Cover page

Title: Mitigation of radiation pneumonitis and fibrosis

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Protocol for “Mitigation of radiation pneumonitis and fibrosis”

Cohen VA 1531-01, CLIN-004-12S

Original from Oct 31, 2012 Registration packet, incorporating amendments through July 2015

Objective

This project will test the effect of enalapril, an angiotensin-converting-enzyme inhibitor, to mitigate radiation pneumonitis and fibrosis in veterans undergoing radiation therapy for lung cancer and other cancers in the chest. It is based on the hypothesis that human normal tissue radiation injury can be safely and effectively mitigated, and on our extensive studies of radiomitigation in experimental animals. Lung cancer is more common in veterans than in the general population; this project is highly relevant to the medical care of veterans.

Research design and methodology

Enalapril or placebo will commence after the start of irradiation in veterans undergoing radiation therapy for lung cancer and other cancers in the chest, and their effects on radiation pneumonitis and fibrosis will be compared as the primary outcome measure. Enalapril will be used rather than captopril, because enalapril is given in single daily doses. This is a prospective, double-blinded, randomized, placebo-controlled trial, in a secondary-tertiary care setting. Subjects will join this trial voluntarily, based on their planned radiotherapy for lung cancer, and it is planned to enroll 200 subjects over the five years of this study. The intervention of this study is the use of enalapril or placebo, which will be maintained for the lifetime of the study subject.

2. To test the mechanism of mitigation of radiation lung injury by enalapril.
   a. Angiotensinogen, plasma renin activity, and angiotensin II will be measured as renin-angiotensin system markers in all subjects.
   b. The effect of enalapril on each marker will be assessed, as compared to placebo.

3. To confirm that enalapril in this use does not adversely affect cancer treatment outcomes.
   a. Cancer recurrence and death from cancer will be compared for the enalapril and placebo groups.

These studies will be done in men and women undergoing radiation therapy for lung cancer and other cancers in the chest. Enalapril, or identical-appearing placebo, will be started within a day

to up to 30 days of the beginning of the radiation treatments. The effect of the enalapril or placebo will be tested by their effect to reduce grade 2 or greater clinical radiation pneumonitis, by their effect on the renin-angiotensin system markers angiotensinogen, plasma renin activity, angiotensin II, and their effect to reduce radiographic evidence of pneumonitis and fibrosis.

NARRATIVE SUMMARY - HUMANS

1. **PURPOSE.** Provide the purpose or objectives of the study. Do not indicate "N/A" for this category.

To test the benefit of enalapril, an angiotensin-converting-enzyme-inhibitor, to mitigate radiation pneumonitis and fibrosis in humans.

2. **SCIENTIFIC RATIONALE.** Provide the reasons for doing the study. Do not indicate "N/A" for this category.

This project will test the effect of enalapril, an angiotensin-converting-enzyme inhibitor, to mitigate radiation pneumonitis and fibrosis in veterans undergoing radiation therapy for lung cancer and other cancers in the chest. It is based on the hypothesis that human normal tissue radiation injury can be safely and effectively mitigated, and on our extensive studies of radiomitigation in experimental animals. Lung cancer is more common in veterans than in the general population; this project is highly relevant to the medical care of veterans.

3. **BACKGROUND**. Provide information from previous studies leading up to this study, either from your laboratory or from those of others. If this is a treatment study involving investigational drugs, devices, or therapies, standard treatment must be clearly identified. Do not indicate "N/A" for this category.

Lung cancer is an important health problem for veterans. It is more common in them than in the general population, and lung cancer survival is less in veterans. Radiation therapy for lung cancer is used in over half of the cases, and it can be followed by radiation pneumonitis and fibrosis. These add significant morbidity and mortality, and they limit the doses of curative irradiation. Standard treatments for radiation pneumonitis and fibrosis are very limited. Mitigation is a new approach, being the use of an agent after initial irradiation but before the expression of radiation injury.

Our studies in rats show significant mitigation of radiation pneumonitis and fibrosis by angiotensin converting enzyme (ACE) inhibitors.

Our recent clinical trial shows the mitigation of radiation nephropathy by the ACE inhibitor captopril.

Our retrospective clinical studies show that concurrent use of ACE inhibitors reduces the occurrence of radiation pneumonitis [and fibrosis], without lowering cancer-related survival.

