Final Evaluation Report

Of the Statewide Tumor Tissue Biorepository Feasibility Study and Lung Tissue Biorepository Demonstration Project

April 25, 2012

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Executive Summary

The Department of Public Health (DPH) contracted with the University of Connecticut Health Center (UCHC) to conduct two related tasks: a Feasibility Study for the development of a statewide biorepository for tumor tissue (Feasibility Study), and a Demonstration Project for a lung tissue and serum biorepository (Demonstration Project).

The Connecticut DPH subsequently contracted with Professional Data Analysts, Inc. (PDA) to conduct an evaluation of the Feasibility Study and Demonstration Project. The evaluation was to assess the comprehensiveness of the Feasibility Study to assure that all required components were addressed, including coordination of all appropriate partners, required legislation, cost estimates, confidentiality issues, and a completed development plan. Similarly, the Demonstration Project, including all policies and protocols, standard operating procedures (SOPs) and memoranda of understanding (MOUs), was to be evaluated for adherence to relevant best practices and standards. The evaluation was to consider estimated costs, anticipated demand, sustainability and the strength of the proposed marketing and sales plan. This Executive Summary provides PDA's assessment of these areas.

Several contextual changes occurred during the study period which affected implementation and limited the viability of a future statewide biorepository. These include the NCI decision to discontinue its RTR efforts, resulting in the loss of a potential source of future funding, as well as regulatory changes and ongoing IRB challenges.

The team of investigators had significant departures from the study timeline and deliverables, which adversely affected the implementation of both studies as well as the final products. Certain deliverables were never produced, despite the fact that DPH issued two no-cost extensions for the projects.

The investigators successfully assembled an Executive Team and Advisory Panel which were representative of all important stakeholder groups and included expansive expertise. The Advisory Panel meetings were well-planned and expertly delivered. Meeting materials were expertly prepared, but more time should have been allotted for advance review of materials. However, delays in holding the Advisory Panel meetings limited the time available for members to provide feedback on materials, especially the Final Report.

The investigators developed a high-quality survey to solicit input on the different types of biorepositiories under consideration and to gauge hospitals' potential to engage in a statewide biobanking activity. Response to the survey was lower than desired, which reduces the generalizability of the survey findings. The final report does not provide enough documentation of the follow-up methodology to determine whether best practices in survey research were followed, or whether better methodology might have increased survey response.

The evaluation of the Feasibility Study finds that the study largely accomplished its objectives, despite its delayed implementation and reporting. The investigators kept abreast of the changing biorepository landscape, and repeatedly consulted with national experts. They appropriately shared current guidelines, recent publications and current and proposed regulations with the Advisors. Although the Survey response rate was modest, the investigators acknowledged that limitation, and emphasized the importance of basing any suggestions moving forward on the compendium of the project results, with significant focus on the Advisors' input.

The evaluation of the Demonstration Project concludes that essentially, none of the three components was fully implemented. All project outcomes were subsequently limited to cost estimates; planning and design considerations; and development of general protocols, procedures and clearance documents. All projects fell short of securing participation and IRB approvals of other hospitals. The components of the Common Agreement White Paper for a Statewide Virtual Biorepository were largely completed, but the process deviated substantially from the proposed work plan. Notably, the protocols, procedures and IRB applications were developed in parallel with the Advisory Panel discussions instead of following their completion. The investigators were the primary authors of the component documents and final content, and the Advisory Panel had a very limited timeframe to review the Final Report.

It was ultimately decided to leave elements of the **CSR** project to individual hospitals and research consortia as their funding allows. This decision was appropriate and informed by survey findings and Advisor input indicating the cryopreservation is rare and would probably not increase. In addition, costs would be significant with no evident source of funding.

Multiple steps and challenges remain in the implementation of the two remaining recommended projects, the **ATA** and one year **RTR**. The endpoint of the Biorepository Project fell well short of its original goals with the Feasibility Project comprising the majority of accomplished work plan. Although funding concerns may have obviated the implementation of specimen collection and transfer in the CSR and RTR Demonstration Projects even if the contracted timeline had been followed, the ATA project could certainly have been further progressed beyond general protocol development and IRB application to further implementation and beginning educational efforts at the individual hospital level. Significant further support of DPH or other public or private entities will be required for furtherance and final implementation of this initiative.

Finally, PDA considers the justification for the establishment of a one-year RTR pilot project weak. The costs would be considerable, even for one year, with minimal evidence that specimen collection and demand would be sufficient to support requests for additional funding. In fact, the investigators themselves at one point noted that a five year commitment to the project would need to be made at the outset for it to be productive.

Introduction

The University of Connecticut Health Center (UCHC) was contracted by the Department of Public Health (DPH) to conduct two related tasks: a Feasibility Study for the development of a statewide biorepository for tumor tissue (Feasibility Study), and a Demonstration Project for a lung tissue and serum biorepository (Demonstration Project). The Demonstration Project was comprised of three sub-projects:

i) a Demonstration Biorepository of Fresh-Frozen Tissue and Serum (Cryopreserved Specimen Repository or CSR);
ii) a Demonstration Biorepository of Formalin-Fixed Paraffin-Embedded (FFPE) Tissues that would otherwise be discarded (Residual Tumor Repository or RTR); and
iii) a Demonstration "Virtual" biorepository in which the FFPE specimens would remain in the hospital archives, but tissue information and access are centrally organized (Accelerated Tumor Access or ATA).

The project was to build upon previous work in Connecticut including a Surveillance, Epidemiology, and End Results (SEER) Special Study in 2001 which involved a survey of state pathology laboratories and a DPH Feasibility Study for a statewide biobank that examined risk factors for preterm births and reviewed many ethical, legal, and social issues common to a tumor biorepository. The stage for the project was set by the implementation of Public Act No. 09-232, October 1, 2009 which stated that the DPH could enter into a contract for the storage, holding and maintenance of the reportable tumor tissue samples under its control and management.

The primary investigator on the project was Richard Everson, MD, MPH, Deputy Director for Cancer Prevention and Control, UCHC, and Helen Swede, PhD, Cancer Epidemiologist, UCHC, was Co-investigator. Rajni Mehta, MPH, Director, Rapid Case Ascertainment was also on the project team. The Connecticut DPH team consisted of Lloyd Mueller, Principal Investigator, CT Tumor Registry; Lou Gonsalves, Epidemiologist, CT Tumor Registry; Cathryn Phillips CTR, Manager, CT Tumor Registry; and Joan Foland, Planner, Office of Genomics.

The Connecticut DPH subsequently contracted with Professional Data Analysts, Inc. (PDA) to conduct an evaluation of the Feasibility Study and Demonstration Project. The evaluation was to assess the comprehensiveness of the Feasibility Study to assure that all required components were addressed, including coordination of all appropriate partners, required legislation, cost estimates, confidentiality issues, and a completed development plan. Similarly, the Demonstration Project, including all policies and protocols, standard operating procedures (SOPs) and memoranda of understanding (MOUs), was to be evaluated for adherence to relevant best practices and standards. The evaluation was to consider estimated costs, anticipated demand, sustainability and the strength of the proposed marketing and sales plan.

The PDA evaluation team consisted of Anne Betzner, the Principal Investigator on the project, and Ann Wendling, the Project Director who was responsible for the day-to-day management of the project. Dean Troyer and Dan Kavanaugh were sub-contractors as content experts in the area of biorepositories. The evaluation was participatory in nature in which PDA shared findings regularly with DPH for the purpose of program improvement. PDA was invited to participate in project conference calls and observe the Advisory Panel meetings. An overview of the Evaluation Process may be found in Appendix A.

After reviewing the final work plan for the University of Connecticut Feasibility Study, PDA identified an opportunity to produce useful evaluation information in several additional areas. The attached final evaluation plan focused on the Feasibility Study since it was the first to be implemented (Appendices B and C). A specific plan for the Demonstration Project was not developed due to project delays and lack of development of a clear and detailed project work plan informed by the Feasibility Study.

The evaluation questions guiding the evaluation of the Feasibility Study were:

1. To what extent do the 'Terms of Reference' address all necessary issues for the Feasibility Study? What are the strengths and weaknesses of the group membership in the Executive Team, Advisory Panel, Advisory Sub-groups, and External Reviewers? For each of the above, what sectors of expertise or issues, if any, are under-represented?
2. What are the strengths and weaknesses of the content of the survey questionnaires for the hospital pathology laboratories and IRBs? What content areas, if any, are underrepresented?
3. What are the strengths and weaknesses of the methodology of the survey questionnaire for the hospital pathology laboratories and IRBs? How adequate is the sampling plan and execution? What is the response rate of the survey and how representative is the response group? To what extent does survey administration mirror best practice?
4. What are the strengths and weaknesses of the content of the Advisory Panel meetings, including external communications as appropriate? How adequate is participation of Advisory Panel members for the purpose of the Feasibility Study?
5. To what extent does the Final Feasibility Study Report reflect key content areas?
6. Overall, what are the strengths and weaknesses of the Feasibility Study Report and what do we judge its overall anticipated success?

The elements of the Demonstration Project which were implemented near the end of the project timeline were evaluated on the original contracted evaluation parameters including the development of policies and protocols, standard operating procedures and memoranda of understanding and their adherence to relevant best practices and standards. Detailed work plans were not established for the Demonstration Project and correlatively, more detailed evaluation questions were not developed.

