Asian Journal of Current Research in Clinical Cancer
ISSN: 3062-4444
2021, Volume 1, Issue 1, Page No: 28-37

Available online at: www.galaxypub.co/page/journals

Galaxy Publication

Galaxy Publication

Obstacles in Enrolling Men under Active Surveillance for Prostate Cancer in Clinical Chemoprevention Studies

J. Van Der Merwe[1*], P. Nkosi[1], R. Botha[1]

[1]Department of Molecular Oncology, Faculty of Health Sciences, University of Pretoria, Pretoria, South Africa.

***E-mail** ✉ molecular.oncology.4@yahoo.com

Received: 23 November 2020; **Revised:** 19 February 2021; **Accepted:** 21 February 2021

ABSTRACT

Clinical trials are fundamental to evidence-based medicine, as they employ rigorous scientific methods to evaluate the efficacy and safety of new therapies aimed at preventing or treating diseases, including cancer. Successful completion of these trials relies heavily on participant enrollment. Although over 70% of Americans express willingness to participate in clinical trials, fewer than 5% of adult cancer patients actually enroll, highlighting a substantial gap between intent and participation. This challenge is evident in trials involving men with prostate cancer (PCa) on active surveillance (AS), where the target population is predominantly over 50 years old, and recruitment and enrollment difficulties have been widely reported. Current participation rates for men in primary and secondary chemoprevention trials remain unknown. Moreover, unforeseen environmental events, such as pandemics or natural disasters that disrupt the economy, personal circumstances, travel, or in-person study procedures, underscore the importance of continuously identifying recruitment obstacles and developing solutions to ensure the timely completion of early-phase chemoprevention trials. Evidence from recent studies indicates that cancer prevention trials were disproportionately affected by the pandemic compared to treatment trials. This manuscript aims to share our experience in systematically assessing both protocol- and patient-level barriers to recruiting men on AS for PCa within a chemoprevention trial at the Comprehensive Cancer Center (CCC), while describing the current strategies employed to sustain enrollment. Using data from our ongoing trial as an example, we discuss approaches to enhance clinical trial recruitment overall, which may guide the design of future cancer chemoprevention studies and help prioritize strategies that efficiently target and engage the intended population.

Keywords: Prevention trials, Challenges in clinical trial recruitment, Prostate cancer, PCa trial

How to Cite This Article: Van Der Merwe J, Nkosi P, Botha R. Obstacles in Enrolling Men under Active Surveillance for Prostate Cancer in Clinical Chemoprevention Studies. Asian J Curr Res Clin Cancer. 2021;1(1):28-37. https://doi.org/10.51847/1epNMY0BUe

Introduction

The American Cancer Society projects that in 2022, the United States will see 268,490 new cases of prostate cancer (PCa), with 34,500 men dying from the disease [1]. Approximately 84% of diagnosed PCa cases are low-grade, for which the 5-year survival rate approaches 100%, in contrast to 31% for men with metastatic disease. This shift reflects the widespread use of serum prostate-specific antigen (PSA) screening, which has markedly increased the detection of low-grade PCas (Gleason ≤ 6), tumors that generally pose minimal risk of progression or mortality [2–5]. However, overdiagnosis of PCa can lead to overtreatment of low-risk disease, exposing patients to unnecessary morbidity without meaningful improvement in cancer-specific survival [4, 6]. As a result, active surveillance (AS) has emerged as the preferred management approach for men with low-grade disease, offering individualized monitoring of disease progression through PSA kinetics, imaging, and periodic biopsies, with timely intervention when needed [6]. In a 15-year follow-up of a large AS cohort, Klotz *et al*. (2015) [7] reported a 98% disease-specific survival for Gleason 3+3 tumors, findings corroborated by other prospective studies that confirm the relative safety and efficacy of AS [8].

Despite these advantages, several challenges exist for men on AS. Data from the US National Cancer Database (2010–2011) [9] highlight concerns about undergrading and variability in defining low-risk patients eligible for

AS. For instance, low-risk eligibility ranged from 39.8% (Klotz criteria, least stringent) [10] to 28.5% (D'Amico criteria, intermediate) [11], and 10.7% (modified Epstein criteria, most stringent) [12]. Nationally, Maurice *et al*. (2015) [9] reported much lower AS utilization—6.5%, 7.4%, and 12.1% across the same criteria—reflecting continued overtreatment despite evidence-based recommendations from 2012 [13]. Leyh-Bannurah *et al*. [14] assessed rates of insignificant prostate cancer (iPCa) after robot-assisted radical prostatectomy (RARP) in contemporary patients preoperatively eligible for AS, finding that stricter AS criteria excluded patients who nonetheless harbored iPCa, increasing overtreatment risk, particularly in older men. Patient-related factors, such as anxiety, depression, and decisional conflict about choosing AS, further influence treatment decisions, sometimes prompting patients to opt for therapy despite unchanged tumor characteristics [15, 16]. Conversely, men on AS are often highly motivated to adopt lifestyle changes to reduce PCa progression risk [16–18], offering opportunities for pharmacologic chemoprevention [19–21].