The safe mitigation of radiation injury has been identified as a priority by the National

Cancer Institute. We will address this critical problem. We hypothesize that the occurrence of radiation pneumonitis, fibrosis, or both in patients receiving radiation for lung cancer will be decreased by the ACE inhibitor enalapril, started after irradiation.

4. **STUDY DESIGN**. Provide a brief description of the design of the study (multicenter, double-blind, randomized, etc.) in narrative form. Do not provide details of specific procedures in this section (see Item 9 below). Include, as needed, a discussion of the appropriateness of research methods. Describe the statistical design and required sample size. Do not indicate "N/A" for this category.

This is a prospective, double-blinded, randomized, placebo-controlled trial, in a secondary-tertiary care setting. The ZVAMC and referring VAs in VISN 12 are the main centers; the Baltimore VAMC will be added,. Subjects will join this trial voluntarily, based on their planned radiotherapy for lung cancer. We will enroll 200 subjects over the five years of this study. Statistical power analysis suggests the need for 200 subjects for the clinical endpoint, and ~ 100 subjects for the radiographic endpoint.

5. **SUBJECT SELECTION AND EXCLUSION CRITERIA.** Provide the specific criteria for including and excluding subjects in the study. Do not indicate "N/A" for this category.

Men and women undergoing radiation therapy for lung cancer and other cancers in the chest at the Milwaukee VAMC and the Baltimore VAMC are eligible. Subjects will be recruited to this phase 2 trial after their diagnosis of cancer and after referral to Radiation Oncology for treatment. The existence of this study will be posted in the Radiation Oncology clinics. Subjects who require radiation therapy to attempt to cure or to palliate their disease will be eligible for this study. Subjects eligible for surgical resection and who do not need radiation therapy will not be eligible for this study. Subjects already on ACE inhibitors, angiotensin blockers, or renin antagonists will be excluded, but may participate if these medications are stopped by their treating physicians before the start of their participation in this study. Subjects with past history of allergy to ACE inhibitors will be excluded. Use of other antihypertensives is not an exclusion criterion. There will be no inclusion or exclusion by race or ethnic origin. Women and minorities are eligible. Children are not eligible because children do not develop lung cancer. . Previous surgery and past or current use of chemotherapy are not exclusions. Subjects will have a Karnofsky performance status ≥70, absolute neutrophils > 1000/mm^3, platelets > 75,000/mm^3, and hematocrit > 25%. Liver and kidney function tests will be within normal range, alkaline phosphatase up to 1.2 and serum creatinine up to 1.1 times upper limit of normal, and baseline blood pressure will be systolic > 110 mmHg sitting. Pregnant or nursing subjects are excluded and fertile patients must have a negative pregnancy test and will use contraception. Lung function tests including spirometry, lung volumes and diffusing capacity will be obtained as part of standard of care for patients prior to radiotherapy, but indices from lung function tests will not be a cause for exclusion.

6. **SUBJECT POPULATIONS.** Indicate the subject populations to be recruited for the study.

Provide scientific and ethical justification for use of any vulnerable subject populations or other potentially vulnerable subjects defined on page 3 and outline additional safeguards planned to protect their rights and welfare. If no additional safeguards are required, provide a justification. Provide a scientific and ethical justification for exclusion of women or minorities or other classes of subjects who might benefit from the study. Include a justification for the use of non-veterans, if applicable. Do not indicate "N/A" for this category.
Note: Exclusion of pregnant women does not require justification.

Men and women undergoing radiation therapy for lung cancer and other cancers in the chest at the Milwaukee VAMC and the Baltimore VAMC are eligible. Vulnerable populations will not be recruited.

7. **RECRUITMENT AND ENROLLMENT PROCEDURES.** Describe the methods used to obtain information about individuals who may be recruited to participate in study. Indicate if medical records, OR schedules, appointment logs, rounding lists, or procedure posting boards will be reviewed to search for potential study subjects. Address all of the following that apply:
Financial enrollment bonuses to investigators personally or added to study budget for fast enrollment or for additional numbers of subjects.
Additional financial or non-financial incentives offered by the sponsor.
If a multi-center trial, whether there is competition between sites to fill available subject slots on a first-come, first-serve basis, and whether this affects authorship on journal articles.
Identification of eligible patients from investigators' own patient pools and how coercion will be avoided.
Referrals from local physicians and whether fees will be offered.
Distribution of study information for subject recruitment purposes to appropriate disease advocacy groups, student groups, or local community organizations, perhaps by giving lectures or presentations or at health fairs or medical screenings.
Use of advertising and whether ads will be used within the ZVAMC or in newspapers, radio, television, or on Internet sites. Attach all advertising to protocol.