This report addresses the Feasibility Study evaluation questions above, as well as the contracted areas for evaluation of the Demonstration Project. The report is comprised of four sections. The first is a process evaluation that describes some key contextual factors and changes that effected how the Feasibility Study and Demonstration Project were implemented and evaluated. The process evaluation also describes overall project timeliness and compliance with work plans, as well as management strategies that may positively impact any future funded endeavors. The second section assesses the Feasibility Study with regard to the study plan and participation, the Pathology and IRB surveys, the Advisory Panel, and the Feasibility Report. The third section assesses the Demonstration Project, specifically: the work plan and implementation of the FFT and Serum Demonstration Biorepository Project, the FFPE Tissue Demonstration Biorepository Project, the ATA White Paper, and Final Report are described here. The last portion of the Demonstration Project section discusses the overall success of the Demonstration Project. The fourth and final section of the report summarizes findings and provides conclusions regarding the evaluation of the Feasibility Study and Demonstration Project.

Process Evaluation

Lung tissue biorepositories encompass complicated financial, scientific, ethical and legislative issues. The first part of the process evaluation discusses several changes that occurred within these areas that impacted how the Feasibility Study and Demonstration Project were conducted and evaluated. Due to these and other factors, the timelines and work plans of the Feasibility Study and Demonstration Project were also subject to substantial changes. The process evaluation also discusses overall project timeliness and compliance with the original and revised work plans. A final area for consideration is the management of this complex grant and potential strategies to positively impact any future activities that may be funded.

Contextual Changes

Key contextual changes in four areas are discussed below: funding, state of the science, IRB clearance, and legislative and regulatory issues.

Funding

Since a significant focus of the project on was on developing a Residual Tumor Repository (RTR) in conjunction with the Connecticut Tumor Registry (CTR), it was anticipated that pilot work could be used to support an application for sustaining the resource through NCIs SEER program. However, during the course of the project, NCI decided to discontinue its RTR program, requiring a search for other funding sources. This was a particular concern for infrastructure development and sustainability of the project which led to the decision to limit implementation to development of cost estimates, procedures, and IRB protocols instead of assembling tissues and storing them in facilities that might not be able to be maintained. The changes in the funding landscape also resulted in exploring the potential use and funding of an RTR by other sectors in biomedical research, including pharmaceutical and biotechnology programs.

Funding considerations also affected the implementation of the Fresh-Frozen Tissue (FFT) and Serum (Blood) Demonstration Project. Initially, the investigators expected there would be a second year of funding from the Connecticut Tobacco Trust Board in the amount of $250,000 that would expand the overall study and sustain tissue collections initiated by pilot work, but these funds were not received. This led to significant concerns about the sustainability of any pilot project. Additional sources of funding that could sustain the pilot efforts were not available.

State of the science

FFPE tissues, which are widely available, are morphologically well preserved, but DNA and RNA may be fragmented and tumor proteins may be linked to other cellular components. In the past several years, a new generation of genomic analytical methods was developed that can greatly enhance the analysis of the extensive bank of FFPE tissues. This will allow greatly expanded use of archived tissues instead of relying on the more costly and labor intensive analysis of cryopreserved specimens. The investigators noted that new methods will be available for analyzing tissues with arrays such as the whole genome cDNA-mediated annealing, selection, extension, and ligation (DASL) assay that obtains gene expression levels for over 24,000 genes; assays for microRNAs; and large scale single procedure sequencing for cancer mutation screening providing data on millions of short fragments of genomes. The newer FFPE technology allows use of archived specimens for various endpoints including multiple tumor mutations.

Use of FFPE tissues will allow rapid completion of retrospective investigations of important clinical endpoints, such as molecular differences predicting clinical recurrence and survival. Survival analyses using FFPE studies are faster to complete than cryopreservation based studies due to the availability of larger numbers of tissue samples collected over many years, including autopsy specimens allowing access to tissues not usually available from surgical specimens. Also, studies of rare conditions and sub-group populations from whom specimens may be infrequent at a given hospital, such as minority populations or people at the extremes of age, would be facilitated by use of FFPE specimens from multiple hospital sites.

IRB clearance

The Connecticut Institute for Clinical and Translational Science (CICATS) was created in 2009 by the University of Connecticut, in partnership with regional hospitals, state agencies and community health care organizations. CICATS serves as a regional IRB in the advancement of translational research in the Hartford area. CICATS IRB approval would cover clearance at multiple hospitals including Hartford Hospital, St. Francis Hospital, John Dempsey Hospital, Hospital of Central Connecticut, and others in the Hartford area. It was hoped this would facilitate implementation of the Demonstration Projects by eliminating the cumbersome need for individual IRB clearances at each hospital and for each study. It would ease the establishment of the Virtual Biorepository, subsequently relabeled ATA. For more information: http://cicats.uchc.edu/services/irb.html

Legislative and regulatory

A change in the minimum medical retention policy was implemented by the DPH in 2009; Department of Public Health 19.28 Hospitals, Child Day Care Centers, Other Institutions and Children's General Hospitals. The previous policy required record retention for 25 years. The new statute stated, "Medical records shall be filed in an accessible manner and shall be kept for a minimum of ten years after discharge of patients, except that original medical records may be destroyed sooner if they are preserved by a process consistent with current hospital industry standards. The hospital shall provide the Department of Public Health with a list of the process or processes it uses." This change in retention policy might affect the availability of clinical data to associate with pathology specimens preserved longer than ten years.

Overall Project Timeliness and Compliance with Original and Revised Work Plans

The Connecticut Department of Public Health (DPH) contracted with the University Connecticut Health Center (UCHC) for grant activities starting on January 26, 2010. The DPH provided UCHC two no cost extensions, essentially doubling the project duration to December 31, 2011 with a Final Report due within 60 days of completion. PDA assessed progress on the Feasibility Study and Demonstration Project based on the timeline outlined within the original work plan in a Progress Memo sent to DPH June 17, 2011 (Appendix D), and again in a second Progress Memo to DPH on October 24, 2011 (Appendix E). These progress memos were not specifically outlined in PDA's work plan; however, we conducted this activity in order to be response to DPH's needs.

This section describes timeliness and compliance with the original and revised work plans for the Feasibility Study first, followed by the Demonstration Projects. The scheduled dates of completion for key milestones and deliverables are determined by the number of weeks from the inception of the project. Since the contract was fully signed and executed on January 26, 2010, progress on the timeline is judged from that date. The last portion of this section discusses progress towards completion of the revised timeline that was developed three months before the end of the grant, in October 2011.

Progress of the Feasibility Study according to the original work plan

The state-wide surveys of Connecticut hospital pathology departments and IRBs and Advisory panel tasks were largely completed, but were submitted approximately one year late, according to the original work plan. The final report of survey findings was due by Week 20 (June 15, 2010) and was actually completed in July 2011. The Advisory Panel meetings were scheduled to be finished Week 24 (July 13, 2010), but were actually completed about 15 months later, November 10, 2011. The completion of the set of Panel meetings was a critical step upon which many other deliverables of the project depended. These include establishment of principles and procedures and outstanding issues for the Demonstration Project, most notably the Statewide Virtual Biorepository (VB) (referred to subsequently as Accelerated Tissue Access, or ATA).

Likewise, the Interim Feasibility Study Report, originally due by Week 26 (July 27, 2010) was submitted about 15 months late on October 10, 2011. The original work plan stipulated that External Reviewers comment on the report prior to its submission to DPH; however, the evaluators are not aware that the report was reviewed by either the Advisory Panel or a unique team of External Reviewers.

Progress of the Demonstration Project according to the original work plan

By Quarter 6, August 1-October 31, 2011, some UCHC made some progress in implementing the Prospective Collection and Storage of Fresh-Frozen Tissue and Serum Project (CSR), but Hartford Hospital and a third participating hospital, which was not secured, never began implementation which was scheduled for Week 26 at the latest (July 27, 2010). Similarly, the implementation of the Physical Biorepository of Formalin-Fixed Paraffin-Embedded (FFPE) Tissue Project at Hartford and a third hospital was to start by Week 24 (July 13, 2010). PDA received no documentation that the FFPE project was implemented at any hospitals besides ongoing specimen collection at UCHC. Interim reports, subsequent to implementation were to be submitted by Week 44 at the latest (November, 30, 2010). These reports were not completed, but components of the interim reports were submitted as part of the Draft Final Report approximately one year after the due date, on October 10, 2011, and embedded in the narrative and Appendices of the project Final Report.

The third project is the Statewide Virtual Biorepository (ATA). Criteria for additional partner hospitals, and the number thereof, to join UCHC and HH in the project were to be determined based on hospital surveys and Feasibility Study findings. Operating principles and procedures were to be developed based on the requirements identified in the statewide surveys of hospitals and the findings from the Feasibility Study. These tasks were not completed as scheduled. Acceptance of the IRB submission including principles and procedures is pending, a Master Agreement for CT hospitals has yet to be established, and possible hospital specific requirements have yet to be determined. A period of 20 weeks, from weeks 24 to 44 (July 13, 2010 to November 30, 2010), had been allotted to draft a Common Agreement White Paper to be submitted as a deliverable to DPH. UCHC had reported in quarterly updates that the paper was early in development, however multiple stakeholders had yet to be identified and invited to participate. It was not clear at the end of the second and final contract extension on December 31, 2011, how much progress had been made on the White Paper.

