CSP597: Diuretic Comparison Project (DCP)

Informed Consent Documentation

February 19, 2021

NCT02185417

01. Provider Informed Consent Information Sheet v2.5 October 25, 2018
02. Patient Informed Consent Information Sheet v2.6 June 6, 2019
03. Patient Informed Consent Script v3.3 February 19, 2021

Informed Consent Overview

Appendix B.3 Provider Information Sheet
To be included as a Progress Note accompanying the initial test patient order in CPRS.

VA COOPERATIVE STUDY (CSP#597)

DIURETIC COMPARISON PROJECT (DCP)

PROVIDER INFORMATION NOTE

CONTACT INFORMATION: 1-800-XXX-XXXX OR HYPERLINK

Site Liaison: name

STUDY OVERVIEW
The Diuretic Comparison Project is the first national study to implement the VA Point of Care design which embeds clinical research into routine medical care to create a 'learning healthcare system'.

The purpose of the trial is to compare the effects of hydrochlorothiazide and chlorthalidone, on cardiovascular outcomes in older veterans with hypertension who are currently taking HCTZ.

Patients will be randomized to continue on HCTZ or switched to Chlorthalidone.

Primary Care Provider Participation:

- A **'ZZTEST PATIENT' Order** will be sent to PCPs asking for their participation and approval to contact potentially eligible patients in their panel.
- **PCPs, on average, will have 3-4 eligible patients**. Enrollment is limited to 2 patients per week.
- **Randomization** - For each eligible patient, two additional View Alert Orders will be sent: 1) to approve randomizing an individual patient and 2) to sign the randomization assignment text order and corresponding medication orders (chlorthalidone order and HCTZ discontinue order if patient is switched).
- Once randomized, all care is managed by the PCP.

WHAT IS THE PURPOSE OF THE RESEARCH STUDY?
The DCP is a large randomized trial designed to compare the effects of two thiazide-type diuretics, hydrochlorothiazide and chlorthalidone, on cardiovascular outcomes in patients with hypertension. 95% of current VA thiazide-type diuretic prescriptions are for hydrochlorothiazide. Indirect comparisons of randomized trial results have suggested that chlorthalidone may be more effective at reducing cardiovascular events (Roush et al. Hypertension 2012;59:1110-7), though a large observational study did not support this (Dhalla et al. Ann Int Med 2013;158:447-55).

To determine whether chlorthalidone might be a better choice for our VA patients, we plan to enroll 13,500 veterans, over 65 years old, who are receiving 25 or 50 mg hydrochlorothiazide daily from VA pharmacies as a single-agent preparation. Participants will be randomly assigned to continue their hydrochlorothiazide or to have their prescription changed to chlorthalidone at a

suggested equipotent dose (12.5 or 25 mg respectively, where 12.5 mg requires cutting a pill in half).

DCP employs a new Point of Care Clinical Trial design which integrates clinical research into routine medical care. Subject recruitment and enrollment will be accomplished by embedding processes using View Alerts within CPRS, the VA electronic medical record.

Because the DCP is a new type of study, we are also studying providers to see how effectively the protocol is implemented. Thus, participants in this study include both patients and providers. Your decision to participate or not will be kept confidential.

WHO IS CONDUCTING THE STUDY?

VA Cooperative Study (CSP#597)

Study Chairman: Areef Ishani, M.D. Minneapolis VAMC
Study Co-Chairman: William Cushman, M.D. Memphis VAMC

WHAT WILL HAPPEN DURING THE STUDY?

'ZZTEST PATIENT' ORDER - The first step is to obtain your approval for the study team to contact your potentially eligible patients. You are receiving a 'ZZTEST PATIENT' (imaginary) ORDER that would allow DCP investigators to contact your patients. If you do not wish us to contact your patients at this time, discontinue the order. We will give you a second opportunity to consider participating at a later time. We may send you one additional 'ZZTESTPATIENT' order to seek your participation in about 8 weeks. If you discontinue this second order and do not wish to participate, you will receive no further correspondence from the study.

