(systematic review PRISMA checklist)
<table>
<thead>
<tr>
<th>Section/topic</th>
<th>Checklist Item</th>
<th>#</th>
<th>Reported on Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>TITLE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABSTRACT</td>
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<tr>
<td>INTRODUCTION</td>
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<tr>
<td>METHODS</td>
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<tr>
<td>SUPPLEMENTARY</td>
<td></td>
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</tr>
</tbody>
</table>

**Methods**

- **Protocol and registration number**: Include a protocol or registration number if available.
- **Search**: Describe the search strategy and databases used.
- **Information Sources**: Describe any additional sources used.
- **Eligibility criteria**: Describe the inclusion and exclusion criteria used.
- **Registration information**: Include any registration information.
- **Data collection process**: Describe the process for extracting data.
- **Data items**: List and define all variables sought.
- **Risk of bias in individual studies**: Describe the methods used to assess bias.
- **Summary measures**: State the principal summary measures.
- **Synthesis of results**: Describe the methods of handling data and combining results of studies.

**Introduction**

- **Structured summary**: Provide a structured summary including background, objectives, data sources, design, study design, and key findings.
- **Conclusions**: Provide conclusions and implications of key findings.

**Abstract**

- **Title**: Identify the report as a systematic review, meta-analysis, or both.
- **Checklist Item**: #
### Results

- **Risk of bias across studies**
  - Provide a general interpretation of the results in the context of other evidence, and implications for future research.
  - Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified studies).

- **Additional analyses**
  - Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.
  - Report any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selection bias).
Appendix D: Chapter 3, supplementary file 1
(recruitment promotional material)
Radio advertising

T4DM Study Radio Advertisement Script #1
So you’ve hit your fifties and your six pack is now a keg, you’re not sleeping well and you need a whizz in the night. And you can’t find your mojo when you need it most. Well you might have low testosterone and be at risk of developing Type 2 Diabetes. Now is the chance to join a research trial with a proven weight loss program that is testing the effect of testosterone treatment to prevent progression to type 2 diabetes. So if you’re aged between 50 to 74 you might be a suitable candidate for the study. Find out more at diabetesprevention.org.au. You’ve nothing to lose except excess weight and you might even find your mojo.

T4DM Study Radio Advertisement Script #2
[Sound of ticking clock] That’s time ticking away. You’re over fifty. Are you really going to spend the rest of your life leaning over that gut just to see if your shoes are shiny? You could have low testosterone and be at risk of developing Type 2 Diabetes. It’s time to get your strut back! Join a research program which may prevent progression to diabetes. A free Weight Watchers program is also included. If you’re male, aged 50 to 74 see diabetesprevention.org.au.

T4DM Study Radio Advertisement Script #3
New Year, new man! Right? Wrong! You’re over fifty now, you’re tired, maybe you’ve lost your mojo. You might be at risk of Type 2 Diabetes and have low testosterone. Now is the chance to join a research trial with a proven weight loss program that is testing the effect of testosterone treatment to prevent progression to diabetes. If you’re aged between 50 and 74 why not make it a resolution to join the study today? At diabetesprevention.org.au. New Year, new man? You betcha!
Google Adwords ads and associated keywords

Diabetes prevention advertisement

Keywords:

Nocturia advertisement

Keywords:
urinating at night, frequency urination at night, frequency of urine at night, excessive urination at night, urine frequency at night, night time urination, constant urination at night, urine at night, urination frequency at night, why do i get up at night to urinate, frequency of urination at night, urge to urinate at night, urinating at night while sleeping, normal urination frequency at night, excessive night urination, more urine at night, night urination frequency, excessive urine at night, excessive urination at night is called, urinate at night, night time urination frequency, over urination at night, frequency in urination at night, urinate more at night
Facebook advertisements and boosted posts

**T4DM Diabetes Prevention Study**

A research study for men aged 50-74 looking at testosterone, weight and pre-diabetes.

Government-funded study

Learn more at www.diabetesprevention.org.au

---

**T4DM Diabetes Prevention Study**

If you are male, overweight and aged 50-74, our research study could be for you.

Focus on men's health

We're investigating whether a testosterone boost could reduce the risk of diabetes and other health problems. Join today!

Learn More

---

**T4DM Diabetes Prevention Study**

We're looking for Perth men aged 50-74 to join our diabetes prevention study.

Channel 9 News

We're running this study in Perth also, watch the interview to find out more.

Learn More

---

**T4DM Diabetes Prevention Study**

Poor sleep, obesity and low testosterone - what's the story?

Men's health research

Our study team looks at the ties and explains how our government-funded research could help you.