Revised work plan and reporting

In a meeting on October 3, 2011 among UCHC investigators, DPH staff and PDA staff outlined the delays in progress and reviewed the deliverables of both the Feasibility Study and a Demonstration Project that were not likely to be accomplished (Appendix F). One week subsequent to that, the investigators

submitted a revised work plan and timeline which guided the work until project completion on December 31, 2011. Also, a draft Final Report was submitted on October 10, 2011. It outlined progress to date and proposed modified contracted project deliverables. The draft Feasibility Study Interim Report and the three Demonstration Project Interim Reports, originally designated as separate reports, were submitted as part of the Draft Final Report in limited forms and with limited review of stakeholders. The Feasibility Study Report and the Common Agreement White Paper for a Statewide Virtual Biorepository were also eventually subsumed in the Final Report. These documents were submitted later than was specified in the original project deliverables and associated timelines.

Lastly, quarterly project reports were consistently submitted late to DPH. The following table includes scheduled due dates for the Quarterly Project Reports and the Receipt Dates as noted by DPH. The discrepancy in the numbers of reports, 8 due, 7 submitted, is likely due to the investigators' consideration that the Update on Activities report submitted in April 2011 covered two quarters, 11/1/2011 through 5/31/2012. Alternatively, the report for the period 3/1/2012 through 5/31/2012 was missed. The report labeled Progress Report 5 covered the period 5/1/2011 to 07/31/2011. Progress Report 6 submitted very late on February 21, 2012 and the draft Final report submitted on October 10, 2011 provided important information on the redesigned scope of the Demonstration Project and related progress which would have been useful for DPH to have on a more timely basis.

Goal	Activity	Due Date	Date Received
a. Document progress and problems for all projects in written quarterly reports.	Quarterly progress reports submitted to DPH.	5/1/2010 8/1/2010 11/1/2010 2/1/2011 5/1/2011 8/1/2011 11/1/2011 2/1/2012	7/28/2010 1/27/2011 1/27/2011 4/27/2011 6/7/2011 8/26/2011 2/21/2012 2/21/2012
b. Submit quarterly reports to DPH.			

The evaluation plan did not include an evaluation question addressing adherence to project timelines and work plans. However, the evaluation team concludes that delays in implementation, delays in submission of reports and other deliverables, and the failure to complete certain deliverables adversely impacted the overall quality and utility of the final products produced by the Feasibility Study and Demonstration Project. We believe that the delay in completing the Advisory Panel meetings one of impediments, since several other study activities, including the majority of the Demonstration Project tasks, were dependent upon completion of the Advisory Panel meetings and tasks. The delays in quarterly reporting hindered the ability of DPH to provide informed feedback on project performance. The delays in providing minutes and transcripts from the Advisory Panel Meetings and the draft Final Report to its members was not conducive to careful review and commentary.

Some delays in timeline and deliverables were ultimately overcome by the project team by the time of the final report. These include submission of IRB applications including SOPs for the Multi-Hospital Master Protocol for Research Requiring Residual Tumor Tissue and De-Identified Clinical Data and the Statewide Physical Repository of Residual Tissue, the Research Registry/Repository for Prospective Studies of Tumor and Blood, and the Multi-Hospital Master Protocol for Research Requiring Residual Tumor Tissue and De-Identified Clinical Data: Accelerated Tumor Acquisition (ATA). However, as noted

in subsequent report sections, multiple tasks, especially related to the Demonstration Project were never completed.

Reflections on Contract Progress

This section reflects on the contextual factors that impacted the progress of the biorepository contract, and the overall patterns of timeliness and completion of contract activities. It considers how management practices may improve any future activities that may be funded in this area.

As is described above, the DPH contracted with the UCHC to conduct activities clearly itemized in the contractor's work plan. The DPH specifically selected the contractor to complete the activities because they are well respected experts in the field, with both academic and practical experience that would enable them to complete the specified activities. Informal interviews with PDA suggest that DPH expected that the advanced credentials of the selected contractor would be the primary factor that would lead to project success.

PDA observed the progress of contract activities throughout the contract period and participated in two Evaluation meetings with the contractor and DPH on March 22, 2010 and July 28, 2010 (Appendices G, H), which noted substantial delays and several aspects of the contract which were not completed. It is important to note that some of the activities were delayed or not completed because the contractor appropriately responded to changing funding, scientific, legislative, and regulatory conditions relevant to the project (also described above). In witnessing the progress of the contract, PDA speculates that another factor that may have contributed to the delays include understaffing at UCHC such that staff were not available to participate in the project in a timely fashion. This may be related to the advanced credentials of the contractor and external demand for the project team's time. PDA is unclear as to the extent to which understaffing may have impacted project progress. Undoubtedly, many other factors impacted project progress that PDA is not aware of and are not outlined here.

Even without fully understanding the reasons that contracted activities were not completed in a timely manner or at all, PDA has observed that communication between the contractor and DPH was insufficient to keep all parties apprised of the progress and changes to activities, and to develop a mutually agreeable plan for moving forward on a timely basis. A revised work plan and timelines were developed in the latter part of the one year no-cost extension, on October 10, 2011. However, this planning occurred too late in the contract to ensure that more activities would be completed. Additionally, quarterly reporting was not consistently submitted on a timely basis.

More timely communication between the contractor and DPH would significantly improve project functioning in future cycles. PDA believes this is most appropriately ensured by DPH management. Such management would be most effectively employed by closely monitoring the project timeline in the contract, instigating communication to understand why delays are occurring, demanding quarterly reporting on a timely basis, actively renegotiating project timelines and deliverables periodically as necessary, and making clear that project funding is dependent on successful completion of project deliverables. Termination of the contract should be considered if the contractor does not adequately respond to the terms of the contract and DPH management of the contract.

It is important to note that the funded project is complex in its scientific content, in the group process that was selected to implement the contract, and in the array of contextual factors that surround the project. For this reason, management of the contract requires skills in several areas, most notably in the

substantive area of biorepositories and biorepository development, as well as in contract management and negotiation. It is possible that management of the contract at DPH may require participation of more than one person in order to bring all the necessary skills to the table. Future contracts would likely be well served by developing a structure that ensures that individuals with the required skills are available and accessed to participate in contract management. DPH staff require funding and departmental support in order to meaningfully participate contract management at this level.

In summary, PDA's observation is that some delay in project activities and changes in deliverables was necessary due to changing contextual factors in the field; the contractor was responsible for other delays. In addition, we believe that some delays and uncompleted deliverables could be avoided in the future if more structured management practices are implemented.

Evaluation of the Feasibility Study

The evaluation team was asked to assess the extent to which the Feasibility Study addressed all necessary issues, and the strengths and weaknesses of group membership. To this end, PDA assessed the Feasibility Study in four areas: the study plan and participation, the Pathology and IRB surveys, the Advisory Panel, and the Feasibility Report. Each area is discussed in greater detail below.

Study Plan and Participation

The following section describes the extent to which Terms of Reference were defined, group membership, their participation, and the strengths and weaknesses.

Terms of reference

In the Project Work Plan, it is stated that by Week 8, the 'Terms of Reference' (TOR) would be defined, outlining the scope and duties for each of the following groups: Executive Team, Advisory Panel, Advisory Sub-groups and External Reviewers. These groups were to assist UCHC in advising and directing the projects required under this MOA, according to their respective area(s) of expertise. The evaluator found that TOR were outlined primarily for one of these groups, the Advisory Sub-groups. In the Advisory Panel Planning Document on Feb 8, 2010, it was noted the Advisory Sub-groups were to review the interim reports and were identified as Pathologists, Informatics and Tumor Registrars. These constituents changed slightly by the end of the contract. In the Final Report, the groups were identified as Pathologists, IRB, ELSI (Ethical, Legal, Social implications), Cancer Partnership, Research/biobank, Cancer Centers, Consultant, Project Team and DPH staff. Terms of Reference for the Executive Team, Advisory Panel, and External Reviewers were largely undefined.

Expert representation and contributions

Executive Team

Members of the Executive Team were not defined in reports submitted to DPH and PDA, but PDA assumes that this group consists of project members at the University of Connecticut and Yale according to quarterly reports. It is assumed that DPH staff were included, but this is not clear. PDA has no documentation that definitively states how frequently the Executive Team met. There were approximately 15 conference calls noted in the first three quarterly reports, however, the frequency was not detailed in subsequent quarters. Documentation on the specific contributions of the Executive Team was not available to PDA. In an Advisory Panel planning document, it was noted that there would be discussions with the Executive Team and the updates would be sent to the Advisors. PDA has no documentation that this occurred.

Advisory Panel

The Advisory Panel was selected over a period of several months with potential members first identified in a February 9, 2011 Advisory Panel planning document. The Advisory Panel consisted of 30 members in nine categories. The number of members in each of the categories is as follows: Research/biobank (N=7), Pathology (N=5), IRB (N=3), Cancer centers (N=3), ELSI (N=2), CT Cancer Partnership (N=2), Biobusiness Consultant (N=1), Project Team (N=3), and DPH (N=4).