PATIENT INFORMED CONSENT - If you allow your patients to be contacted by signing the order, a letter will be sent to your potentially eligible patients, including those of your residents, informing them about the study. Patients who do not opt out by voicemail will then be contacted by phone to describe the study in more detail and to seek oral informed consent. An easily understood summary of the consent document will be mailed to patients prior to the phone call.

APPROVE RANDOMIZATION - Once a patient's eligibility has been confirmed and they have consented, a View Alert order will be sent to you, to approve (sign) or disapprove (discontinue) randomization. Reasons for disapproval include: 1) impaired decision-making capacity rendering the patient unable to provide informed consent (which we will also try to assess when the study team calls the patient), 2) life expectancy less than 6 months, 3) unlikely to comply with treatment, or 4) any other reasons you believe make participation in this study inappropriate for that particular patient. The study team will follow-up with you by email if you do not take action on the randomization View Alert order within 4 weeks.
If you do not approve randomization the patient will receive a letter notifying him of your decision.

MEDICATION ORDERS - After you approve a patient's randomization, a note confirming randomization will be entered by the study staff for your acknowledgment. For patients assigned to chlorthalidone, a prescription order for the proposed dose will be sent to you as a View Alert, at which time you can make any dosage change and order any laboratory tests as you see fit. At that time you will also receive an alert to cancel the existing hydrochlorothiazide prescription. Patients randomized to chlorthalidone will be reimbursed for their co-pay for any discarded hydrochlorothiazide pills.

Patients assigned to continue on hydrochlorothiazide will remain on their current prescription. No new orders for hydrochlorothiazide will be entered by the study team.

We will try to enroll patients about a month or two before a planned appointment with you to facilitate your evaluation of diuretic treatment at the appointment. There will be no designated study visits for the patients.

FOLLOW-UP CARE - All further management is directed by you in the usual way, including blood pressure and laboratory measurements, dose changes, drug discontinuation (which may prompt a query to you from the study team), and management of any other antihypertensive agents. All outcome measures, specifically major cardiovascular events, will be determined from the VA electronic medical record and associated Medicare databases. In some cases, we may ask for your assessment of these events.

PATIENTS FOLLOWED BY RESIDENTS - As a participant you will receive View Alerts to sign study related orders; your resident will NOT be alerted to sign these orders. Notes entered by study staff describing the randomization assignment will be sent to both you and your resident for acknowledgment.

The study team will collect data on diuretic management within the study and may contact you from time to time by phone or email to learn your reasons for declining a particular patient or discontinuing a new chlorthalidone order or an ongoing diuretic prescription. If it is necessary to include PHI in follow-up communication regarding patient orders, the email will be encrypted.

RISKS AND BENEFITS

There is minimal risk for your participation in the study. Participation in the study will not affect your job performance evaluation and we will not inform your supervisors regarding your decision to participate. Your decision to participate or not will be kept confidential.
There is no direct benefit to you from your participation; however it is hoped that the VA can learn which drug may have the most benefit in reducing cardiovascular events.

INJURY

Every reasonable safety measure will be used to protect your well-being. If you are injured as a result of taking part in this study, the VA will provide necessary medical treatment at no cost to you unless the injury was due to your not following the study procedures.

If you should have a medical concern as a result of taking part in this study, call the study PIs (Areef Ishani, MD and William Cushman, MD) at 612-467-4431 or 901-577-7357

CONFIDENTIALITY

Information collected about the diuretic management of your patients will be kept confidential in encrypted and protected files on secure VA servers. Only members of the study team that are properly research credentialed and are compliant with VA security trainings will have access to the data. The VA Central IRB; the VHA Office of Research Oversight, the Office of Human Research Protections and the Government Accountability Office may have access to the study's research records. At the end of the study, the data for CSP#597 will remain property of the Cooperative Studies Program and be stored and shared according to CSP guidelines and procedures. Retention and destruction of data will be conducted according to CSP operating procedures and federal and local VA regulations. A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

You can reach the VA Central IRB Toll Free at 1-877-254-3130 if you have any questions or concerns, or would like to verify that this is a valid VA approved study.

