intervention limited to the office visit, 40% of eligible men at participating sites could enroll (n=40 per year for three years) in the Northern Plains and Alaska combined (this is a conservative estimate-most Mayo Clinic decision aid trials accrue 70% of patients approached). We have access to several urban sites from which to draw African American and Hispanic/Latino men, making their recruitment less difficult. The long term success of this line of research will hinge on decision aids being successfully used and their having a positive impact on patient knowledge and risk-concordant treatment decision making. Because of less geographic clustering, men of Hispanic/Latino ethnicity will be recruited from all study sites with a similar overall accrual target, reserving two slots minimum for them during the first year of accrual.

What if we do not accrue enough minority men? The primary outcome of this study is knowledge. Aggressive accrual targets for minority men are feasible, but there is no guarantee that they can be achieved. Suppose we only achieve accrual of half of the African American and American Indian/Alaska Native sample sizes and resorted to fill the remaining enrollment with men of self-described White/Asian race. Under this scenario (109 Hispanic/Latino, White, or Asian, 21 African American, and 21 American Indian/Alaska Native race) we would only be able to make the most preliminary (exploratory) inferences about differential outcomes in those subgroups, but our power to test our primary outcome, knowledge, would be preserved. (Part of such an exploratory analysis could include looking for White vs. all others differences, but such analyses are conceptually flawed and would be of limited utility.) Even under this scenario, this trial would make an important contribution to the literature on prostate cancer shared decision making and would represent the most robust minority representation of any such trial in North America to date.

___ **3.2.7 Patients must be able to read and comprehend English.** Non-English-speaking patients may participate so long as an interpreter (e.g., family member, clinic staff, etc.) is present for consent, for the Decision Aid administration, and gathering of baseline and follow-up measures.

___ **3.2.8 Age ≥ 18 years**

4.0 PATIENT REGISTRATION

4.1 CTEP/DCP Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account [redacted]. In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN, Rave, or TRIAD or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) [redacted] Documentation requirements per registration type are outlined in the table below.

Documentation Required	IVR	NPIVR	AP	A
FDA Form 1572	✔	✔		
Financial Disclosure Form	✔	✔	✔	
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔	
HSP/GCP training	✔	✔	✔	
Agent Shipment Form (if applicable)	✔			
CV (optional)	✔	✔	✔	

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval

Additional information can be found on the CTEP website at [redacted] For questions, please contact the RCR Help Desk by email at [redacted]

4.2 CTSU Registration Procedures

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

10.3 Expanded Prostate Cancer Index Composite Short Form (EPIC-26)

The Expanded Prostate Cancer Index Composite[66] measures health-related quality of life and returns summary scores for urinary, bowel, sexual, and hormonal domains with high test-retest reliability and internal consistency.

The questionnaire will be administered once; 12 months after the patient's initial consultation. The instrument contains 26 items, and will take approximately 10-15 minutes to complete.

10.4 Decisional Regret Scale

The Decisional Regret Scale[73] is a short, 5-item scale measuring "distress or remorse after a (health care) decision." The instrument has been validated in other decision aid studies.[74] Questions are answered on a 5-point agreement scale.

The questionnaire will be administered once; 12 months after the patient's initial consultation and will take approximately 1-3 minutes to complete.

11.0 END OF INTERVENTION

11.1 Duration of Treatment

The study intervention will take place in one day and follow-up assessments will occur at 12 months following the intervention.

11.2 Managing ineligible patients and registered patients who never receive protocol intervention

Definition of ineligible patients

A study participant who is registered to the trial but does not meet all of the eligibility criteria is deemed to be ineligible.

Follow-up for ineligible patients who continue with protocol intervention

Patients who are deemed ineligible after registering may continue the protocol intervention, provided the treating physician, study chair, and executive officer agree there are no safety concerns if the patient continues protocol intervention. All tests and data submission are to continue as if the patient were eligible. Notification of the local IRB may be necessary per local IRB policies.

Follow-up for ineligible patients who discontinue protocol intervention

For patients who are deemed ineligible after registering to the trial, who start the study intervention, but then discontinue the intervention, the same data submission requirements are to be followed as for those patients who are eligible and who discontinue study participation.

Follow-up for patients who are registered, but who never start study intervention

For all study participants who are registered to the trial but who never receive study intervention (regardless of eligibility), baseline and off-treatment notice data submission required. See the Data Submission Schedule accompanying the All Forms Packet.