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External Reviewers
External reviewers were to be selected at the First Advisory Panel, however, there is no documentation that a separate group of External Reviewers was intentionally chosen. PDA's best understanding is that the entire Advisory Panel serves as External Reviewers.

Advisory Sub-groups
Advisory Sub-groups were defined through categorical listing on the Advisory Panel documents, as described above. In an Advisory Panel planning document, it was noted that Advisory Sub-groups would meet to provide interim feedback between the first and second Advisory Panels. PDA has no documentation that this occurred. However, one contribution of the Advisory Sub-groups was to comment on the draft Final Report, which was sent to them via email eight days prior to the Final Report Due Date. Only a few members of the Advisory Panel were not included in the email request for commentary. It is not known if these members were requested to provide feedback. Additionally, on December 29, 2012, a face-to-face meeting was held with a sub-group of the Advisory Panel, including contracted consultant Lisa Miranda, President and Chief Executive Officer, Biobusiness Consulting, Inc. Meeting attendees included Drs. Everson and Swede, and several Advisors: Paul Pescatello, Pramod Srivastava, James Thibeault, and, later by telephone, L.Gonsalves, L. Mueller, and P. Checko, for additional input.

Evaluation Question: To what extent do the 'Terms of Reference' address all necessary issues for the Feasibility Study? What are the strengths and weaknesses of the group membership in the Executive Team, Advisory Panel, Advisory Sub-Groups, and External Reviewers? For each of the above, what sectors of expertise or issues, if any, are under-represented?

The Executive team included knowledgeable state experts in cancer control and epidemiology with access to critical leadership in Connecticut to form the Advisory Panel. The membership of the Advisory Panel and its Sub-Groups was representative of all important stakeholder groups: Pathology, IRB, ELSI (Ethical, Legal, Social implications), CT Cancer Partnership, Research/biobank, Cancer centers, and a Biobusiness Consultant. The representation was diverse with expansive expertise to serve as valuable contributing Advisors. All of the Sub-groups were represented at the Advisory Panel meetings. However, to the best of our knowledge, the expertise of membership was under-utilized. It is not evident how many, if any members of each Sub-group provided any additional feedback during the limited time given for review of the Draft Final Report. It was not apparent that specific feedback was elicited from members of particular Sub-groups with the exception of the Biobusiness Consultant. This is also the case for the External Reviewers, in general, which are assumed to be the entire Advisory Panel. Finally, Advisory Sub-groups and the Executive Team were assigned roles in an Advisory Panel Planning document, but PDA has no documentation that these bodies fulfilled those roles.

Surveys (Pathology and IRB)
This section describes how the vendor developed, implemented, and reported the Pathology and IRB surveys, and PDA's initial assessment of survey methodology. It also describes PDA's assessment of the survey implementation and reporting after our initial assessment

Research questions
The surveys were designed to help determine the feasibility of different types of biorepositories. Identifying potential barriers to implementation and possible solutions at the hospital level were considered key to success of a statewide biorepository. The purpose was to learn more about current archival practices and to understand perceptions and realities of individuals who would have staffing

and administrative responsibilities for collecting and transferring samples. Answers to these questions were considered crucial to gauge the hospitals' potential to engage in a statewide biobanking activity.

Development

According to quarterly reports, a draft questionnaire for the Pathology Department Chairs was completed by May 1, 2010. It was pilot tested at University of Connecticut Health Center (Chair, Dept. of Pathology; Director, UCHC Bio-Repository.)

Content of the survey was based on:

i. Relevant issues covered in survey mailed in 2000 regarding discard repository.
ii. Issues recorded in meeting minutes for DPH Biobank Committee (2008-09)
iii. Expertise of Dr. Lou Gonsalves and Rajni Mehta.
iv. Topics raised at biobanking conference Dr. Swede attended (2009)
v. Discussions with NCI and UCLA with Dr. Everson (April 2010)
vi. Identification of language to describe the three basic design options for assessment in surveys: Residual Tumor Repository (RTR), Post-Diagnostic Repository (PdTR) and Expedited Tissue Access (ETA).

The language was refined after discussion with L. Gonsalves and R. Mehta with focus on how to present the relevant scenarios (i.e., anonymous, de-identified with codes, or identifiers included in data) within each of the three approaches. The staff of the UCHC Department of Pathology also provided feedback on draft survey. Comments were incorporated after discussion with the Executive Team.

PDA provided feedback on the Pathologist Survey and Cover Letter and Survey Methodology on August 25, 2010 (Appendices E,F,G). PDA was charged with reviewing the survey methodology for the upcoming Biorepository Feasibility Study, and making recommendations for improvements. To improve the survey methodology, PDA made recommendations in two categories: changes to improve data quality (Appendices I, J), and those to elicit higher response rates (Appendix K). The recommendations regarding response rate were based on the work of Don Dillman, a well-known researcher in the field of survey methodology who has conducted research in the areas of mail survey design and implementation. They were also based on PDA's understanding of the Biorepository Feasibility Study survey methodology[1].

PDA stressed that multiple contacts are important. According to Dillman, "Multiple contacts have been shown to be more effective than any other technique for increasing response to surveys by mail." Five contacts are recommended. Therefore, PDA recommended three additional contacts to the mailing of the questionnaire and the final follow-up. These additional contacts include: 1) a prenotice letter sent up to a week before the initial questionnaire is sent, 2) a thank you post card sent approximately a week after the initial questionnaire is sent, and 3) a replacement questionnaire sent approximately two to four weeks after the post card is sent (and a few weeks before the participant is contacted by telephone).

For the Pathology survey, the Evaluation team anticipated that respondents would be busy and benefit from multiple respectful and carefully worded reminders, even if all of the recommendations described

[1] A mail survey will be sent to all chairs of Pathology and IRB panels in the state. The survey will be sent with a cover letter explaining the purpose, and with a self-addressed stamped envelope in which to return the survey. Non-respondents will be contacted by telephone three to four weeks after the survey is sent. It is our understanding that this contact will be used to remind them to complete the survey, but that the survey would not be completed by phone.

above could be implemented. If the response rates remained low after 5 contacts, PDA recommended a sixth contact be made to non-respondents so that they may complete the survey by telephone.

The IRB survey format was developed in parallel with the Pathology Survey. Unique focused questions were developed for the survey of IRB Panel Chairs. Dr. Ronald Kadden, a UCHC IRB Chair, provided feedback and identified additional topics to include. The final IRB survey was completed after the Pathology Survey since many questions were shared and the format was similar.

A Human Subjects Determination Form was submitted to UCHC IRB and approval was received for Exempt Status. As the project was judged to not be Human Subjects research, submission of revised versions of surveys for subsequent approval was not required. The application to DPH Human Investigations Committee (HIC) was also submitted and approved when the surveys were completed. The Yale application prepared by R. Mehta, Rapid Case Ascertainment (RCA), also received approval.

Survey instrumentation

The draft Cover Letter and Pathology surveys were examined by PDA staff. Overall, we consider the quality of the instrument to be strong. In our assessment memo, PDA recommended some changes to improve data quality. Commentary was embedded in the survey as "tracked changes". The investigators incorporated the vast majority of changes into the final Pathology and IRB instruments. Dr. Everson signed the cover letters, but noted in the body of the letters that the survey was being administered by the Rapid Case Ascertainment Shared Resource (RCA) at Yale, under the supervision of the Director, R. Mehta. Survey packets were mailed to the UCHC Chair of Pathology and UCHC as a trial run before being sent to the Pathology and IRB Chairs at the 29 Connecticut hospitals. The packets included an excerpt of **Public Act No. 09-232**, effective Oct 1, 2009. Descriptors of the types of biorepository were noted in the surveys' introductions as context for the respondents to avoid confusion regarding terms. This facilitated a basic level understanding among respondents of the types and conditions associated with each type of biorepository.

Sampling frame and strategies

All survey packets were mailed out in Fall 2010. The Pathology Cover letter was dated December 6, 2010 with a deadline for survey return of January 30, 2011. The IRB Cover Letter was not dated but included a return deadline of November 22, 2010. No further information regarding dates of follow-up or final acceptance of surveys is available to PDA. The project notes stated, "Survey reminders were sent" and reports did not confirm that any of the PDA recommended additional contacts were made. It is also not clear if a final contact by another means was accomplished.

Response rate

The project reports note that of 29 Hospitals in Connecticut, 11 Chairs of Hospital IRB panels and 14 Chairs of Hospital Pathology labs responded. The table provided by the investigators presents survey response for each type of survey, and describes response in terms of the number and percentages of beds covered at each responding facility. There is a discrepancy between this table in which 10 hospitals are listed as IRB survey responders and the survey result presentation to the Advisory Panel in which 11 hospitals are listed as responders.