Submit "Request for Waiver of Subject Authorization" as appropriate. See "HIPAA" at the beginning of this packet.

The existence of this study will known to Radiation Oncology staff. At Milwaukee, Dr Gore (co-investigator) and her study coordinator will ensure recruitment. At Baltimore, Dr Jackson and his staff will ensure recruitment. Non-participation in this study will not affect the clinical care of the patient.

8. **INFORMED CONSENT PROCEDURE.** Describe the circumstances surrounding the consent procedure, including setting and whether privacy interests are protected during the consent procedure, subject autonomy concerns, language difficulties, vulnerable populations, and other details. Include the procedures for assessing the subject's capacity to consent. Outline the procedures for ensuring sufficient opportunity for subjects to decide, and the procedures to ensure that subjects give consent without coercion. Describe the procedures for documentation of informed consent, including chart documentation, using witnesses, translators, and document storage. Indicate the procedures for informing subjects of new findings.

(Please also read "Obtaining Informed Consent" at the beginning of this packet.)

Waiver of informed consent requires completion of a "Request for Waiver of Informed Consent" form and a "Request for Waiver of Subject Authorization."
Waiver of documentation of informed consent requires completion of a "Request for Waiver of Documentation of Informed Consent" form and an information sheet (format on our web site).

The consent procedure takes place in the Radiation Oncology clinics at the ZVAMC or the Baltimore VAMC. Privacy and autonomy will be ensured by standard clinical practice. The purpose of the study, the procedures of the study, its risks and benefits, and alternatives will all be explained as part of the consent process. Vulnerable populations will not be used. Assessment of capacity to consent will be identical to assessment of capacity to consent to usual treatment, including radiation treatment. This includes assessment of orientation and understanding of risk and benefit. Subjects will be able to view the consent form in writing, will be able to ask questions of the coordinator and the co-investigator, and will not be coerced. Documentation will be in writing and will be stored on the VA CPRS record. Witnesses will participate as required. The coordinator and co-investigator have ample experience with clinical studies and will adhere to their existing high standards for securing consent. New findings will be communicated to all study participants when these findings are available.

Names and qualifications of those obtaining informed consent.

Dr Elizabeth Gore, Radiation Oncologist, Milwaukee
Joseph Berman, Study coordinator, Milwaukee

Dr Eric Cohen, Medicine, Baltimore

9. **PROCEDURES.** *REVISED* Describe all procedures involving the participation of human subjects, chart review, or collection of samples. Provide details. Include the location where the study will take place. Do not indicate "N/A" for this category.

If the protocol involves "usual care," you must clearly differentiate the research intervention(s) from "usual care" (whether the "usual care" is limited to one arm of the study or is being delivered to all study subjects). You must also clearly designate the individual or entity (e.g., the appropriate research personnel vs the subject's health care provider) responsible for relevant aspects of both the research and the "usual care."

The study drug, enalapril or placebo, will be in addition to usual clinical care of subjects undergoing radiation therapy for lung cancer. Enalapril, or placebo, will be given orally, started within a day to up to 30 days of the beginning of the radiation treatments. They will be enrolled at the start of radiation therapy (RT), stratified for cancer stage, then randomized to enalapril or identical-appearing placebo. Randomization will be done by the Department of Biostatistics, Medical College of Wisconsin, using random number tables; the center pharmacies will be notified of the assignment to enalapril or placebo. There will be no stratification by age, gender, lung cancer histology, or use of chemotherapy since these do not have a consistent relation with the occurrence of RP. There is no stratification by center. Study drug is obtained from Expert Pharmacy Inc, with identical appearing enalapril and placebo tablets. It is held in the VA research pharmacy at Milwaukee, in a restricted access area under the aegis of the research pharmacist.It will be sent to patients at the Baltimore site upon their enrollment. The study drug dose will be