Given these considerations, men on AS represent an ideal population for chemoprevention interventions aimed at reducing progression and alleviating anxiety during surveillance. Previous large phase III trials investigating agents such as 5-alpha-reductase inhibitors (finasteride, dutasteride) [22–24] or trace elements like selenomethionine and vitamin E [25] were limited by increased risk of high-grade disease or lack of efficacy, constraining clinical adoption. Other approaches, including dietary and nutraceutical interventions evaluated in the WHEL study [26] and studies of isoflavones [27], lycopene [28], and green tea catechins (GTCs) [29], have also been explored. Among these, epigallocatechin gallate (EGCG), the primary catechin in green tea, appears particularly promising. Our ongoing recruitment efforts target men on AS both at a Comprehensive Cancer Center (ClinicalTrials.gov Identifier: NCT04300855) and nationally through the National Clinical Trials Network (ClinicalTrials.gov Identifier: NCT04597359).

Although over 70% of Americans indicate willingness to participate in clinical trials, fewer than 5% of adult cancer patients actually enroll [30–32], revealing a substantial gap between intent and participation. Participation rates for men in primary and secondary chemoprevention trials remain unknown. Trials involving men with PCa on AS, predominantly over 50 years old [33], face documented recruitment challenges. External factors, including pandemics or natural disasters such as hurricanes in Florida, can further disrupt travel, personal safety, and in-person study procedures, highlighting the need to continuously identify and address recruitment barriers to ensure timely completion of early-phase chemoprevention trials.

The purpose of this manuscript is to share our experience in systematically evaluating both protocol- and patient-level challenges in recruiting men on AS for PCa within a chemoprevention trial at the Comprehensive Cancer Center (CCC), and to describe contemporary strategies we are employing to maintain enrollment. Using data from our ongoing trial as an example, we discuss approaches to improve overall clinical trial recruitment, which can guide future cancer chemoprevention study design and help prioritize strategies that most effectively engage the target population.

Materials and Methods

The following sections summarize the cancer chemoprevention clinical trial and the proactive strategies implemented across several domains: (a) infrastructure, (b) study protocol and procedural design, (c) factors related to physicians and the research team, (d) recruitment methods including social media, advertisements, mass mailings, clinic posters, and digital marketing, and (e) participant-related considerations. With the onset of the pandemic within six months of trial initiation, which necessitated a temporary halt in recruitment, we also discuss additional challenges encountered and the strategies adopted to enhance enrollment. Data on the number of participants screened, those eligible, those who consented to participate, and the recruitment methods utilized are presented in tabular form. When possible, eligible participants were asked to provide reasons for declining participation.

Overview of the PCa trial

Study Design Summary: The study is designed as a randomized, double-blind clinical trial to assess the bioavailability, safety, and efficacy of a standardized Green Tea Catechin formulation (Sunphenon 90D®, Taiyo International, Inc., Minneapolis, MN, USA), providing 400 mg EGCG twice daily, compared to placebo over 24 months in men undergoing active surveillance (AS) for prostate cancer (PCa). Approval from both the IND and IRB will be obtained before trial initiation.

The primary endpoint is to evaluate clinical progression from baseline to 24 months in men on AS (per NCCN guidelines for very low, low, and favorable intermediate risk) with PCa (Gleason score 3+3 or predominant Gleason grade 2; 7 (3+4), ≤33% of biopsy cores positive, ≤50% involvement in any core) treated with GTC versus placebo. Clinical progression is defined as a composite outcome of >33% of biopsy cores positive, >50% involvement in any core, or Gleason sum reclassification (>3+3 or >3+4) at the end-of-study (EOS) biopsy.

Secondary endpoints include evaluation of intermediate endpoint biomarkers (IEBs) such as (a) PSA levels and kinetics (PSA, PSA doubling time, PSA density), (b) a 17-gene expression panel (Decipher), and (c) cancer incidence in post-intervention biopsies comparing GTC and placebo groups. Safety monitoring will follow NCI common toxicity criteria, with assessments of complete blood counts (CBC) and comprehensive metabolic profiles (CMP). Compliance will be tracked through pill counts and daily self-reported intake logs, with adherence verified via plasma EGCG levels from baseline through the end of the trial. Patient-reported outcomes, including lower urinary tract symptoms (LUTSs) using the LUTS Symptom Scale and quality of life (QOL) assessed by the RAND Short-Form (SF-36), will also be collected.

This design enables rigorous evaluation of both safety and treatment effects of GTC, informing potential Phase III trials for secondary chemoprevention in low-grade PCa. The study will establish a specimen repository for future testing of novel hypotheses and molecular targets beyond the proposed genomic markers. Whole blood, serum, urine, and prostate biopsy samples will be stored for DNA, RNA, and protein analyses, allowing assessment of additional genetic, environmental, and molecular factors that may influence PCa incidence and progression.