Appendix B.2 Patient Information Sheet

Informed Consent Information

What is the purpose of the research study? The Diuretics Comparison Project is a nationwide VA research study examining two diuretics, or water pills, used to treat high blood pressure. The medications are called hydrochlorothiazide (which you are currently prescribed) and chlorthalidone. Both drugs are believed to be the best treatment for high blood pressure, are approved by the FDA, and have been prescribed by doctors for over 50 years.

There is no specific reason for doctors to pick one medication over the other. Some doctors think that chlorthalidone may be better in preventing strokes and heart attacks; however, hydrochlorothiazide is the more commonly used of the two drugs. This study will compare the benefits of these two drugs in our Veteran population.

Who is conducting the study? This is a VA study and the lead researchers are Dr. Areef Ishani of the Minneapolis VA and Dr. William Cushman of the Memphis VA. They are experts in the treatment of high blood pressure and in leading research studies.

Who will be asked to participate? We hope to enroll more than 13,000 Veterans.

What will happen during the study? There is very little to participate in this study. If you agree to take part, you will have a 50:50 chance (like the flip of a coin) of staying on hydrocholorothiazide (what you are currently taking) or being switched to chlorthalidone.

If you are switched to chlorthalidone, you will receive the new drug in the mail with instructions. If you are assigned to hydrochlorothiazide you will continue to take it as you do now.

Both you and your VA providerwill know which medication you are taking.Your doctor has given permission for their patients to participate and will continue to care for you as usual. This includes checking your blood pressure and blood tests and making any changes to your medicines as needed. If your provider decides that either of the drugs is not right for you, he or she can change your medicine at any time.

You will not have any added tests, clinic visits, or forms to fill out because of the study. You will not be asked for any information. All of the information for the study will be collected from your health records.

If you decide to participate, you agree to allow us to collect data from your electronic health records over the next 10 years. **You will not be asked for any information.** We will get data from your VA health record and other national databases, like Medicare. Specifically, we will collect demographic information, blood pressure readings, lab tests, and all medicines that you take. We will also collect data on medical conditions and any hospitalizations that may be due to high blood pressure.

Are there risks, inconveniences or discomforts associated with my participation? For most people, the dose of chlorthalidone will be half of their current hydrochlorothiazide dose. This change may not be exact for everyone, so there may be some changes in your blood pressure (either higher or lower) and your lab tests (potassium and kidney function). Your provider will routinely check these results and treat them as needed. You may need to cut chlorthalidone tablets in half to receive the correct dose – if you do, you will be mailed a pill splitter. If you are assigned to chlorthalidone, you will need to throw away

your old hydrochlorothiazide pills. We will reimburse you for the cost of any co-pay you have made for the pills that are thrown away.

The risks related to taking chlorthalidone are very similar to those of taking hydrochlorothiazide. The safety concerns for both drugs are very well understood and both drugs are believed to be the best treatment. Both medications often lower blood potassium levels and many people using these drugs are also treated with potassium supplements. New diabetes, new gout, and reduced kidney function (by 25%) may occur in about 2% of people. Serious allergic reactions may occur in 1 in 1000 persons. There could be unforeseen risks of switching medications, so if you experience side effects from either drug, you should contact your doctor.

Are there any benefits to me from participation? There is no direct benefit to you from being in this study. However, your participation may help other veterans and other people with high blood pressure in the future.

What if I get injured? Every reasonable safety measure will be used to protect your well-being. If you are injured as a result of taking part in this study, the VA will provide necessary medical treatment at no cost to you unless injury was due to your not following the study procedures. If you require emergency medical attention, please contact your provider directly. If you should have a medical concern or get hurt of sick as a result of taking part in this study, call 1-800-863-1604.