2.5 mg to start, and will be increased in increments of 2.5 mg to 10 mg per day, as tolerated. Clinical follow up of study subjects will be identical to that of subjects undergoing radiation therapy for lung cancer but who are not participating in this study, with the addition of four blood samples. One blood sample one week after starting the study will be to check for adverse effects of the study drug. Three more blood samples will be obtained for renin-angiotensin system (RAS) assays, done on three blood samples from each subject, at the start of the study, at 3 weeks after the start, and at the end of radiation therapy. Each of these four research-related blood samples will be approximately one teaspoon of blood obtained by venipuncture. Compliance is assessed by monitoring the requests for study drug refills. It will be verified at the end of the study by the elevation in plasma renin in subjects on enalapril compared to those on placebo. Study subjects will be monitored for adverse effects of study drug. The development, or not, of radiation pneumonitis and fibrosis will be assessed in the study subjects, as part of ongoing regular care, as are the periodic radiographic imaging and lung function testing. Quality of life will also be assessed.

10. **RISKS AND PRECAUTIONS.** Provide a description of all risks (physical, psychological, social, legal, and/or economic) for each drug or procedure used. Indicate how risks will be minimized, including a description of procedures already being performed on the subjects for diagnostic or treatment purposes that will be used. Provide a description of these procedures. ***Distinguish risks associated with research from risks of therapies subjects would receive even if not participating in research.*** Include precautions to be taken to minimize the danger and/or pain. Provide a plan for notifying subjects of new findings that may affect their willingness to participate in the project. If there are no risks to participating in the study, this should be stated. Do not indicate "N/A" for this category.

Investigational devices: Include the risks of procedures involved in the use of investigational device and risks of investigational device compared to risks of alternative devices or procedures.

Enalapril is an angiotensin-converting-enzyme inhibitor in common use, for treatment of hypertension, kidney disease, and heart failure. It is used to lower blood pressure, and is also used in normotensive subjects with heart failure. Subjects with normal blood pressure who would use enalapril to mitigate radiation injury could develop low blood pressure which could cause dizziness and drug intolerance. This will be avoided by starting with low doses and increasing the drug dose, as tolerated. Elevation in serum potassium could occur; we will test for this in one extra blood sample, and monitor for it in subsequent usual clinical follow-up. Between 2 and 5% of subjects using enalapril could develop a cough, which resolves within a few days of stopping the drug. Intolerable cough will lead us to stop the study drug. The safety of enalapril in this use is very likely, because we have documented the safe use of lisinopril, another angiotensin-converting enzyme inhibitor and a congener of enalapril, in veterans at ZVAMC undergoing radiation therapy for lung cancer. These were subjects already on lisinopril when they underwent radiation therapy for lung cancer. We found no adverse effects of this use of lisinopril. In another study, we used captopril compared to placebo in bone marrow transplant patients, to mitigate chronic renal failure. There was no difference in drug tolerance in patients on captopril compared to those on placebo.
The therapeutic risk is that of the medical care by, during, and after radiation therapy for

lung cancer. The research risk is that of the use of the study drug, enalapril or placebo, as detailed above. There is also the risk of obtaining blood for RAS studies. There is no alternative to the therapeutic risk, for subjects undergoing radiation therapy, because it is the standard of care for those subjects. The alternative to the research risk is to not participate in this study. The alternative is to undergo usual and customary care, by radiation therapy for the patient with lung cancer.
Data security and confidentiality will be maintained according to the rules of the Department of Veterans Affairs. Risks to breach of privacy and confidentiality will thereby be avoided. All data for this study will only be stored on password-protected VA computers. Data collection for complications of treatment, adverse and severe adverse events will be done by a dedicated study coordinator who will prospectively track all of the subjects of this study.

11. **ANTICIPATED BENEFITS OF THE STUDY AND RISK/BENEFIT ASSESSMENT.** Describe the benefit to the subject and/or benefit to science. State if subjects will receive no benefit.

Investigational devices: Benefits of investigational device compared to benefits of alternative devices or procedures.

Subjects in this study may have a fifty percent or more reduction in the occurrence of radiation pneumonitis. Based on pre-clinical data in laboratory animals, we expect that to occur in subjects on enalapril compared to subjects on placebo. But this is not known or guaranteed, which is why this study of enalapril compared to placebo must be done. Based on extensive use of enalapril for other indications, and on our study of its congener, lisinopril, in veterans undergoing radiation therapy for lung cancer, the risks of this study related to use of study drug are small, and reasonable in relation to the anticipated benefits to subjects and others.