Based on prior experience, protocol- and patient-related challenges likely to affect participation were carefully considered, and proactive strategies were developed to mitigate these barriers. These approaches were informed by input from genitourinary oncologists, urologists, clinical research coordinators, and representatives from the target patient population.

Proactive strategies to address protocol-related challenges

Recruitment infrastructure

Recruitment for this project involves a multidisciplinary team including faculty from nutritional sciences, genitourinary oncology (GU), pathology, molecular biology, and biostatistics at the Moffitt Cancer Center, Department of Oncologic Sciences. The GU oncology program provides a strong infrastructure for chemoprevention trials, with a proven track record of successfully enrolling PCa patients across various treatment stages. The program's objectives are to (1) elucidate the mechanisms of key molecules in prostate carcinogenesis and tumor progression and evaluate their impact on therapeutic efficacy, and (2) prospectively determine the clinical utility of molecules/agents for therapeutic and chemoprevention interventions. The overarching goal is to improve the standard of care for individuals at risk for, or diagnosed with, PCa. Faculty members in this program participate actively in patient education, research, and personalized management of cancer patients. Subjects are recruited from the Moffitt Cancer Center's GU Oncology Department, which has an established and robust infrastructure for conducting chemoprevention trials.

Protocol and design of the study procedures

Subjects will be recruited both from the Moffitt Cancer Center and from referring physicians at affiliate sites. Previous experience demonstrates that these strategies are effective, using a staged, tailored, and interactive recruitment process emphasizing communication and relationship-building with community-based physicians, oncologists, and institutions. Information sessions are provided to affiliate and community physicians, support staff, and the public, and trial staff are available in clinical offices and institutions for education, training, and recruitment purposes. Only referring MDs who consent to allow patients to be followed at Moffitt Cancer Center are included in the trial. This infrastructure is critical for both recruitment and retention.

Several strategies are used to identify patients meeting eligibility criteria for PCa trials at Moffitt, including: (a) weekly GU Tumor Board meetings to identify newly diagnosed patients with Gleason 3+3 or 3+4 scores who are placed on active surveillance, (b) patient notifications by treating MDs, physician assistants (PA), or nurse practitioners (NP) via phone or Zoom after biopsy and receipt of pathology results, and (c) leveraging Moffitt's formal active surveillance program, which enrolls over 200 new patients annually, with ongoing patients referred to the research team for study information and enrollment consideration.

Recognizing that hospitals can be overwhelming, efforts are made to reduce patient burden and anxiety. Clear written instructions are provided before the initial screening visit. Upon arrival, the clinical research coordinator (CRC) guides participants through procedures including signing the informed consent form (ICF), clinical laboratory procedures, a brief physical with the treating MD team, and other data collection measures, all conducted in the same building. Appointments are scheduled to minimize wait times, and research and clinical staff are kept updated on patient status.

The phase II randomized trial has a 24-month intervention period. Although this duration is relatively long for phase II trials, study visits are aligned with standard active surveillance visits (initial biopsy, follow-up visits every six months, and follow-up biopsy at 24 months) to reduce participant burden. Narrow eligibility criteria have been identified as a barrier to trial participation [34–37], particularly among older adults, where exclusion is often due to comorbidities [38]. To enhance access and ensure generalizability, while maintaining safety, exclusion criteria were minimized for comorbidities unrelated to cancer or hepatitis B/C. Participants with no major organ dysfunction were included, with periodic safety monitoring relevant to the study agent (CBC, CMP, liver function tests, and Common Terminology Criteria for Adverse Events (CTCAE) monitoring). Participants unable to come to the research site for safety lab draws may use their nearest clinical laboratory (e.g., Quest Labs). Since most men over 50 take vitamin or mineral supplements, any supplement containing GTC was restricted, and all participants were provided a standard vitamin supplement to discourage use of other supplements. To reduce wait times, study agent supplies are mailed securely to participants by the investigational pharmacy upon randomization.

Physician- and study-team contributions

Our experience and that of others indicate that committed and experienced physicians, along with dedicated research staff, are critical to successful clinical trial enrollment. Studies have shown that a physician's personal preference or decision is often the main reason eligible patients decline participation, even when the trial is open [36, 37]. High clinical workload and limited availability have been consistently cited as the most significant barriers preventing physicians from referring patients to trials [39–41]. While other factors, such as access to alternative therapies, may influence participation in some settings [39, 40], this is unlikely to affect men on active surveillance (AS) for low-grade prostate cancer, as no approved alternatives exist. To minimize the time required from physicians, the trial protocol allows the treating MD to provide only a brief introduction, with detailed trial discussions and informed consent conducted by nurse practitioners (NPs) or physician assistants (PAs). Notably, all participating MDs are co-investigators fully engaged in the study and played a central role in designing the trial in accordance with NCCN AS guidelines [42].