What if I decline to participate? If you decide not to participate, your provider will continue to treat you as they do now. You will continue to receive all the VA care to which you are entitled. Your participation in this study is completely voluntary. You have the right to refuse participation or leave the study at any time. Leaving the study will not result in any penalty or loss of benefits. The study has been approved by the VA Human Rights Committee in Boston and by the VA Central Institutional Review Board.

Will my research results be kept confidential? Only members of the study team that have been trained on VA security will have access to the data. The researchers who collect this information will keep your health information confidential in encrypted and protected files on secure VA servers. We will only share data with approved researchers and officials who monitor VA research studies, including VHA Office of Research Oversite, Office of Human Research Protections, and the Government Accountability Office . You will not be personally identified in any papers, reports, or presentations from this study.

If you agree to participate, you will be asked to state that agreement. After the phone call we will get final approval from your provider. You will receive a letter stating which medication you have been randomized to. If your medication is switched, we will send you your new prescription in the mail.

Will I incur any costs or receive any compensation for participating in this study? If your prescription changes from hydrochlorothiazide to chlorthalidone we will reimburse your first co-pay. If your prescription does not change, we are unable to reimburse you. We are not able to compensate you for your normal doctor's appointments.

Where can I find additional information? A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

If you have questions about your rights as a study participant, you may contact the VA Central Institutional Review Board (IRB) toll free at 1-877-254-3130. For questions about the research or to withdraw from the study, call 1-800-865-3384 extension 44562.

Appendix B.1 Patient Telephone Informed Consent Script

Hello, my name is <Caller's Name> and I am calling from the Veterans Affairs. May I speak to Mr. (Ms.) <Veteran's Name>?

I'm calling today to follow up on a letter we sent to you about a research study called the Diuretic Comparison Project. The letter was about your high blood pressure medication, hydrochlorothiazide. Do you recall if you received that letter from us?

[Yes] Do you have any questions about the study I might answer for you?

[Yes] *See FAQ*

[No] Do you have a little time to go over the study? It should only take a few minutes of your time.

[Yes] *Proceed to Page 2*

[No] When would be a better time to call you back?

Thank you for your time today <Veteran's name>. I will be in touch with you at <the stated date and time>.

[No] Okay. In order to improve our service to our Veterans, may I ask, is there any particular reason?

Thank you for your time today and for your service.

May I confirm the current address we have on file for you? We have: XX Street, City, State, Zip. Is that correct?

[No] I will go ahead and update that in our study system. What is your current address?

I have [read back new address given to confirm accuracy], is that correct?

Please be aware that I can only update your address as it applies to this study.

Would you like me to send you a new letter?

[Yes] Okay. I will have that sent to you. Do you have time now to talk about the content of the letter?

[Yes] *Proceed to page 2*

[No] Okay I will send you the letter and we will be back in touch with you in about two weeks after you've had a chance to review it. Is this a

good time of day to reach you? Thank you for your time today and for your service.

[No] Okay. I take it that you are not interested in this study?

[Yes] Well thank you for your time today and for your service . Do you mind telling me why you are not willing to participate? This information will help us with future studies.. We will remove you from our system.

The Diuretic Comparison Project is a nationwide VA research study comparing two diuretics, or water pills, to treat high blood pressure. The medications are called hydrochlorothiazide (which you are currently prescribed) and chlorthalidone. Both are believed to be the best treatment for high blood pressure, are approved by the FDA, and have been used for over 50 years.

There is no specific reason for doctors to pick one medication over the other. Hydrochlorothiazide is the more commonly used of the two drugs, but some doctors think that chlorthalidone may be better in preventing strokes and heart attacks. This study will help us learn which drug is more effective in our Veteran population.

We hope to enroll more than 13,000 Veterans.