11.3 Extraordinary Medical Circumstances

If, at any time the constraints of this protocol are detrimental to the patient's health and/or the patient no longer wishes to continue protocol participation, protocol participation shall be discontinued. In this event:

- Document the reason(s) for discontinuation of protocol participation on data forms.
- Follow the patient for protocol endpoints as required by the Study Calendar.

12.2.2 Sample Size and Power Considerations

Sample size and power calculation: We first consider power and sample size under the assumption that patients within the same site are uncorrelated**.** As this is unlikely to be the case in a group randomized trial, we will discuss the adjustment of the sample size estimate to account for this correlation between patients in the next subsection. A recent Cochrane review suggests that most patients can accurately answer 50% (standard deviation of 12%) of the questions asked of them.[70] On average, DAs increase that knowledge by 20% to 60% of questions asked being answered correctly, but 95% of trials show absolute knowledge increases of 10% or greater. We will consider an absolute 8% increase in knowledge as a clinically meaningful effect size for either during-consultation Prostate Choice or pre-consultation DA in this clinical trial. Note that the four arms of this study make up a 2 X 2 factorial design. Thus, it is natural to consider evaluating the decision aids using a two-way analysis of variance (ANOVA). In this case, the two factors in the ANOVA will be having received during-consultation Prostate Choice (yes or no) and having received pre-consultation DA (yes or no). We will consider simultaneously testing (at a significance level of 0.025 for each test) the main effects of the two decision aids as our primary analysis. That is, we will simultaneously test the null hypothesis that the average knowledge (i.e. the proportion of correct responses to questions) among those who received the pre-consultation DA is equal to that among those who did not (vs. an alternative that these two averages are not equal), and the null hypothesis that the average knowledge among those who received the during-consultation Prostate Choice is equal to that among those who did not (vs. an alternative that these two averages are not equal). A total sample of 100 patients (25 patients per arm) would give us approximately 85% power to detect a difference between those receiving pre-consultation DA and those not receiving pre-consultation DA, under the alternative that the average knowledge among those receiving pre-consultation DA is 58%, and that the average knowledge among those not receiving pre-consultation DA is 50%, using a two-sample t-test (with two-sided alternative) with a 2.5% significance level (this is equivalent to the F test for the main effects in the ANOVA). Under a similar alternative, the same can be said for the during-consultation Prostate Choice decision aid. Thus, if patients within each site were not correlated with each other, our target sample size would be 100 patients. There will be some, but insufficient power to detect an interaction between the two decision aids, but such effects are rare and not anticipated in this study. Therefore, we will not test for such an interaction in the primary analysis.

Sample size adjustment due to cluster randomization: As mentioned above, we do not believe that subjects within each site will truly be independent of each other. Thus, the application of the standard sample size calculation, as above, may lead to an underpowered study. Since we expect k=20 sites to participate in this clinical trial, we would need about m = 5 patients to be enrolled from each site (on average) to achieve a total enrollment of 100 patients. Assuming the intra-site correlation coefficient ρ will be approximately 0.1 (rather than zero) for all study sites, we must inflate the target sample size by a factor[71] of $1+(m-1)\rho=1+(5-1)*0.1=1.4$ to achieve comparable power to that in a patient-level randomized trial. This comes about as follows (we consider the pre-decision DA here, but the same derivation holds for the during-consultation Prostate Choice). Suppose the variance of knowledge (Y) is the same for all patients, and is equal to σ^2, and that n is our total sample size, with n/2 patients receiving the pre-consultation DA and n/2 not receiving the pre-consultation DA. Assuming no correlation between patients within the same site, the variance of the sample mean of knowledge among those receiving pre-consultation DA ($\bar{Y}_1$) will be $\sigma^2/(n/2)$, as will that for the sample mean of knowledge among those not receiving pre-consultation DA ($\bar{Y}_2$), and our test statistic would have the form $[(\bar{Y}_1 - \bar{Y}_2) - (\mu_1 - \mu_2)]/[\sigma^2/(n/2) + \sigma^2/(n/2)]^{(1/2)}$ (note that the denominator of this statistic simplifies to $[4\sigma^2/n]^{(1/2)}$). However, this is not a correct assumption in our case. In particular, suppose that we have 20 sites, and within each site, we have m (5) patients, between each of whom the

Prostate Cancer Treatment Questionnaire

Please check the TRUE or FALSE box for each statement based on your knowledge of prostate cancer treatments. If you are not completely sure, mark 'Unsure'.