Recruitment and retention team organization

A dedicated Recruitment/Intervention and Retention Team was established early in the trial design to guide and oversee enrollment procedures. The team, comprising the principal investigator (PI) and clinical trial coordinators, ensures consistent execution of all recruitment, intervention, and retention protocols. They also contribute to developing recruitment strategies and hold monthly teleconferences to address challenges, share successful approaches, and make procedural adjustments. Each site maintains a monthly screening and recruitment log submitted to the PI, documenting the number of biopsies reviewed (pre-screening), potentially eligible patients, those deemed ineligible, participants randomized, anticipated AS follow-up, and reasons eligible patients were not enrolled.

Quarterly, the PI reviews the screening logs, recruitment practices, team meeting minutes, and other relevant communications to classify barriers as patient-, protocol-, or infrastructure-related. Findings are then used to inform protocol adjustments that improve recruitment while maintaining the study's primary objectives.

Media and community outreach for recruitment

After obtaining IRB approval, a coordinated media and outreach campaign was launched with assistance from institutional public relations and marketing teams. This included national and local promotion through social media, print, and web-based channels. A decision aid brochure was created to explain the study rationale, eligibility criteria, participant responsibilities, and contact information, and was distributed at men's health events, community clinics, churches, pharmacies, and other community organizations. The trial was also registered on ClinicalTrials.gov. Previous experience has shown that culturally and literacy-competent recruitment strategies—

including radio, newspaper advertisements, mailings, web postings, and decision aids—can effectively reach target enrollment goals in cancer prevention trials. Nevertheless, the clinical team adopted a conservative approach to digital media, exercising caution when using social media for clinical intervention trial recruitment [43, 44].

Subject-related factors

Patient-related considerations have historically posed significant challenges in clinical trial enrollment. Evidence shows that research teams who closely monitor recruitment, retention, and randomization logs, and use this information to refine trial procedures, achieve substantially better recruitment outcomes.

Ultimately, participation decisions rest with the patients themselves, who often consult family or close friends in making their choice [45]. Some individuals are motivated primarily by altruism [46], while others participate to access the best possible care for their condition, particularly when no alternative treatment exists other than active monitoring [47, 48]. Commonly reported barriers include reluctance to be randomized and a preference to know in advance which study arm they will be assigned to, with fear of randomization cited as a frequent reason for non-participation [46]. Additional factors include travel distance, time commitment, costs, and completing study-related monitoring tasks [49]. Previous studies and advocacy groups have also highlighted anxiety arising from the informed consent process, particularly regarding potential side effects, as another deterrent [50].

To address these issues, the study covers all costs related to trial procedures, while routine care expenses remain the responsibility of the patient's insurance. This is clearly explained during the informed consent process. The consent form itself was carefully reviewed by multiple team members to ensure clarity and compliance with IRB requirements. Recognizing that frequent visits, study compliance, monitoring tasks, dietary restrictions, and invasive procedures such as biopsies can create substantial burden, the study schedule was aligned with standard AS program requirements to minimize unnecessary visits. Telephone follow-ups are conducted at least monthly by research staff to support adherence, and patients are permitted to use local laboratories for blood draws to reduce travel and clinic visits.

Chemoprevention trials targeting high-risk individuals can face additional challenges, as anxious participants may prefer assignment to the intervention arm rather than placebo. Furthermore, many investigational agents are also commercially available as over-the-counter supplements or in "natural" forms, which can lead potential participants to decline trial enrollment to avoid randomization. To improve willingness to enroll and increase the probability of receiving the active intervention, participants are randomized in a 2:1 ratio to receive GTC with 400 mg EGCG BID (treatment arm) versus placebo.

Pandemic-related barriers

The onset of COVID-19 presented unforeseen challenges for trial recruitment. To mitigate infection risk, Moffitt Cancer Center placed a temporary hold on most in-person research activities, including this clinical trial, as the safety risks for participants—especially those with cancer—were unknown and potentially high. Patients over 65, often with multiple comorbidities, were particularly vulnerable to severe disease and mortality. Consequently, the trial protocol was revised to minimize clinic visits wherever possible. After COVID-19 vaccines and booster doses became available, the cancer center provided them free of charge to patients and their spouses. Despite initiating recruitment in August 2020, many men on AS for PCa were hesitant to attend in-person study visits. Periods of greatest reluctance corresponded to the major waves of the pandemic, specifically from 1 March to 25 April 2020 and later from October 2020 to January 2021.

Natural disaster-related factors

In 2022, Florida experienced two major hurricanes—Ian, a Category 4 storm that struck the Gulf Coast in October, and Nicole, which made landfall in November. These events affected the Cancer Center's patient catchment area, leading to disruptions such as property damage, loss of homes, and temporary closure of clinical sites, all of which negatively impacted recruitment for the clinical trial.