There is very little that you will need to do to participate in this study. If you agree to take part, you will have a 50:50 chance of staying on hydrochlorothiazide (what you are currently taking) or being switched to chlorthalidone.

If you are switched to chlorthalidone, you will receive the new drug in the mail with instructions. There will also be the name and phone number of someone to call if you have any questions. If you are assigned to hydrochlorothiazide you will continue to take it as you do now.

Both you and your VA provider will know which medication you will be taking. Your doctor has given permission for their patients to participate and will continue to care for you as usual regardless of your participation in this study. If you or your provider decides that either of the drugs is not right for you, they can change your medicine at any time.

You will not have any added tests, clinic visits, or forms to fill out because of the study. You will not be asked for any information. All of the information for the study will be collected from your health records.

If you decide to participate, you agree to allow us to collect data from your electronic health records over the next 10 years. We will get data from your VA health record and other national databases, like Medicare. Specifically, we will collect demographic, blood pressure readings, lab tests results, and all medications that you take. We will also collect data on medical conditions and any hospitalizations that may be due to high blood pressure.

For most people, the dose of chlorthalidone will be half of their current hydrochlorothiazide dose. This change may not be exact for everyone, so there may be some changes in your blood pressure (either higher or lower) and your lab tests (specifically potassium and kidney function). You may need to cut

chlorthalidone tablets in half to receive the correct dose – if you do, you will be mailed a pill splitter. If you are assigned to chlorthalidone, you will need to throw away your hydrochlorothiazide pills. We will reimburse you for the co-pay on the pills that are thrown away.

The risks related to taking chlorthalidone are very similar to those of taking hydrochlorothiazide. The safety concerns for both drugs are very well understood. Both medications often lower blood potassium levels and many people using these drugs are also treated with potassium supplements. Other side effects, which may occur in about 2% of people, include: new diabetes, new gout, and reduced kidney function (by 25%). Serious allergic reactions may occur in 1 in 1000 persons. As with any change in medication there could be unforeseen risks, so if you experience side effects from either drug, you should contact your doctor.

This study has been approved by the VA Human Rights Committee in Boston and the VA Central Institutional Review Board.

Your health information will be kept confidential through physical and electronic security measures, such as encryption and protected files on secure VA servers. Only member of the study team trained on VA security, will have access to the data. We will only share data with approved researchers and officials who monitor VA research studies, including Veterans Health Administration (VHA) Office of Research Oversite, the Office for Human Research Protections, and the Government Accountability Office. If you have any questions about your rights as a study participant, you may contact the VA Central Institutional Review Board (IRB) toll free at 1-877-254-3130.

As required by U.S. Law, a description of this clinical trial will be available on the internet at, www.ClinicalTrials.gov. This website will never include information that can identify you. You will not be personally identified in any papers, reports, or presentations from this study. At most, the website will include a summary of the results. You can search the website at any time.

There is no direct benefit to you from being in this study. However, your participation may help other Veterans and other people with high blood pressure in the future.

If you decide not to participate, your provider will continue to treat you as they do now. You will continue to receive all the VA care to which you are entitled. Your participation in this study is completely voluntary. You have the right to refuse participation or leave the study at any time. Leaving the study will not result in any penalty or loss of benefits.

Every reasonable safety measure will be used to protect your well-being. If you are injured as a result of taking part in this study, the VA will provide necessary medical treatment at no cost to you unless the injury was due to your not following the study procedures.

If you require emergency medical attention, please contact your provider directly. If you should have a medical concern or get hurt or sick as a result of taking part in this study, call 1-800-863-1604.

If you do agree to participate, I will ask you to state that agreement to me. After the phone call we will get final approval from your provider. You will then receive a letter stating which medication you have been randomized to or if you are determined to be ineligible. If your medication is switched, we will send you your new medication in the mail. This process can take a while. If you have any questions

about the status of your consent, please do not hesitate to call the study number. All letters sent to you will contain a phone number for you to call if you have any study related questions. All medical questions should be directed to your provider.