The broad, long-term objective of our work is to achieve effective and safe mitigation of normal tissue radiation injuries for any tissue type. We and others have successfully mitigated normal tissue radiation injury (NTRI) of kidneys, lungs, skin, and brain, using laboratory rat models. The success of these human studies will have a high impact for subjects at risk of NTRI to the lungs. This will improve the health of veterans with lung cancer, which is highly relevant to the mission of the Department of Veterans Affairs. That success will be a significant impetus to extend the radiomitigation concept to other normal tissues at risk during radiation therapy, such as spinal cord or brain.

12. **DATA SAFETY MONITORING.** *REVISED* A data and safety monitoring plan is required for all interventional clinical research protocols that involve more than minimal risk to subjects. Provide the following information:

a. *The type of data or events* to be captured under the monitoring plan, including SAEs, and how will safety information be collected (e.g., with case report forms, at study visits, by telephone calls with subjects).
b. *Who will be responsible* for monitoring the data collected (investigators, sponsor, a coordinating or statistical center, an independent medical monitor, a data safety monitoring board (DSMB) or data monitoring committee (DMC), or some other entity)? **If there is a data safety monitoring board (DSMB), describe its composition and indicate if it is**

independent of the sponsor. If no DSMB, provide the statistical tests for analyzing the safety data to determine if harm is occurring.
c. Procedures for communicating to the IRB, the sponsor, and other appropriate entities the outcome of the reviews by the monitoring entity. If *DSMB reports* will be forwarded to the IRB, include the interval they will be submitted. Members of DSMBs/DMCs are encouraged to complete human subjects research training.
d. Process for *monitoring and reporting adverse events and unanticipated problems* to the monitoring entity and IRB, and include the time frames for reporting these events. Include the following statement: Unanticipated problems involving risks to subjects or others (UAPs), internal serious adverse events (SAEs), and protocol deviations/violations will be reported to the IRB using the local reporting form within 5 days of notification of the event.
e. The *frequency of data collection and assessments* of data or events captured by the monitoring plan, such as points in time or after a specific number of participants are enrolled.
f. The *definition of specific triggers or stopping rules* that will dictate when some action is required (e.g., studies may be stopped when there is a greater than expected rate of morbidity or mortality or when the experimental arm of a head to head comparison study is shown to be better or worse statistically than the standard care arm).

For retrospective studies, include whether or not you will discuss with the subjects potential study outcomes that may have an effect on their health or well being and when and how you will notify individual subjects or their health care providers of these findings.

Additional information is provided in "Data Safety Monitoring Plans" at the beginning of this packet

a. *Data or events* to be captured included the development of adverse reaction s to study drug, including cough, low blood pressure, elevation in serum potassium, fall in white blood cell count, or red blood cell count (anemia). It is estimated that each of these have a risk of less than 5%. This information will be collected at study visits, upon report by study subject, will be documented on report forms, and will be verified by monthly chart reviews for all active subjects on this study. Serious adverse events (SAE) are those that cause significant morbidity or threat to life.
b. Investigators and the study coordinator will *be responsible* for monitoring the data collected, and will report safety data to a central VA DMSB, the Data Monitoring Committee (DMC) at Hines VAMC, upon enrollment of 50, 100, 150 and 200 subjects.
c. *DSMB reports* will be forwarded to the IRB at least yearly.
d. Unanticipated problems involving risks to subjects or others (UAPs), internal serious adverse events (SAEs), and protocol deviations/violations will be reported to the IRB and the DMC using the local reporting form within 5 days of notification of the event.
e. The *data collection will be continuous. The safety assessments* will be upon enrollment of 50, 100, 150, and 200 subjects.
f. Studies will be stopped when there is a greater than expected rate of morbidity or mortality or when the experimental arm of a head to head comparison study is shown to be better or worse statistically than the standard care arm, taking into account any multiple comparison statistical issues.

13. **COMPENSATION OF SUBJECTS.** Provide the terms of the subject participation agreement and the amount of payment. Substantiate that proposed payments are reasonable

and commensurate with expected contributions of the subject and that they do not constitute (or appear to constitute) undue pressure on the subject to volunteer for the research study. Describe any non-VA compensation for injured research subjects.