Results and Discussion

Following initial funding approval from the National Cancer Institute (NCI), the study protocol received clearance from the Moffitt Scientific Review Committee (SRC) and Advara Institutional Review Board (IRB). Approval for the Investigational New Drug (IND) application for the study agent and placebo was obtained from the FDA

(IND# 143615, Kumar NB). The trial was registered on ClinicalTrials.gov (Identifier: NCT04300855), with patient accrual commencing on August 21, 2020.

A total of 201 individuals were initially screened for participation **(Table 1)**. Upon detailed review, 51 men were deemed ineligible. Reasons for ineligibility included death (2), disease progression (2), elevated serum PSA levels (22), initiation of other treatments such as radiation or hormone therapy (15), relocation out of state (9), and diagnosis of a different cancer (1). Fifteen of these individuals were successfully recruited, while 39 men on active surveillance remain interested and are undergoing screening. An additional 17 potential participants were unresponsive to phone or email communications, and 54 declined participation, with specific reasons detailed in **Table 2**.

Among the 25 participants who were ultimately randomized, the trial experienced a 16% attrition rate, with four subjects discontinuing for various reasons: one relocated out of state, one experienced disease progression, and two found the study burdensome or were unable to travel.

Table 1. Summary of eligible subjects contacted.

Summary	As of 11/10/2022
Recruited and Randomized	25
Additional Enrolled/Scheduled	12
Patient has agreed and awaiting follow up biopsy/MRI in the next 6 months	3
On AS–CRC will contact patient based on AS follow up schedule	39
Left voicemails or sent emails	17
Declined	54
No longer eligible	51
Total contacted	**201**

Table 2. Reasons for declining trial.

Reason for Declining Participation	Number
Things are going well/does not see benefit	5
Not comfortable with end of study biopsy	3
Concerned about experimental drug, anti-drugs, placebo	2
Does not want to discontinue green tea supplements or not limit green tea drinking	2
Does not have time to commit/long duration of study	8
Distance (e.g., 2 patients live far away and cannot drive)	4
Currently seeing too many doctors, too many appointments	2
Illness (Parkinson's disease; gastrointestinal issues; cirrhosis; thyroid and kidney disease; wife in hospice, cancer)	7
Not interested (looked over protocol and no interest)	5
No specific reason	16
Participated in another trial	1
Total	**54**

Although reasons for declining participation were collected and analyzed to identify trends that might necessitate protocol adjustments, no clear pattern emerged aside from 16 of 54 individuals who simply were not interested and could not specify a reason. These figures are comparable to those reported in other trials; however, residual anxiety related to the pandemic continues to influence enrollment. Despite employing various recruitment approaches, including advertising and social media, the proportion of subjects recruited for trials targeting early-stage disease with long intervention periods (1–2 years) remains under 1%. Consistent with our prior experience [51], strategies such as social media campaigns, posters, mass mailings, and digital marketing yielded no additional recruitment. The most effective approach continues to involve an initial trial presentation by the

patient's MD, PA, or NP, followed by referral to the senior clinical research coordinator (CRC) for further screening and enrollment. Notably, 100% of participants recruited and those pending were initially referred through this physician-mediated process.

Unger *et al*. recently reported that one year after the onset of the COVID-19 pandemic, cancer control and prevention trials experienced decreased enrollment, whereas treatment trials did not show a significant reduction [52]. They categorized barriers to enrollment into structural factors (clinic access, trial availability), clinical factors (patient eligibility), attitudinal physician factors (offering the trial), and attitudinal patient factors (patient decision) [30]. In prior work [51], we broadly classified barriers as protocol-related (trial design) and patient-related. In the present study, barriers were initially categorized as: (I) protocol-related (a) recruitment infrastructure; (b) study procedures; (c) physician and study team factors; (d) media and outreach); (II) subject-related; (III) pandemic-related; and (IV) natural disaster-related. This framework allowed proactive planning of strategies, yet the pandemic and natural disasters highlighted unforeseen challenges, emphasizing the need for continuous assessment and adaptation. Our data demonstrate that despite prior strategies informed by experience and literature, the COVID-19 pandemic substantially disrupted PCa trial recruitment, necessitating protocol refinements. All trial data described here were collected post-pandemic vaccination availability and after the second variant wave affecting Florida and the US. This experience reinforces the importance of ongoing evaluation of protocol, patient, and environmental factors to develop timely and effective recruitment strategies.

Recruitment officially commenced in August 2020; however, consistent with national trends in prevention trials, participation remained low, particularly among men on AS who are not undergoing active treatment. Traditional face-to-face recruitment strategies were challenged by reduced clinic capacity and limited in-person visits, requiring recruitment efforts to be conducted virtually. While interventions such as exercise or yoga have been successfully delivered via telemedicine [53, 54], chemoprevention trials involving IND study drugs are not well-suited to remote enrollment or intervention. Because timely enrollment is essential to preserve trial validity and impact cancer outcomes, efficient recruitment remains a priority.