---

**T4DM Diabetes Prevention Study**

T4DM on the news in South Australia this week. What a great boost for study. And thanks to our participant Graham for appearing in the interview. [https://www.youtube.com/watch?v=4uX_dUJwhw&feature=youtu.be](https://www.youtube.com/watch?v=4uX_dUJwhw&feature=youtu.be)

Diabetes Study | 9 News Adelaide

Researchers at the University of Adelaide are exploring whether a simple injection could stop diabetes in its tracks.

YOUTUBE.COM

---

"It's not inevitable that sex drive and erectile function wane with increasing age. And getting up at night more than once to pass urine doesn't have to be the norm either."

Our study chair, Prof Gary Wittert, is writing about men's health issues today. Read more here: [http://goo.gl/jkbq](http://goo.gl/jkbq)
T4DM Diabetes Prevention Study

Testosterone, obesity & risk of diabetes: what's the link? How could our research help?

WWW.DOCS.COM
Talking to Steve Price
Listen to an interview with our study chair, Prof Gary Wirtz...

T4DM Diabetes Prevention Study

Only 4 weeks left to get your screening blood tests done. We have 913 men enrolled on the study already and we’d love you to help us reach 1000. Visit www.t4dm.org.au for more details.

Time is running out to join T4DM

T4DM Diabetes Prevention Study

Join our government-funded research today and put your health first.

WWW.SNSEWS.COM.AU
Mens health research
Men aged 50-74 join our research into testosterone, weil...

T4DM Diabetes Prevention Study

"Being overweight can directly affect erectile dysfunction by lowering testosterone levels." An interesting article from the Sydney Morning Herald.

Lose weight for better sex
With obesity rates on the rise, the effects of being overweight have attracted increasing attention, but one aspect of this problem is too often overlooked - the impact on male sexual dysfunction.

SRH.COM.AU
TV news coverage

Please note that the links listed below are to third party websites not maintained by the authors. These links may not remain permanently available.

Channel 9 news Adelaide, June 2014

ABC Catalyst, September 2014

Channel 7 news, Perth, July 2013
Are you male?
Aged 50 - 74?

Why not join T4DM, a research study using diet and testosterone treatment to prevent type 2 diabetes?

To find out how to join; and receive free access to Weight Watchers plus treatment with either testosterone or a placebo, visit www.t4dm.org.au or contact the study coordinating centre on tel: 1300 865 436 or email: askt4dm@ctl.usyd.edu.au

The T4DM study proudly supported by the University of Adelaide and the National Health and Medical Research Council (NHMRC)
Are you male and aged 50-74?
Overweight and wondering what happened to the younger, healthier you?

We invite you to join our government-funded T4DM Diabetes Prevention Study

You will receive (at no cost to you):
✔ 2 years of treatment with testosterone or placebo
✔ 2 years of Weight Watchers membership
✔ Regular support from our dedicated study team

3 ways to join

1. ONLINE: visit www.diabetesprevention.org.au
2. SMS: text ‘JOIN’ to 0417 140 314 for the cost of a regular text message
3. PHONE: call our team on 1300 865 436 for the cost of a local call

Why not join today? This could be the change you’ve been waiting for.
Mail out by Department of Human Services
(N.B. the mail out also included a cover letter from the Department of Human Services which provided information on privacy and ethical approval)
Dear Sir

The T4DM Diabetes Prevention and Testosterone Study

You are invited to participate in a research study which is investigating the use of testosterone to reduce the risk of diabetes in men who are at high risk of developing diabetes.

What is the T4DM study?
The T4DM study aims to recruit 1500 men around Australia. All men who join the study will receive a 2 year Weight Watchers membership at no cost to them. Half will receive 3-monthly injections of testosterone and the other half will receive injections of placebo. Participants will not be told which treatment they are receiving.

Participants attend 11 clinic visits over a 27 month period. For more information on what is involved please visit our website (www.diabetesprevention.org.au).

Who can join the T4DM study?
You can join the study if you are a man aged 50-74 years who is overweight or obese (if you have a waist circumference of 95cm or more).

We are looking for men who have impaired glucose tolerance and lower than normal testosterone. However, we'll check these as part of our screening process so don't worry if you don't know your glucose and testosterone levels.

Unfortunately you will not be able to join if you:
- already have type 2 diabetes,
- have a history of any cancer (except skin cancer),
- have another serious medical condition that might make the study unsafe for you (complete our online questionnaire or contact us for more info).

Who is doing this research?
The T4DM study is run by the University of Adelaide in collaboration with the National Health and Medical Research Council Clinical Trials Centre and is conducted at 6 hospitals around Australia by senior endocrinologists. The research is majority funded by the National Health and Medical Research Council.