Table 1. Survey Response

Surveys Returned	Hospital	Beds	Pct
None (n=8)	Bridgeport	391	.05
	Day-Kimball	104	.01
	Greenwich	174	.02
	Griffin	160	.02
	JDH - UCHC	204	.02
	Middlesex	275	.03
	Norwalk	328	.04
	St. Vincent	397	.05
	Subtotal	2033	.24
IRB Only (n=7)	Charlotte Hungerford	109	.01
	Hartford	819	.10
	Hosp Central CT (NB, Bradley)	414	.05
	MidState	130	.02
	Milford	106	.01
	St. Mary	345	.04
	Waterbury	357	.04
	Subtotal	*2280*	*.27*
Path Only (n=11)	Bristol	134	.02
	Danbury	345	.04
	ECHN (Manch, Rockville)	249	.03
	New Milford	85	.01
	Sharon	78	.01
	St. Francis	617	.07
	Stamford	305	.04
	VA (WH, Vet Home)	229	.03
	Windham	130	.02
	WW Backus	213	.02
	Yale	944	.11
	Subtotal	*3329*	*.40*
Both (n=3)	Johnson Mem	92	.01
	Lawrence Mem	280	.03
	St. Raphael	511	.06
	Subtotal	*883*	*.10*
	Returned 1 or more surveys: 72.4% (21/29) Coverage by bed number: 76%	8525	1.00

Analysis techniques

Drs. Everson and Swede exported the Excel data file to SPSS and formatted data files which they subsequently analyzed and initially reported at a DPH meeting on 5/12/2011. A full analysis was prepared for Advisory Panel Meeting I.

Representativeness and generalizability

The investigators reported that approximately 38% of IRB chairs (11 of 29 respondents) and 48% of Pathology Department chairs (14 of 29 respondents) returned surveys. In terms of the number of hospitals participating in the survey, 72% of all hospitals (21 of 29 respondents) in Connecticut were represented by a completed Pathology Survey, IRB Survey, or both. In terms of the percent of hospitals beds covered, the participation rate reflects coverage of 76% of beds with the investigators indicating that more large-size hospitals returned surveys. RCA reported that reasons for lack of participation were varied: IRB and Pathology Chairs were the same person or only recently appointed to position and discomfort in committing to a position about a statewide repository. RCA conducted a follow-up contact to all non-responders at least once, and only a handful did not respond at all to inquiries. While the

findings from the surveys helped inform discussions at the Advisory meetings, the investigators cautioned that the comparatively low participation rate may affect generalizability.

The target response rate was 80%. The response rates to the Pathology and IRB surveys, 48% and 38% respectively, do not lend themselves to generalizability. Including all possible individual respondents in the denominator (58), the calculated response rate was 36.2%. The low response rate likely would have improved if multiple follow-up contacts had been initiated. Details on follow-up are not known. The project team tried to compensate for the low response rate by inviting non-responders to join the Advisory Panel. They noted that 97% returned the survey and/or were invited to Advisory Panel. Although this tactic may have increased the representativeness of expert input into the project, this combined approach does not impact the survey data and increase the generalizability of its results.

In the best possible light, the combined response rate of 72%, with coverage of 76% of beds, is more encouraging. Assuming that there would be some crossover between the Pathology and IRB responses if both departments in each of the responder hospitals had completed the surveys, the results may be more representative than the individual rates would suggest.

Survey results

The following key survey findings were accurately represented by the investigators. A PowerPoint presentation with data presented in tables and pie charts was given at the first Advisory Panel Meeting (Final Report Appendix A). The investigators noted the results as follows:

Requests for Tissue Blocks. Demand for tissue blocks appears to be low at this time. About 82% of IRB Chairs (9 of 11 respondents) indicated that they receive requests for tissues from external researchers once every few years. About 57% of Pathologists (8 of 14 respondents) indicated that they release blocks for less than 50 patients per year to outside researchers, about 25% of Pathologists indicated(3 of 14 respondents) that they released blocks for 50-100 patients per year, and fewer still (14%, or 2 of 14 respondents) indicated that they released blocks for greater than 100 patients in a given year. The survey did not ask how many blocks, typically, are released per patient but we assume it would be 1-2 blocks per case.

Number of years Blocks are maintained. About 57% of Pathologists (8 of 14 respondents) reported that they keep blocks only for the ten year mandate. The remaining Pathologists (43%) indicated that FFPE blocks are kept for 15 years or more.

Proportion of Blocks Re-tested after Diagnosis. About 77% of Pathologists estimated that less than 5% of archived blocks need to be retrieved for re-testing within the first year after the initial diagnostic tests were conducted. The remaining 23% indicated that 5% to 10% of blocks are retrieved for re-testing within the first year. This need, though small, levels off with time. About 83% of Pathologists reported that 1% or fewer of the archived blocks need to be retrieved within 1 to 5 years after diagnosis. All Pathologists indicated that 1% or fewer of blocks are retrieved after the 6-year point.

Requests for Anonymous Data. About 70% of IRB Chairs (8 of 11 respondents) reported that they never receive requests for strictly anonymous data (i.e., no random code accompanying dataset given to Investigator or neutral third party.)

Percent of Tissues Crypopreserved. The majority of Pathologists (76%) reported that they did not cryopreserve tissues in 2009, and about 84% projected that they do not expect or are unsure that cryopreservation would increase in practice in the next 3-5 years.

Potential Agreement to Send Blocks to a Statewide Repository. About 69% of Pathologists (9 of 14 respondents) indicated that they would be very or somewhat likely to send blocks or archived slides to a central RTR in the future. About 26% of Pathologists (4 of 14 respondents) indicated that would be very likely to send blocks to a Post-Diagnosis RTR whereas the remaining 74% indicated that they would be somewhat or very unlikely to do so. One-half of Pathologists reported that they might consider sending archived slides to a Post-Diagnosis RTR, however.

Statewide IRB for RTR. As seen in the following table, likelihood of acceptance among IRB Chairs (n=11) of a Statewide IRB panel as the mechanism for approving tissue-based studies varied somewhat according to the level of patient identification requested by the research team. Support ranged from 82% when no Identifiers are requested (i.e., Anonymous) to 55% when requesting Patient Identifiers along with tissue samples.

Acceptance of an ATA Program. As seen below, likelihood of acceptance among IRB Chairs (n=11) of a Multi-Hospital Master Agreement also varied somewhat according to the level of patient identification requested by the research team. The majority (82%) of IRB Chairs expressed likely support for a Master Agreement for either anonymous or coded data. There was less support (55%) for this mechanism if Patient Identifiers were requested.

Evaluation Question: What are the strengths and weaknesses of the content of the survey questionnaires for the hospital pathology laboratories and IRBs? What content areas, if any, are underrepresented?

In summary, the surveys were well designed with the expertise of Drs. Everson and Swede, Dr. Gonsalves and Rajni Mehta, with content thoughtfully representative of and consistent with the current environment and science and informed by discussions with NCI and UCLA. Additional input on the IRB survey was appropriately elicited from an IRB Chair at UCHC. The survey background information clearly described the three types of proposed biorepositories to assist the Pathologists and IRB Chairs in understanding the specific proposals in this complex field of varying definitions.

Evaluation Question: What are the strengths and weaknesses of the methodology of the survey questionnaire for the hospital pathology laboratories and IRBs? How adequate is the sampling plan and execution? What is the response rate of the survey and how representative is the response group? To what extent does survey administration mirror best practice?

In summary, the survey implementation process was flawed with lack of documentation of multiple contacts to improve response rate. It was reported that RCA conducted a follow-up contact to all non-responders at least once, and only a handful did not respond at all to inquiries. The overall response rate was modest; thus, it is not clear if there were some responses that did not include survey completion. There is no documentation that the investigators followed best practice methodology recommended by the evaluator that included three contacts, noted previously, in addition to mailing of the questionnaire and the final follow-up. A sixth contact was recommended if the response rate was low, which was the case.

The response data did help to answer the research questions and inform further project development, but the response rate among all potential IRB and Pathology chairs was only 36.2%. This was too low to consider the data representative and generalizable, limiting their sole use to inform the implementation of the various potential biobank models (e.g., RTR, pdRTR, ATA, or combinations thereof).

Advisory Panel

This section describes how the contracted vendor planned Advisory Panel membership, who attended Advisory Panel meetings and their areas of expertise, and summaries of the two Advisory Panel meetings that were convened. Finally, this section assesses the overall success of the Advisory Panel meetings.

Planning

Planning activities spanned a very long period of time. In the first quarterly report, it was noted that planning for membership of the review groups was partially complete and a rough draft of the agenda was created. Dr. Everson had discussed project membership with individuals at NCI and UCLA and Dr. Swede recruited Carol Stone, Ph.D., who led the successful Feasibility Study on developing a statewide biorepository for research on pre-term birth. Other conversations were conducted to identify possible experts. However, in the second report it was noted that the planning was in abeyance while surveys were being finalized. Planning resumed in the third quarter. The investigators aimed for advisory meetings in late March/early April 2011 to allow for surveys to be returned, and data collated and analyzed. In February 2011, a more detailed planning document was released which included proposed members of the Panel and Guest speakers, the invitation process, a more detailed agenda and proposed logistics.

Representation

A total of 17 advisors attended the Advisory Meeting I in addition to Project Team, DPH staff and Evaluators. These members represented experts in the areas of Pathology, IRB, ELSI, the CT Cancer Partnership, Cancer Centers, DPH, Research/Biobank, Consultants, the Project Team, and Evaluators. Please see Appendix L for a listing of advisors by area of expertise.