To mitigate pandemic-related delays, additional recruitment sites were added, including George Washington University Cancer Center (Washington, DC) and the University of Kansas Cancer Center (Westwood, KS), with PIs and research teams experienced in PCa clinical trials. These sites are estimated to provide approximately 25 eligible participants annually. A centralized Recruitment and Retention Team now includes members from all three sites, and the protocol has been amended accordingly. Procedures for drug distribution, generic multivitamin provision, monitoring, data safety, and regulatory compliance have been established, with Moffitt Cancer Center's External Site Coordination (ESC) team supporting smooth trial operations. The protocol, informed consent, and regulatory approvals (IRB, FDA) have been updated to reflect these changes.

Conclusion

Consistent with our previous findings [51], the involvement of the treating MD and clinical team is crucial for successful recruitment in cancer prevention trials. In this study, all enrolled participants were referred by their MD, PA, or NP. Future trials should continue to proactively consider challenges related to infrastructure, protocol design, research teams, and patient factors during study planning. Maintaining detailed records of reasons for non-participation allows ongoing evaluation and, when necessary, revision of trial design to reduce barriers. The COVID-19 pandemic illustrated the importance of flexibility and rapid protocol adaptations to maintain trial conduct without compromising scientific integrity [55]. Emerging strategies such as artificial intelligence for patient identification [56], telemedicine for patient communication, and reassessment of the necessity for frequent in-person visits for laboratory and biopsy procedures can help optimize recruitment and trial efficiency. While frequent protocol amendments may slow initial implementation, fostering strong relationships with SRCs, IRBs, and the FDA can expedite approvals and improve the conduct of cancer prevention trials in the future.

Acknowledgments: None

Conflict of Interest: None

Financial Support: None

Ethics Statement: None

References

1. American Cancer Society. Prostate cancer — Key statistics. Atlanta, GA; 2022 Nov 20 [cited 2022 Nov 20]. Available from: http://www.cancer.org/Cancer/ProstateCancer/DetailedGuide/prostate-cancer-key-statistics/
2. Bruinsma SM, Bangma CH, Carroll PR, Leapman MS, Rannikko A, Petrides N, et al. Active surveillance for prostate cancer: a narrative review of clinical guidelines. Nat Rev Urol. 2016;13(3):151-67.
3. Ip S, Dahabreh IJ, Chung M, Yu WW, Balk EM, Iovin RC, et al. An evidence review of active surveillance in men with localized PCa. Evid Rep Technol Assess (Full Rep). 2011;(204):1-341.
4. Klotz L. Active Surveillance for Prostate cancer: For Whom? J Clin Oncol. 2005;23(32):8165-9.
5. Thompson I, Thrasher JB, Aus G, Burnett AL, Canby-Hagino ED, Cookson MS, et al. Guideline for the Management of Clinically Localized Prostate cancer: 2007 Update. J Urol. 2007;177(6):2106-31.
6. Stainsby GD, Hamdy FC, Donovan JL, Neal DE. 10-Year Outcomes in Localized Prostate cancer. N Engl J Med. 2017;376(2):178-81.
7. Klotz L, Zhang L, Lam A, Nam R, Mamedov A, Loblaw A. Clinical results of long-term follow-up of a large, active Surveillance cohort with localized prostate cancer. J Clin Oncol. 2010;28(1):126-31.
8. Klotz L. Active Surveillance for Low-Risk Prostate cancer. Curr Urol Rep. 2015;16(24):24.
9. Maurice MJ, Abouassaly R, Kim SP, Zhu H. Contemporary Nationwide Patterns of Active Surveillance Use for Prostate cancer. JAMA Intern Med. 2015;175(9):1569-71.
10. Klotz L. Active surveillance and focal therapy for low-intermediate risk prostate cancer. Transl Androl Urol. 2015;4(3):342-54.
11. D'Amico AV. Personalizing the Use of Active Surveillance As an Initial Approach for Men With Newly Diagnosed Prostate cancer. J Clin Oncol. 2015;33(30):3365-6.
12. Oon SF, Watson RW, O'Leary JJ, Fitzpatrick JM. Epstein criteria for insignificant prostate cancer. BJU Int. 2011;108(4):518-25.
13. Cooperberg MR, Carroll PR. Trends in Management for Patients with Localized Prostate cancer, 1990–2013. JAMA. 2015;314(1):80-2.
14. Leyh-Bannurah S-R, Wagner C, Schuette A, Addali M, Liakos N, Urbanova K, et al. The impact of age on pathological insignificant prostate cancer rates in contemporary robot-assisted prostatectomy patients despite active surveillance eligibility. Minerva Urol Nephrol. 2022;74(4):437-44.
15. Orom H, Underwood W, Biddle C. Emotional Distress Increases the Likelihood of Undergoing Surgery among Men with Localized Prostate cancer. J Urol. 2017;197(2):350-5.
16. Watts S, Leydon GM, Eyles C, Moore CM, Richardson A, Birch B, et al. A quantitative analysis of the prevalence of clinical depression and anxiety in patients with prostate cancer undergoing active surveillance. BMJ Open. 2015;5(5):e006674.
17. Avery KNL, Donovan JL, Horwood J, Neal DE, Hamdy FC, Parker C, et al. The importance of dietary change for men diagnosed with and at risk of prostate cancer: A multi-centre interview study with men, their partners and health professionals. BMC Fam Pract. 2014;15(81):81.
18. Horwood JP, Avery KNL, Metcalfe C, Donovan JL, Hamdy FC, Neal DE, et al. Men's knowledge and attitudes towards dietary prevention of a prostate cancer diagnosis: A qualitative study. BMC Cancer. 2014;14(812):812.
19. Kelloff GJ, Lieberman R, Steele VE, Boone CW, Lubet RA, Kopelovitch L, et al. Chemoprevention of PCa: Concepts and strategies. Eur Urol. 1999;35(5-6):342-50.
20. Kumar N. Molecular targeted therapies using botanicals for prostate cancer Chemoprevention. Transl Med. 2012;1(Suppl 2):005.
21. Lieberman R. PCa chemoprevention: Strategies for designing efficient clinical trials. Urology. 2001;57(4):224-9.
22. Andriole GL, Bostwick DG, Brawley OW, Gomella LG, Marberger M, Montorsi F, et al. Effect of dutasteride on the risk of prostate cancer. N Engl J Med. 2010;362(13):1192-202.
23. Hamilton RJ, Kahwati LC, Kinsinger LS. Knowledge and Use of Finasteride for the Prevention of Prostate cancer. Cancer Epidemiol Biomark Prev. 2010;19(9):2164-71.