		True	False	Unsure
1.	**Most prostate cancer spreads quickly to other parts of the body**	1☐	2☐	3☐
2.	**Other illnesses can make treating prostate cancer more difficult**	1☐	2☐	3☐
3.	**Some treatments are better than others at stopping prostate cancer**	1☐	2☐	3☐
4.	**Radiation therapy from a machine for prostate cancer requires weeks of daily treatments**	1☐	2☐	3☐
5.	**Radiation seed therapy for prostate cancer requires weeks of daily treatments**	1☐	2☐	3☐
6.	**Radiation for prostate cancer can cause rectal pain**	1☐	2☐	3☐
7.	**Surgery for prostate cancer can cause urine leakage**	1☐	2☐	3☐
8.	**For most men, radiation therapy for prostate cancer has no effect on urinary control**	1☐	2☐	3☐
9.	**Both surgery and radiation can decrease sexual function**	1☐	2☐	3☐
10	**Low-risk prostate cancer can be safely monitored**	1☐	2☐	3☐
11.	**After prostate cancer surgery, a man will go home with a catheter**	1☐	2☐	3☐
12.	**Hot flashes is a side-effect of hormone treatment**	1☐	2☐	3☐

Investigator developed.

Expanded Prostate Cancer Index Composite—Short Form (EPIC-26)

This questionnaire is designed to measure Quality of Life issues in patients with Prostate cancer. To help us get the most accurate measurement, it is important that you answer all questions honestly and completely.

1. Over the **past 4 weeks**, how often have you leaked urine?

☐ More than once a day
☐ About once a day
☐ More than once a week
☐ About once a week
☐ Rarely or never

2. Which of the following best describes your urinary control **during the last 4 weeks**?

☐ No urinary control whatsoever
☐ Frequent dribbling
☐ Occasional dribbling
☐ Total control

3. How many pads or adult diapers per day did you usually use to control leakage **during the last 4 weeks**?

☐ None
☐ 1 pad per day
☐ 2 pads per day
☐ 3 or more pads per day

2.0 OBJECTIVES

2.1 Primary objective

To test the comparative effectiveness of decision aids (DA's) on patient knowledge.

2.2 Secondary objectives

2.2.1 To test the impact of in-visit DA's alone compared to usual care on quality of life outcomes and treatment utilization.

2.2.2 To test the impact of out-of-visit DA's alone compared to usual care on quality of life outcomes and treatment utilization.

2.2.3 To test the impact of combined in-visit and out-of-visit DA's compared to both usual care and individual DAs on quality of life outcomes and treatment utilization.

2.2.4 To test the comparative effectiveness of DA's on minority men's knowledge.

2.2.5 To compare clinic time required to administer the DA's across arms.

3.0 PATIENT SELECTION

For questions regarding eligibility criteria, see the Study Resources page. Please note that the Study Chair cannot grant waivers to eligibility requirements.

3.1 On-Study Guidelines

This clinical trial can fulfill its objectives only if patients appropriate for this trial are enrolled. All relevant medical and other considerations should be taken into account when deciding whether this protocol is appropriate for a particular patient.

Although they will not be considered formal eligibility (exclusion) criteria, physicians should recognize that the following may seriously increase the risk to the patient entering this protocol:

- Psychiatric illness which would prevent the patient from giving informed consent.

3.2 Eligibility Criteria

___ **3.2.1 Documentation of disease:** Patients must have prostate biopsy within 4 months prior to registration showing newly diagnosed prostate cancer, stage $T_{1-3}N_{0\ or\ X}M_{0\ or\ X}$. In addition, patients must have:

___ • Gleason score 6-10

___ **3.2.2 PSA < 50 ng/mL**

___ **3.2.3 Patients who have had a history of non-cutaneous malignancy in the previous 5 years are not eligible.** Exception: Patients with history of non-melanoma skin cancer are eligible.

___ **3.2.4 Scheduled prostate cancer consultation to be the first consultation after diagnosis** (i.e. not a second-opinion or a consultation following previous discussions of treatment options).