For Advisory Meeting II, a total of 15 advisors attended, in addition to the Project Team, DPH staff and Evaluators. Please see Appendix L for a listing of these members.

A total of five advisors were not present at either meeting.

Summary of Advisory Meetings

Advisory Meeting I was held on July 12, 2012. Beginning in March 2011, the contractor invited some 30 experts to participate in the first Advisory meeting via telephone call or personalized email; 27 agreed to participate; and 17 eventually attended. Also in attendance were four members of the Executive Project Team, two Evaluators and two students. Significant planning components included inviting Dr. Sean Altekruse, NCI, to give a brief overview of central biobank-related NCI activities. Dr. Swede contacted the director of New Jersey Cancer Center about information on research permissions in surgical consents. Dr. Everson, working with a UCHC Biomedical Graduate student, developed design features and projected costs for a physical repository based on operational data provided in surveys and estimates from UCHC Pathology. Meeting materials sent four days prior to the meeting included two publications: **Who Owns Diagnostic Tissue Blocks? Sarah Dry, MD** DOI: 10.1309/LM3XP8HBKDSGICJH

and **Storage and use of residual newborn screening blood spots: A public policy emergency,** *Beth A. Tarini, MD, MS; Genetics IN Medicine,* DOI: 10.1097/GIM.0b013e31822176df.

At the meeting, three formal presentations were made followed by an open discussion. Dr. Everson presented background of the current feasibility project and the increased research value of fixed tissues in hospital archives due to advances in molecular technology. Dr. Altekruse reviewed lessons learned in California, Hawaii and Iowa and NCI programs related to the establishment of central biobanks associated with the NCI-SEER tumor registry. Dr. Swede provided a summary of results from surveys conducted of Chairs of IRB panels and Departments of Pathology at all hospitals in CT. Data were presented on resources, financial and infrastructure, required for establishing and maintaining a physical biorepository. The Advisors discussed six specific challenges including tissue availability and quality, consent, IRB issues, funding for infrastructure and maintenance, assessment, and public education (Appendix L). The transcript of the meeting discussion was sent to L. Gonsalves, R. Mehta and L. Mueller on September 19th for review and subsequently to the Panel on October 5th.
Advisory Meeting II was held on November 11, 2012. The investigators consulted with the following advisors during agenda development: Wendi Cozen, University of Southern California Cancer Center and Sean Altekruse, National Cancer Institute Chair of IRB, Robert Wood Johnson Medical School.

The invitation and link to a meeting scheduling tool was sent on October 5, 2011 for Advisory Meeting II. Meeting materials were sent two days prior to the meeting. The background journal article, *Forsberg, et al.* **Biobank research: who benefits from individual consent?** *BMJ, 2001,* was included along with agenda and administrative details. A description of the change in Medical Retention Policy in Connecticut was also included.

The meeting started with a follow-up discussion on some key issues raised at Meeting I. Highlights of this discussion included follow-up on consent issues. The remainder of the meeting centered on discussions of the RTR and ATA options, protocols and projected costs. Two tables cataloging a range of options related to operation of an ATA and RTR were used to structure the discussion. The RTR discussion included housing the facility at a physical site to be determined, possibly under contract with DPH. Handouts were provided on cost estimates for the ATA as well as suggestions for future planning by statewide work groups. The meeting closed with these suggestions. The investigators noted that they were planning to have a meeting(s) on sustainability aspects, and would be in touch with some advisors. They also stated they were in the process of identifying external reviewers of Final Report due at the end of February. Please see Appendix L for a more detailed summary of Advisory Meeting II.

A third small meeting with the investigators, consultant Lisa Miranda, and a few Advisors to discuss sustainability occurred on December 29, 2011. Ms. Miranda is a market consultant with expertise on product development that involves a lab and setting up biobanks for academic centers and industry. The group reviewed potential sources of startup and sustainable funding including grants, foundation, private, Private/Public Partnership and, consortia membership. They also reviewed options for user-fee revenue structures and various types of organizational structure (academic center, hospital, 501c3, etc.). Limitations of working with Pharma/Biotech and Public/Private Partnerships under the auspices of state support were referenced. Although Pharma involvement would have unique challenges, it likely would also increase demand for tissue, another significant concern for sustainability. DPH representatives were invited to attend the latter part of the meeting for continued discussion. However, the Final Report did not further delineate any results of subsequent discussion with DPH. Highlights of the meeting, summarized from the transcript provided in Final Report Appendix A, are noted in Appendix L.

The transcript from the first meeting was sent to the attendees on October 5, 2011. There were no minutes, but a bulleted list of key points was included. No summary of the second meeting was sent to attendees prior to completion of the project. The transcript was included in the Draft Final Report sent on February 21, 2012. A summary transcript was provided for the December 29th meeting, but no summary notes or comments were provided.

Evaluation Question: What are the strengths and weaknesses of the content of the Advisory Panel meetings, including external communications as appropriate? How adequate is participation of Advisory Panel members for the purpose of the Feasibility Study?

The Advisory Panel meetings, held in the last two quarters of the project, were completed 15 months later than originally planned. The invitations were sent with adequate lead times of one month and greater, however, the materials were sent out four days prior to Meeting I and two days prior to Meeting II. In consideration of the extent of these materials, including multiple publications, more time should have been allotted for review of materials. The materials appropriately provided thorough background information and updates on biorepository science, regulatory concerns and relevant issues in other states. The agendas were well organized with input from subject matter experts. The presentations at Meeting I by Drs. Altecruse, Everson and Swede were very well prepared and delivered, focusing on the current state of biobanking in the U.S., cost considerations of each of the proposed biorepository types and the IRB and Pathology Survey results. The second meeting appropriately started with a review of open issues from Meeting I. The use of tables subsequently used to present various operational options for the ATA and RTR was very helpful in guiding the discussion of these complex topics. The transcripts from the meetings were not delivered to the members on a timely basis, approximately three months after Meeting I and two and one half months after Meeting II. The delay in providing transcripts may have been deleterious in eliciting member feedback due to fading recall. There was also limited time for feedback on the transcript from the second meeting. Although five members of the Advisory Panel were not present at either of the meetings, each of the Sub-groups was represented adequately at each meeting. There was no documentation in the reporting that any of the absent Advisory Panel members provided input outside of the Panel meeting, with the exception of the Consultant, Lisa Miranda. Ms. Miranda did not attend the second meeting. Her input on framing a business model and exploring additional funding sources would have been beneficial to the group's discussion. Pharmaceutical representatives also were unable to attend the second meeting. To obtain Ms. Miranda's input, an additional third smaller meeting was held at the end of the project. It was also noted in the reporting, that she provided input into the Final Report.

Feasibility Report

Evaluation Question: To what extent does the Final Feasibility Study Report reflect key content areas?

No Interim Feasibility Report was submitted. The elements to be contained within were submitted through meeting materials, progress reports and the Final Report. The information necessary for evaluation was eventually obtained, albeit with more difficulty than it would have been if a separate Feasibility Report had been delivered. Evaluation comments on the Surveys and Advisory Panels are included in the preceding sections. The legal and consent issues, IT needs and potential for sustainability of various models are discussed in the Demonstration Project and Final Report sections. Key content areas were adequately addressed by the project's end. The lack of interim and final consolidated Feasibility Reporting and significant delay in completion of the Feasibility Project components were significant impediments to planning and implementation of the Demonstration Project, even to a limited extent, which was to be informed by the Feasibility findings.

Evaluation Question: Overall, what are the strengths and weaknesses of the Feasibility Study Report and what do we judge as its overall anticipated success?

The success of the Feasibility Study is gauged on reporting in meeting materials, progress reports and the Final Report. The Feasibility Study largely accomplished its objectives, despite its delayed implementation and reporting. The investigators throughout the project kept abreast of the changing biorepository landscape, especially those including consent, funding and public reaction. They repeatedly consulted with national experts. They appropriately shared current guidelines, recent publications and current and proposed regulations with the Advisors. Although the Survey response rate was modest, the investigators acknowledged that limitation, and emphasized the importance of basing any suggestions moving forward on the compendium of the project results, with significant focus on the Advisor's input. The Feasibility Study comprised the bulk of the entire Biorepository Project since the Demonstration Project was limited to the development of proposed protocols, procedures and IRB applications that are currently being processed.

Evaluation of the Demonstration Project

Planning for the Demonstration Project commenced early in the contracted period and included discussion of hospital collaborations, followed by IRB clearance and an evolving understanding of the virtual repository concept. For example, in the first quarterly report, it was noted that UCHC and Hartford Hospital had established an initial agreement to work together on the Demonstration Project. Collaboration details continued to be refined and criteria for an additional hospital were discussed at an Executive Team meeting. As discussions with Hartford Hospital to plan tissue transfer agreements continued, a series of meetings was conducted with UCHC pulmonary and surgery groups to ensure maximal access to lung cancer specimens from UCHC.