24. Thompson IM, Goodman PJ, Tangen CM, Lucia MS, Miller GJ, Ford LG, et al. The influence of finasteride on the development of PCa. N Engl J Med. 2003;349(3):215-24.
25. Lippman SM, Klein EA, Goodman PJ, Lucia MS, Thompson IM, Ford LG, et al. Effect of Selenium and Vitamin E on Risk of Prostate cancer and Other Cancers: The Selenium and Vitamin E Cancer Prevention Trial (SELECT). JAMA. 2009;301(1):39-51.
26. Parsons JK, Pierce JP, Mohler J, Paskett E, Jung S-H, Humphrey P, et al. A randomized trial of diet in men with early stage prostate cancer on active surveillance: Rationale and design of the Men's Eating and Living (MEAL) Study (CALGB 70807 [Alliance]). Contemp Clin Trials. 2014;38(2):198-203.
27. Kumar NB, Pow-Sang J, Spiess P, Dickinson S, Schell MJ. A phase II randomized clinical trial using aglycone isoflavones to treat patients with localized prostate cancer in the pre-surgical period prior to radical prostatectomy. Oncotarget. 2020;11(14):1218-34.
28. Kumar NB, Besterman-Dahan K, Kang L, Pow-Sang J, Xu P, Allen K, et al. Results of a Randomized Clinical Trial of the Action of Several Doses of Lycopene in Localized Prostate cancer: Administration Prior to Radical Prostatectomy. Clin Med Urol. 2008;1:CMU-S718.
29. Kumar NB, Pow-Sang J, Egan KM, Spiess P E, Dickinson S, Salup R, et al. Randomized, Placebo-Controlled Trial of Green Tea Catechins for Prostate cancer Prevention. Cancer Prev Res. 2015;8(10):879-87.
30. Unger JM, Cook E, Tai E, Bleyer A. The Role of Clinical Trial Participation in Cancer Research: Barriers, Evidence, and Strategies. Am Soc Clin Oncol Educ Book. 2016;35:185-98.
31. Murthy VH, Krumholz HM, Gross CP. Participation in cancer clinical trials: race-, sex-, and age-based disparities. JAMA. 2004;291(22):2720–6.
32. Tejeda HA, Green SB, Trimble EL, Ford L, High JL, Ungerleider RS, et al. Representation of African-Americans, Hispanics, and whites in National Cancer Institute cancer treatment trials. J Natl Cancer Inst. 1996;88(12):812–6.
33. Bracken K, Askie L, Keech AC, Hague W, Wittert G. Recruitment strategies in randomised controlled trials of men aged 50 years and older: a systematic review. BMJ Open. 2019;9(4):e025580.
34. Langford AT, Resnicow K, Dimond EP, Denicoff AM, Germain DS, McCaskill-Stevens W, et al. Racial/ethnic differences in clinical trial enrollment, refusal rates, ineligibility, and reasons for decline among patients at sites in the National Cancer Institute's Community Cancer Centers Program. Cancer. 2013;120(6):877–84.
35. Lara PN Jr, Higdon R, Lim N, Kwan K, Tanaka M, Lau DH, et al. Prospective evaluation of cancer clinical trial accrual patterns: identifying potential barriers to enrollment. J Clin Oncol. 2001;19(6):1728–33.
36. Begg CB, Zelen M, Carbone PP, McFadden ET, Brodovsky H, Engstrom P, et al. Cooperative groups and community hospitals. Measurement of impact in the community hospitals. Cancer. 1983;52(8):1760–7.
37. Hunter CP, Frelick RW, Feldman AR, Bavier AR, Dunlap WH, Ford L, et al. Selection factors in clinical trials: results from the Community Clinical Oncology Program Physician's Patient Log. Cancer Treat Rep. 1987;71(6):559–65.
38. Unger JM, Hershman DL, Fleury ME, Vaidya R. Association of patient comorbid conditions with cancer clinical trial participation. JAMA Oncol. 2019;5(3):326–33.
39. Somkin CP, Altschuler A, Ackerson L, Geiger AM, Greene SM, Mouchawar J, et al. Organizational barriers to physician participation in cancer clinical trials. Am J Manag Care. 2005;11(6):413–21.
40. Benson AB 3rd, Pregler JP, Bean JA, Rademaker AW, Eshler B, Anderson K. Oncologists' reluctance to accrue patients onto clinical trials: an Illinois Cancer Center study. J Clin Oncol. 1991;9(12):2067–75.
41. Siminoff LA, Zhang A, Colabianchi N, Strum CMS, Shen Q. Factors that predict the referral of breast cancer patients onto clinical trials by their surgeons and medical oncologists. J Clin Oncol. 2000;18(6):1203–11.
42. NCCN Guidelines for PCa; NCCN: Bethesda, MD, USA, 2017. Available online: https://www.tri-kobe.org/nccn/guideline/urological/english/prostate/pdf (accessed 20 Nov 2022).
43. Sedrak MS, Sun V, Liu J, George K, Wong AR, Dale W, et al. Physician perceptions of the use of social media for recruitment of patients in cancer clinical trials. JAMA Netw Open. 2019;2(5):e1911528.
44. Gelinas L, Pierce R, Winkler S, Cohen IG, Lynch HF, Bierer BE. Using social media as a research recruitment tool: ethical issues and recommendations. Am J Bioeth. 2017;17(3):3–14.
45. Ellis PM, Butow PN, Tattersall MH, Dunn SM, Houssami N. Randomized clinical trials in oncology: understanding and attitudes predict willingness to participate. J Clin Oncol. 2001;19(15):3554–61.