No compensation will be provided

14. **PRIVACY**. Provide provisions to protect the privacy interests of subjects. Indicate that all research personnel will respect the dignity, cultural, psychosocial, spiritual and personal values, beliefs, preferences, and personal privacy of research subjects as outlined in Medical Center Memorandum 00-102. In every subject encounter, members of the research team must be sensitive to the subject's gender, cultural, psychosocial, spiritual and personal values, beliefs and preferences, and how the subject may interact with the procedure to be performed, especially if the procedure involves intimate physical aspects. Personal privacy includes pulling cubicle curtains around a bed, closing the room door while providing care or interviewing a subject, providing auditory privacy, knocking on a room door before entering, covering the subject appropriately both in privacy and in public areas, etc.

All research personnel will respect the dignity, cultural, psychosocial, spiritual and personal values, beliefs, preferences, and personal privacy of research subjects as outlined in Medical Center Memorandum 00-102. In every subject encounter, members of the research team will be sensitive to the subject's gender, cultural, psychosocial, spiritual and personal values, beliefs and preferences, and how the subject may interact with the procedure to be performed. Personal privacy includes pulling cubicle curtains around a bed, closing the room door while providing care or interviewing a subject, providing auditory privacy, knocking on a room door before entering, covering the subject appropriately both in privacy and in public areas.

15. **COSTS TO SUBJECTS.** Describe extra costs to subjects for their participation in the study.
Include extra costs to third party payers because of subjects' participation. Clinic visits for tests and procedures over and above standard care should be considered a cost to subjects in terms of travel expenses and time off work.

There will be no extra cost to the subject for participation in this study.

16. **ROLES OF INVESTIGATORS AND RESEARCH STAFF.** *New Requirements* Describe the protocol-specific duties of all personnel listed on Page 8. Include scientific training, qualifications, degrees and years of experience.

Eric Cohen, MD, Principal investigator. Dr Cohen will supervise all aspects of this study. He will organize the planning and performance of the study. He will meet monthly or more often with study personnel to ensure timely, accurate, and secure data collection. He will ensure reporting of adverse events. He is trained in Medicine and Nephrology, has completed a study of captopril to mitigate renal disease after bone marrow transplantation, and has a MD degree and 25 years of experience with clinical investigation. Elizabeth Gore, MD, co-investigator. Dr Gore will recruit patients to this study in Milwaukee. She will work daily with the study coordinator and will ensure the clinical follow up of the patients, including identification of

adverse events. She is trained in Radiation Oncology, is an active participant in RTOG clinical studies, and has a MD degree and over a decade of experience in clinical investigation.

Andreea Antonescu-Turcu, MD, co-investigator, Milwaukee.

Dr Antonescu-Turcu will enable the radiographic analysis of pneumonitis and fibrosis of the study de-identified patients. She is trained in Medicine and Pulmonary Medicine, has ongoing experience in clinical studies being done at the ZVAMC, and has a MD degree and over ten years of clinical experience.

Aniko Szabo, PhD, co-investigator, Milwaukee.

Dr Szabo will ensure the statistical aspects of this study. She will create the randomization tables for study subject enrollment and randomization. She will enable the statistical analysis of the data from this study. She will assist in the safety analyses done after enrollment of 50, 100, 150, and 200 subjects. She is a PhD statistician, and has abundant experience in statistical aspects of clinical studies, with five years of experience in this area.

Brian Fish, lab manager.

Mr Fish will assist in data organization, analysis, and publication.

Joseph Berman, study coordinator.

This coordinator will secure the enrollment of study subjects, under the supervision of Dr Gore. The coordinator will keep complete records of each study subject. He will administer the quality of life surveys. He will identify and report adverse events to the IRB without delay. He will meet at least monthly with the PI, Dr Cohen, to review progress on the study, and ensure up-to-date records.

To be named, study coordinator, Baltimore

This coordinator will secure the enrollment of study subjects, under the supervision of Dr Cohen. The coordinator will keep complete records of each study subject. He will administer the quality of life surveys. He will identify and report adverse events to the IRB without delay. He will meet at least monthly with the PI, Dr Cohen, to review progress on the study, and ensure up-to-date records.