The UCHC IRB and CICATS regulatory personnel were consulted concerning the most efficient course for IRB clearance of Demonstration Project. Discussions indicated that if it were approved by CICATS, clearance would be granted at multiple hospitals including Hartford Hospital, St. Francis Hospital, and others affiliated with CICATS, the newly established Regional IRB. The creation of CICATS underpinned a revised approach which included inserting a section on Virtual Repository concept (referred to now as Accelerated Tissue Access, or ATA) in the Pathology and IRB surveys and a discussion of issues and requirements specific to an ATA program at the Advisory Meetings. A Regional IRB Regulatory Specialist was invited to serve on the Advisory Panel. Drs. Everson and Swede met with UCHC CICATS IRB to discuss draft protocols for the Demonstration Project in June 2011.

This section describes in greater detail activities conducted towards the completion of specific components of the Demonstration Project. These components include the FFT and Serum Demonstration Biorepository Project (CSR), the FFPE Tissue Demonstration Biorepository Project (RTR), the White Paper for Statewide Virtual Biorepository (ATA), and the Final Report. Lastly, this section assesses the overall success of the Demonstration Project.

FFT and Serum Demonstration Biorepository Project (CSR)

This section describes progress the vendor made towards development of the FFT and Serum Demonstration Biorepository. In the Work Plan section below, the expectations of the contractor are outlined. The following sections discuss the contractor's progress in meeting these expectations. Items assessed include: how partners were identified, identification of partners and storage facilities, developing protocols and submitting the IRB application, specimen collection and reporting.

Work plan

The work plan for the CSR project changed significantly due to several factors. Initially, the proposed project included first collecting cryopreserved specimens at UCHC and then extending pilot collection efforts to additional hospitals. With funding concerns previously noted, the investigators were concerned that if the full work plan were implemented, collection efforts at hospitals other than UCHC might be terminated and the project would be considered a failure. This would make it more difficult to re-initiate the work later, when it could potentially be sustained. In addition, it is important to note that the CSR project relied on contributions from the pathology and IRB surveys and from the Advisory Meetings. Substantial delays in these tasks required the timeline for the CSR survey to similarly delayed.

A key feature of CSR repositories is that prospective collection, cryopreservation and specimen maintenance is labor intensive and costly. They require substantial provider commitment and extensive

institutional support. While ultimately, cryopreserved biorepositories can become at least partially self-sustaining through fees for using their collections, building the collection to a point where this is feasible requires substantial institutional support bridging long intervals. The required cost and commitment limit the numbers of specimens available. An anticipated $250,000 from the Connecticut Tobacco Trust was not received and additional sources of funding were not evident. In addition, while well established for research studies, cryopreserved material is rarely used clinically, limiting the applicability of using this approach. The surveys conducted for this project as well as discussions at the Advisory Meetings strongly indicated little use of cryopreservation in the clinical setting.

In view of these factors, most significantly the concern for funding and clinical utilization, work toward a multi-hospital collaborative CSR was re-focused into the development of protocols, procedures, and clearance documents for a CSR rather than implementing collection of tissues. The evaluator questions whether this development work was appropriate considering the major barriers to successful statewide implementation. Perhaps, the investigators could have better focused their time on the remaining biorepository types for the remainder of the project.

Commented [MSOffice3]: Given the barriers described above, the CSR sounds like it might not be a good strategy, period. Should the CSR have been scrapped even though it's in the work plan? What's the use of developing protocols, procedures and clearance docs given the barriers discussed above? I've forgotten a lot about this project over maternity leave, so forgive me if I'm missing some basic facts about how the project works and my comments are not relevant.

Implementation

The implementation of the work plan included identifying partners and storage facilities, developing protocols and submitting IRB applications, collecting specimens, and reporting progress. Each of these activities is discussed in greater detail below.

Identification of partners and storage facilities

Although the original project was to include additional hospitals, the actual pilot collection occurred only at UCHC. This is a significant departure from the work plan and reflects the investigator's decision that a statewide CSR was probably not a feasible option.

Development of protocols and submission of IRB applications

In Quarter 6, Dr. Everson completed updated drafts of IRB applications and SOPs for the Demonstration Project: Research Registry/Repository for Prospective Studies of Tumor and Blood. Near the end of the project, Dr. Everson responded to CICATS' requests for numerous modifications to the IRB applications for the Research Registry/Repository for Prospective Studies of Tumor and Blood. (Final Report Appendix E) Work on the IRB proposal for extending collection of cryopreserved tissues to area hospitals under the CICATS program continued. Implementation of the project was impeded by protracted negotiations with the CICATS IRB.

For cryopreserved tissues, patients must provide direct consent for use of their tissues in research at the time of surgical biopsy which reduces the complexity of issues related to consent for use of archival tissues. However, prospective collection and cryopreservation of tissue are labor intensive and require significant human and financial resources and institutional commitment, limiting the numbers of specimens currently available. As noted previously, cryopreserved tissues have little use in clinical evaluation. Lack of use of cryopreserved materials collected at UCHC's Biorepository did not make it feasible to seek co-funding for additional collections. It was unclear what would be done with specimens collected if the program were initiated. In addition, lack of sustainable resources led the investigators to limit implementation of the project to continued collection at UCHC and development of clearance and setup for additional hospitals, to be initiated at a time that demand for specimens was demonstrated and sustainable co-funding could be obtained.

Commented [MSOffice4]: Would it be reasonable to stop this entirely? Was it a flaw in the work plan that cryopreservation at UCHC and an expansion was specified? Should the Feasibility Study have indicated that this wasn't a good idea? I'm far away from the project so I may have some big gaps in my understanding and this comment may be irrelevant. But reading it afresh, this is my thought.

Specimen collection

The cryopreserved lung tissue collection was initiated at UCHC, first noted in Quarterly Report 6. Review of consenting and surgical procedures revealed barriers to participation that were ultimately overcome by obtaining patient consent during appointments for evaluation of pulmonary function or bronchoscopy rather than surgery. In the last project quarterly report, it was noted that the Demonstration Project for Prospective Studies of Tumor and Blood continued enrollment of lung cancer patients at UCHC. In the Final Report, it was noted that tissue and serum were obtained from 11 patients at UCHC as of December 5, 2011. Cryopreserved lung tissues are available and will be maintained by the Biorepository at UCHC. No other hospitals initiated specimen collection.

Interim Report

No interim report was submitted. Since the project was implemented in a very limited manner, results in several categories were not obtained: collation and analysis of findings based on the project logs, review of findings at the participating hospitals, cost estimates and sustainability potential based on pilot projects. Other components were incorporated into the Final Report in Sections II, III, IV, and V and Appendices E and F. Although an interim report would have been significantly modified from the original plan, it would have been useful to stakeholders during the project as a summary of the many identified challenges to this biorepository type with commentary regarding any residual feasibility in the state of Connecticut.

Commented [AW5]: Added commentary on lack of interim reporting.

FFPE Tissue Demonstration Biorepository Project

This section describes progress the vendor made towards development of the FFPE Tissue Demonstration Biorepository. In the Work Plan section below, the expectations of the contractor are outlined. The following sections discuss the contractor's progress in meeting these expectations. Items assessed include: how partners were identified, identification of partners and storage facilities, developing protocols, submitting the IRB application, specimen collection and reporting. Completion of the Interim Report is also discussed.

Commented [AW6]: Added introductory structure section.

Work plan

The original work plan called for the identifying participating hospitals; identifying and establishing a storage facility at UCHC; developing IRB protocols for tissue collection, processing, handling and storage that met participating hospital IRB requirements; developing operating principles and procedures; collecting and transfering tissue blocks from all participating hospitals to UCHC; and finally preparing an Interim Report documenting findings, including cost estimates. A decision to alter scope of the RTR component was made in response to a critical funding change at NCI, discussed above. Time was also a factor, in that this component of the project was to be initiated after completing the surveys and Advisory Panel meetings, both of which were significantly delayed. In fact, the Advisory Panel meetings were completed at the end of the contracted project time.

Implementation

As the investigators noted in the Final Report, "prolonged data collection and late scheduling of the Advisory meetings left limited time for implementation." Development of the protocols, clearance documents, and operating procedures for the Demonstration Project required complex protocols that underwent prolonged, multistep clearance processes. Furthermore, cost estimates for the RTR suggested that the multi-year program would require a million dollars of support to set up and maintain, making it unworkable without further support.

Considering the factors described above – notably the delayed timeline, lack of secure financial sourcing and storage constraints – the Residual Tumor Biorepository (RTR) pilot effort was "re-focused to the development of cost estimates, planning and design considerations, protocols, procedures, and clearance document rather than relocation of tissues." The project was also re-focused on the ability of the RTR approach to provide population sampling rather than large numbers of samples, with the timing of specimen collection to be triggered by demonstrated increasing demands on the ATA. Although the funding and lack of clear physical housing were significant barriers, there was limited time to address these issues and foster solutions with the considerable delay in the Feasibility Study timeline. Although, it is not likely that specimen collection would have been possible with the time constraints involved, it would be helpful for the contractor to provide clearer direction on these issues to DPH in order to inform future strategic planning beyond the end of the project period.

Identification of partners and storage facilities

Dr. Everson met with Hartford Hospital personnel on November 22, 2011 to discuss the possibility of transferring two years of FFPE blocks from 1995 and 1996 to UCHC as a pilot for a RTR. He inspected the UCHC facility where specimens would be maintained and space requirements were calculated. Ongoing key considerations were lack of funding for developing and sustaining a full RTR, especially in view of NCI canceling support for the project, and instability of space allocations at UCHC because of construction and commitment to Jackson Laboratories.