___ **3.2.5 Patients may not be concurrently enrolled to another clinical trial for the treatment of cancer.** Co-enrollment to biospecimen studies is allowed. Patients may be enrolled to other clinical trials after completing all of the baseline interventions and measures.

___ **3.2.6 Patients with impaired decision-making capacity (such as with a diagnosis of dementia or memory loss) are not eligible for this study.** Since the primary outcome of the study is knowledge, including patients determined to have impaired decision-making capacity may confound analysis.

IRB Approval:

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to the following:

- An active Federal Wide Assurance (FWA) number
- An active roster affiliation with the Lead Network or a participating organization
- A valid IRB approval
- Compliance with all protocol specific requirements.

In addition, the site-protocol Principal Investigator (PI) must meet the following criteria:

- Active registration status
- The IRB number of the site IRB of record listed on their Form FDA 1572
- An active status on a participating roster at the registering site.

Sites participating on the NCI CIRB initiative that are approved by the CIRB for this study are not required to submit IRB approval documentation to the CTSU Regulatory Office. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRB Manager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study.

4.2.1 Downloading Site Registration Documents

Site registration forms may be downloaded from the A191402CD protocol page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.

- Go to [redacted] and log in to the members' area using your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand
- Click on the Alliance link to expand, then select trial protocol #A191402CD
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided.

4.2.2 Requirements for A191402CD Site Registration

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted).

4.2.3 Submitting Regulatory Requirements

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal, where they will be entered and tracked in the CTSU RSS.

12.0 STATISTICAL CONSIDERATIONS

12.1 Study Design

This is a non-treatment study evaluating Decision Aids (DAs) for patients with newly diagnosed prostate cancer. For this trial, participating institutions are randomized, according to the racial distribution of the patient population, to treat patients to one of 4 treatment arms (see Schema). Patients will complete on-line DAs if not randomized to the Usual Care arm. All patients will complete a baseline knowledge questionnaire after the initial clinic visit and at 12-months following the surgical consultation.

12.2 Statistical Design and Analysis for the Primary Endpoint

Primary Endpoint: The primary outcome, knowledge, will be assessed by a standardized questionnaire (i.e., Prostate Cancer Treatment Questionnaire) administered once, immediately after the clinical consultation while the patient is still at the study site. The number correct from this 12-item measure will be reduced to a percentage of total number correct.

A different method for measuring our primary outcome, knowledge, proposing instead a pre-post approach was considered. However, several factors lead us to favor a one-time post-intervention measurement: 1) Our study's randomized design should control for differences in baseline effects; 2) a pre-post design could be confounded by learning effects associated with the baseline measurement since the baseline and post-intervention measurements would only be 1-2 hours apart. Such learning affects could lead to artificial improvements in our control group which could limit our ability to see "true" differences attributable to the intervention(s); 3) finally, a one-time measurement of knowledge will minimize burden to respondents, particularly during the consenting and baseline measurement period where we seek to impede clinical workflows as little as possible.

12.2.1 Analysis Plan

Although the randomization unit will be participating site, our inferential unit for statistical analysis will be the individual patient. Due to the potential for correlation among patients within the same site, a mixed effects regression model (also known as random effects model or multi-level model) will be utilized to examine the effects of the during-consultation Prostate Choice and the pre-consultation Knowing Your Options decision aids. Specifically, this model will contain a fixed intercept, a fixed effect for having received Prostate Choice, a fixed effect for having received Knowing Your Options, and a random, site-specific intercept to allow patients within the same site to be correlated. Baseline patient-level characteristics including race, ethnicity, severity of disease and site-level characteristics may be incorporated in this model if deemed appropriate. A similar approach will be utilized in the statistical analysis of secondary endpoints. Furthermore, descriptive statistics will be reported after incorporating cluster information, in particular, the empirical cluster size, and the observed intra-cluster correlation.