How to join
You can sign up today by filling in our online screening questionnaire at: www.diabetesprevention.org.au

Click on the Join Now button.
To find out more, contact us on askt4dm@ctc.usyd.edu.au or 1300 865 436.
What if you have previously signed up for the study?
The study has been running for 3 years already. You may have heard about us on the radio in the past. If you have previously completed our online screening questionnaire but haven't yet been for lab screening it isn't too late to join up. Let us know at askt4dm@ctc.usyd.edu.au if you need another copy of your lab screening forms.

Thank you for considering this invitation to participate in this important men's health research. Our aim at the T4DM study is to improve the health of Australian men while also supporting our study participants to lose weight and improve their health.

If you do decide to join the study we will provide you with a participant information sheet containing further details about the study. If you are not interested in being part of the study you are under no obligation to complete our online screening questionnaire.

Kind regards

Prof Gary Wittert MBBch, MD, FRACP, FRCP
Head, Discipline of Medicine
Director, Freemasons Foundation Centre for Men's Health Research
University of Adelaide

T4DM study coordinating centre
Email: askt4dm@ctc.usyd.edu.au
Tel: 1300 865 436
Postcard front

Wondering what happened to the younger, healthier you?
Getting older doesn't have to mean you gain weight and lose your mojo.

Join the T4DM study today.
We'd love to help you find your mojo.

www.diabetesprevention.org.au  Tel: 1300 865 436

Postcard reverse side

T4DM Diabetes Prevention Study
Can testosterone treatment reduce the risk of diabetes in men like you?

Are you male and 50-74 years old? Overweight or obese?
We invite you to join the T4DM Diabetes Prevention Study.

If you join you will receive:
- 2 years of treatment with testosterone or placebo
- 2 years of Weight Watchers membership
- regular support from our dedicated study team

Get started today by completing our quick and easy online questionnaire:

www.diabetesprevention.org.au

For more info or help with the questionnaire
askt4dm@ctc.usyd.edu.au  1300 865 436
Appendix E: Chapter 3, supplementary file 2  
(definition of common Facebook and Google terms)

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Facebook</strong></td>
<td></td>
</tr>
<tr>
<td>Facebook Ads Manager</td>
<td>The online tool provided by Facebook for creation, management and monitoring of Facebook advertising</td>
</tr>
<tr>
<td>Boost</td>
<td>A Facebook option which allows an advertiser to pay to have a selected Facebook story shown to a larger audience than it would otherwise be shown to. The advertiser can define the characteristics of the audience who should be shown the story.</td>
</tr>
<tr>
<td>Impression</td>
<td>The number of times that an advertisement or post is shown on screen. Also used in relation to Google advertising.</td>
</tr>
<tr>
<td>Engagement</td>
<td>A term which encompasses any kind of user interaction with the organisation’s Facebook page including clicking on a link, or liking, sharing or commenting on a post.</td>
</tr>
<tr>
<td>Share</td>
<td>When a user chooses to show content from another Facebook page or website on their own Facebook page</td>
</tr>
<tr>
<td>Split or A/B testing</td>
<td>Functionality which randomises users to receive different versions of an advertisement or website in order to test which version is the most effective. Available within many online applications including Facebook and Google Advertising.</td>
</tr>
<tr>
<td><strong>Google</strong></td>
<td></td>
</tr>
<tr>
<td>Google Adwords</td>
<td>Google’s advertising service. It allows organisations to display advertisements on the Google search results screen when a user searches for keywords from a list defined by the advertiser. Now known as Google Ads.</td>
</tr>
<tr>
<td>Click-through-rate</td>
<td>The number of times an ad was clicked on, divided by the total number of times the ad was shown. Also known as CTR.</td>
</tr>
<tr>
<td>Maximum cost per click bid</td>
<td>An amount set by the advertiser as the maximum amount they are willing to pay per click. The actual amount paid may be less than this depending on how much other advertisers have bid. An automated bidding option is available which allows Google to determine the maximum cost per click.</td>
</tr>
<tr>
<td>Cost per click</td>
<td>The actual amount paid each time a user clicks on an advertisement. Also known as CPC.</td>
</tr>
<tr>
<td>Google Analytics</td>
<td>Web analytics program which supports website owners to perform real-time monitoring of users’ website interactions. For example, it provides statistics on the number of hits and visitors a website receives based on date, time, location and referral source. It also provides metrics on user’s behaviour on the website including which pages were visited and how long was spent on each page.</td>
</tr>
<tr>
<td>Goals</td>
<td>A goal is a website-based desired user action (for example, submitting information on a registration form) which is defined in Google Analytics and tracked. When a user performs the desired action this is called a conversion.</td>
</tr>
</tbody>
</table>