46. Unger JM, Hershman DL, Albain KS, Moinpour CM, Petersen JA, Burg K, et al. Patient income level and cancer clinical trial participation. J Clin Oncol. 2013;31(5):536–42.
47. Cassileth BR, Lusk EJ, Miller DS, Hurwitz S. Attitudes toward clinical trials among patients and the public. JAMA. 1982;248(7):968–70.
48. Daugherty C, Ratain MJ, Grochowski E, Stocking C, Kodish E, Mick R, et al. Perceptions of cancer patients and their physicians involved in phase I trials. J Clin Oncol. 1995;13(5):1062–72.
49. Ford JG, Howerton MW, Lai GY, Gary-Webb T, Bolen S, Gibbons MC, et al. Barriers to recruiting underrepresented populations to cancer clinical trials: a systematic review. Cancer. 2008;112(2):228–42.
50. Coyne CA, Xu R, Raich P, Plomer K, Dignan M, Wenzel L, et al. Randomized, controlled trial of an easy-to-read informed consent statement for clinical trial participation: a study of the Eastern Cooperative Oncology Group. J Clin Oncol. 2003;21(4):836–42.
51. Kumar N, Crocker T, Smith T, Pow-Sang J, Spiess PE, Egan K, et al. Challenges and potential solutions to meeting accrual goals in a phase II chemoprevention trial for PCa. Contemp Clin Trials. 2012;33(2):279–85.
52. Unger JM, Xiao H, LeBlanc M, Hershman DL, Blanke CD. Cancer clinical trial participation at the 1-year anniversary of the outbreak of the COVID-19 pandemic. JAMA Netw Open. 2021;4(1):e2118433.
53. Mishra P, Greenfield SM, Harris T, Hamer M, Lewis SA, Singh K, et al. Yoga program for type 2 diabetes prevention (YOGA-DP) among high-risk people: qualitative study to explore reasons for non-participation in a feasibility randomized controlled trial in India. Front Public Health. 2021;9:682203.
54. Jalkanen K, Järvenpää R, Tilles-Tirkkonen T, Martikainen J, Aarnio E, Männikkö R, et al. Comparison of communication channels for large-scale type 2 diabetes risk screening and intervention recruitment: empirical study. JMIR Diabetes. 2021;6(1):e21356.
55. Karzai F, Dahut WL. Lessons from the impact of the COVID-19 pandemic at the National Cancer Institute. Cancer J. 2022;28(2):118–20.
56. Ibrahim H, Liu X, Rivera SC, Moher D, Chan AW, Sydes MR, et al. Reporting guidelines for clinical trials of artificial intelligence interventions: the SPIRIT-AI and CONSORT-AI guidelines. Trials. 2021;22(1):11.