correlation is ρ (0.1) (meaning the covariance between any two patients in the same site is $\rho\sigma^2$). In this case, the variances of the sample means are not $\sigma^2/(n/2)$, but rather:

$$Var(Y_1) = Var(Y_2) = Var\left(\frac{1}{\left(\frac{n}{2}\right)}\sum Y_i\right)$$

$$= \frac{1}{\left(\frac{n}{2}\right)^2}\left[\left(\frac{n}{2}\right)\sigma^2 + (2)\left(\frac{\left(\frac{n}{2}\right)}{m}\right)\left(\frac{m!}{(m-2)!\,2!}\right)\rho\sigma^2\right]$$

$$= \frac{1}{\left(\frac{n}{2}\right)}\left[\sigma^2 + \left(\frac{1}{m}\right)m(m-1)\rho\sigma^2\right]$$

$$= \frac{1}{\left(\frac{n}{2}\right)}\left[\sigma^2 + (m-1)\rho\sigma^2\right]$$

$$= \frac{\sigma^2}{\left(\frac{n}{2}\right)}\left[1 + (m-1)\rho\right].$$

Thus, the denominator of our test statistic should actually be $[(4\sigma^2/n)(1 + (m - 1)\rho)]^{(1/2)}$. Therefore, if we replace the original sample size (n=100) with $n(1 + (m - 1)\rho = 100*1.4 = 140$ in the denominator of our original test statistic, we will have a test statistic which accounts for the correlation of 0.1 between subjects within each of the 20 sites. Hence, we will target an effective sample size of 140 patients (approximately 35 patients per arm, 7 patients per site). The total sample size may be further inflated by 20% to account for ineligible, cancel and loss to follow-up for longer term secondary outcomes and allow increased power to detect racial/ethnic differences. Therefore, a total number of 172 patients will be enrolled into this clinical trial. These 172 patients, recruited from 20 participating sites (about 9 patients per site) will receive the intervention (or control) to which their location is randomized.

Though we have chosen to power this study based on an absolute meaningful difference of 8%, we determined the necessary sample size for a range of meaningful differences. In each case, the target power was approximately 85% (thought it varied slightly, as we only considered sizes which were divisible by 20, given the number of expected sites) with joint main effect two-sided t-tests with two-sided alternatives at the 2.5% significance level. These sample sizes are as follows (not adjusted for ineligibility, cancel and loss to follow-up):

Meaningful Difference	**Total sample size without correlation within sites**	**Total sample size adjusted for correlation within sites**
4%	360	504
6%	180	252
8%	100	140
10%	60	84
12%	40	56

12.2.3 Study Operating Characteristics

Interim Analysis: An interim analysis will be used to test if intervention arm (either during-consultation Prostate Choice or Knowing Your Options pre-consultation DA) has produced better knowledge than the respective control arm. There will be 5 to 6 interim analyses conducted of this type before the final analysis with this plan. The O'Brien-Fleming boundaries[75] will be

Decisional Conflict Scale

My difficulty in making this choice

A. Which treatment option do you prefer? Please check one.

- ☐ Surgery
- ☐ Radiation (includes Brachytherapy, IMRT, proton beam)
- ☐ Active Surveillance (also called watchful waiting)
- ☐ Unsure

B. Considering the option you preferred, please answer the following questions:	Yes	Unsure	No
1. Do you know which options are available to you?	☐	☐	☐
2. Do you know the benefits of each option?.....	☐	☐	☐
3. Do you know the risks and side effects of each option?	☐	☐	☐
4. Are you clear about which benefits matter most to you?	☐	☐	☐
5. Are you clear about which risks and side effects matter most to you?.....	☐	☐	☐
6. Do you have enough support from others to make a choice?	☐	☐	☐
7. Are you choosing without pressure from others?.....	☐	☐	☐
8. Do you have enough advice to make a choice?	☐	☐	☐
9. Are you clear about the best choice for you?.....	☐	☐	☐
10. Do you feel sure about what to choose?.....	☐	☐	☐

4. How big a problem, if any, has each of the following been for you **during the last 4 weeks**?	No Problem	Very Small Problem	Small Problem	Moderate Problem	Big Problem
a. Dripping or leaking urine	☐	☐	☐	☐	☐
b. Pain or burning on urination	☐	☐	☐	☐	☐
c. Bleeding with urination	☐	☐	☐	☐	☐
d. Weak urine stream or incomplete emptying	☐	☐	☐	☐	☐
e. Need to urinate frequently during the day	☐	☐	☐	☐	☐

5. Overall, how big a problem has your urinary function been for you **during the last 4 weeks**?

☐ No problem
☐ Very small problem
☐ Small problem
☐ Moderate problem
☐ Big problem