For questions about the research or to withdraw from the study, call us at 1-800-863-1604.

Do you understand everything that has been said?

Do you have any further questions?

Do you need more time to think about participating?

Do you want to discuss participating with your family or doctor?

Are you willing to participate?

[Yes] Thank you so much for your time, willingness to participate, and your service. We will let your provider know your decision and as soon as we get final approval, we will send you a letter to let you know if you will continue on hydrochlorothiazide, switch to chlorthalidone, or are ineligible. For now, please continue to take your hydrochlorothiazide. If you have any questions or concerns in the future, feel free to contact us. Have a good day.

[No] Thank you so much for your time. If you wish to participate in the future or have any questions about the study, feel free to contact us. Have a good day.

Reaffirmation Script

Hello, My name is <Caller's Name> and I am calling from the Department of Veterans Affairs. Is this Mr. (Ms.) <Veteran's Name>?

We are contacting you because you previously consented to participate in the Diuretic Comparison Project.

You should have received a letter explaining that you were temporarily ineligible for our study and that we would contact you as soon as you were eligible.

We have confirmed that you are now eligible.

As a reminder, the purpose of this study is to compare the benefits of hydrochlorothiazide and chlorthalidone in our Veteran population.

Both you and your VA Provider will know which medication you will be taking. If you or your provider decides that either of the drugs is not right for you, your Provider can change your medicine at any time.

Your participation in this study is completely voluntary. You have the right to leave the study at any time. Leaving the study will not result in any penalty or loss of benefits. After the phone call we will get final approval from your provider. You will receive a letter stating to which medication you have been randomized. If your medication is switched, we will send you your new medication in the mail.

Voicemail Message Script

1-800-865-3384 extension 44562

Thank you for calling the diuretic comparison project your call is important to us. If you have a question or would like to speak to a representative please leave your name and a detailed message.

If you do not want to receive a call about the study and wish to Opt-out please leave your name, DOB, and last four of your social security number and state that you would like to opt-out of the study. Thank you and have a good day.

1-800-863-1604

During business hours: (0800 to 1600)

Hello, thank you for calling the VA's Diuretic Comparison Project.

1. If you have questions or if you would like to participate, please press one. → **ACD Queue**
   a. If no one is logged in → **To Mailbox A**
2. If you do not wish to participate in the study please press two. → **Mailbox B.**

After business hours: (16:30:01 to 07:59:59)

Hello, thank you for calling the VA's Diuretic Comparison Project. Our center is currently closed. You may leave us a message or call back between 8:00am and 4:30pm Central Time Monday-Friday.

1. For questions you may have about the research study, or if you would like to participate, please press one and leave a message. →**Mailbox A**
2. If you do not wish to participate in the study please press two. → **Mailbox B.**

Mailbox A Greeting:

> We are sorry we could not answer your call at this time; your call is important to us. Please leave your name, date of birth, and telephone number. We will return your call as soon as possible.

Mailbox B Greeting:

If you do not wish to participate in the Diuretic Comparison project research study, please state your name, date of birth, the last four digits of your social security number, and that you wish to decline to participate.

Voicemail Message Script once recruitment is reached

Hello, thank you for calling the VA's Diuretic Comparison Project. Our study is no longer recruiting new participants.

1. If you are currently in the study and have questions or concerns for the study team, please press one. → **Mailbox A**
2. If you no longer wish to participate in the study, please press two. → **Mailbox B.**

Mailbox A Greeting:

> We are sorry we could not answer your call at this time; your call is important to us. Please leave your name, date of birth, and telephone number. We will return your call as soon as possible.

Mailbox B Greeting:

If you do not wish to participate in the Diuretic Comparison project research study, please state your name, date of birth, the last four digits of your social security number, and that you wish to decline to participate.