Development of protocols and submission of IRB applications

The issue of common versus individual hospital IRB submission was a common thread throughout the project from the initial surveys through the second Advisory meeting. The development of the regional CICATS was a promising indication that common agreements might be feasible. During Quarter 6, Dr. Everson completed updated drafts of IRB applications for the Multi-Hospital Master Protocol for Research Requiring Residual Tumor Tissue and De-Identified Clinical Data and the Statewide Physical Repository of Residual Tissue. Near the end of the project, Dr. Everson responded to CICATS project team and IRB requests for numerous modifications to the IRB applications.

The operating procedures and protocols are extensively described in Final Report Appendix F. At their second meeting, advisors did not reach consensus on specimen collection with options being population based sampling of tumors, sampling selected tumors, and hypothesis driven collaborations. Hospitals would not be able to retrieve tissue for additional clinical testing since the RTR would not be CLIA compliant. Also, the recent change in state regulations on retention of medical records from a 25 to 10 year requirement decreases the utility of an RTR since clinical data may no longer be available. Several advisors recommended conducting a pilot program to demonstrate feasibility and value. It was noted that a one year collection period could provide a population based sampling frame; however, residual blocks often are not available for each case. Because the costs are significant, a greater demand is necessary to justify indefinite acquisition.

The Advisors did not recommend the implementation of a Post-Diagnostic Tumor Repository (PdTR) in which tissues would be submitted shortly after diagnosis, since only 25% of Pathologists responding to the Survey supported it. A PdTR would need to be CLIA compliant, significantly raising the costs and adding risk to legal liability. Some tissue would need to be kept for the mandatory 10 year period, necessitating careful recordkeeping.

Specimen collection

No tissues were submitted under the auspices of a Statewide RTR.

Interim Report
No interim report was submitted. Since the project was implemented in a very limited manner, results in several categories were not obtained: collation and analysis of findings based on the project logs, review of findings at the participating hospitals, cost estimates and sustainability potential based on pilot projects. However, some components of the report were incorporated into the Final Report in Sections Section III, IV, and V related to ATA and RTR and Appendices D and F. Stakeholders likely would have found a separate interim report useful, in consideration of the time constraints associated with the altered project timeline. For future planning, it would also be useful for DPH to receive a unique section in the Final Report specifically summarizing the RTR findings from the Feasibility Study including the cost estimates presented to the Advisory Panel at its first meeting and more detail underlying the investigator's proposal for a one year RTR pilot.

Development of Common Agreement White Paper for Statewide Virtual Biorepository (ATA)

This section describes progress the vendor made towards developing the Common Agreement White Paper for Statewide Virtual Biorepository. In the Work Plan section below, the expectations of the contractor are outlined. The Implementation section discusses the contractor's progress in meeting these expectations. Items assessed include: how partners were identified, developing protocols and submitting the IRB application, the potential for project sustainability, and submission of the white paper itself.

Work plan

The investigators were to identify multiple stakeholders and invite them to participate in this project. Criteria for additional partner hospitals and the number thereof, to join UCHC and HH in the project were to be based on hospital surveys and Feasibility Study findings. The contractor was also charged with developing operating principles and procedures based on the requirements and preferences identified in the surveys and the findings from the Feasibility Study.

Implementation

Identification of partners
The contractor did not identify the partners according the parameters outlined in the work plan. While the contract stated that the investigators were to identify partners based on the hospital survey and Feasibility Study findings, these tools do not appear to have been used to identify partners. At their second meeting, Advisors recommended that all or nearly all hospitals would be invited to participate.

Development of protocols and submission of IRB applications
Operating principles and procedures were to be developed based on the requirements and preferences identified in the statewide surveys of hospitals and the findings from the Feasibility Study. Based on available data, this did appear to occur. The paragraphs that follow describe the processes involved. Draft protocols and procedures were drafted from the findings of the two surveys conducted for this project; current literature on biobanking; consultations with experts at University of Southern California, Cancer Institute of New Jersey and NCI; and comments from Advisors. These were presented in tabulated form at the Advisory Panel II meeting. The options were extensively and thoughtfully considered including operational issues of hospital participation, types of specimens, access to tissues, the approval process required after a researcher has obtained approval from the home IRB, the researcher application format, governance, approval criteria, patient identification and information

about tissue status, and fees for tissue retrieval. In addition, issues related to Ethical, Legal and Social Implications**,** IRB reviews and informed consent, were actively discussed.

The agreed upon options were presented in the Final Report with rationale provided where possible (e.g. Advisory Panel discussion, survey, standard procedures). In summary, it was recommended that all specimen types be collected: blocks and slides, blocks only and non-cancer tumors and that access be available to any investigator affiliated with a hospital/research institution in Connecticut with incentives to ATA participating hospitals. There was agreement that in addition to investigators obtaining permission from their home IRBs, a sub-committee of the DPH Human Investigations Committee should review the proposed project for adherence to the ATA Master Agreement criteria including hospital specific requirements. It was suggested that tissue release should be prioritized to projects that are population based using guidelines from the NCI's RTR Program. An Honest Broker would be available to access the CTR database to prepare a tissue block list for investigator retrieval. Subsequently, a tracking system would be established in which the investigators would provide information about specific tissue tests they performed.

An ATA Program Committee, with members from cancer research and IRBs, would finalize the ATA Master Agreement and guide the hospitals' approval processes statewide. Subsequently, it would monitor implementation and renewal applications. The Committee could be part of the proposed CT BioTrust. Extensive discussion regarding consent resulted in the majority of Advisors agreeing with an Opt-out approach, supported by current IRB practice granting waivers of consent for studies involving residual tissue and practices noted in the literature for Newborn Screening programs. Some Advisors advocated for legislation to standardize consent forms across the state. Optimal timing of consent was discussed with IRB Advisors noting consent at time of surgery may be perceived as coercive. Complicating this issue is the proposed USDHHS proposed guidelines which might require direct Informed Consent when using archived tissues. Lastly, it was recommended that the proposed CT BioTrust integrate several tissue based efforts in the state.

Near the end of the project, Dr. Everson responded to the CICATS program team and IRB requests for numerous modifications to IRB applications for the Multi-Hospital Master Protocol for Research Requiring Residual Tumor Tissue and De-Identified Clinical Data: Accelerated Tumor Acquisition (ATA). The protocols for Research Registry/Repository implementation were revised and extended. Dr. Everson corresponded with the Office for Human Research Protection concerning issues related to clearance of the ATA project and proposal. Guidance received was that the project would qualify for clearance as Not Humans Subject Research. Acceptance of this by state hospitals would dramatically simplify establishment and maintenance of the ATA. However, at the end of the project the issue of the extent of the necessity of individual IRB submissions, or at a minimum, inclusion of unique hospital requirements in a common ATA agreement, was unresolved.

Commented [MSOffice7]: Does this relate to what's in the work plan? If not, that's OK, but put some language to help the reader understand what it is and why it's important. I am pretty far from the project so it's hard for me to remember everything and keep it straight. More interpretation and transition language helps me. Given Lou's limited management experience, it might help her too.

Sustainability potential
The sustainability of the RTR and ATA repositories was discussed at both Advisory Panels and in the special meeting with Lisa Miranda, previously described. Options included Pharma, biotechnology and various consortia. Since no summary documentation was provided, it is assumed there was no clear agreement on the most viable source of funding**.**

Interim Common Agreement White Paper for a statewide Virtual Biorepository
The work plan stated that an interim report would be submitted. This was activity was not completed. No interim report was submitted. Instead, components of the Common Agreement White Paper are described in the Final Report Sections III, IV, and V related to ATA and RTR and Appendices C, D and F. Similarly to the RTR Interim Report, a separate interim report submitted at the end of the extended project time period would probably have been useful to stakeholders. However, the White Paper was the primary deliverable for this project. The fact that a completed White Paper was not submitted either is a significant deviation from the contracted work plan.

Final Report

The contractor was expected to accomplish multiple objectives in the Final Project Report. The findings from the interim reports from the Feasibility Study and Demonstration Project including the Common Agreement White Paper were to be integrated into the report. These were to include assessment of the pros and cons of different biorepository types; policies and procedures for operating different biorepository types; discussion of confidentiality and consent issues; infrastructure, IT and logistical requirements; cost analyses; and oversight and governance. These were to be followed with recommendations for the set up and operation of a statewide biorepository for research purposes. Each of these areas is discussed in greater detail below.

Assessment of pros and cons of different biorepository types

The investigators did an excellent job of tabulating pros and cons of the different types and subsets of various operational components (see the assessment in the contractor's Final Report Sections II, III, IV, VII). Please see Appendix M for a brief summary of the advantages and challenges of each biorepository type, identified by the investigators.

Policies and procedures for operation of different biorepository types

Policies and procedures for the operation of different biorepository types may be found in the contractor's Final Report Sections II, III, IV, V and Appendices C, D, E and F. The policies and procedures for the ATA and RTR were thoughtfully developed through input of the Pathology and IRB survey respondents, Advisors and national experts. They were appropriately guided by current legislation, regulations and standards. Additional considerations included cost efficiencies, tissue availability and access, potential demand and evolution of tissue analytic assays. The development of the policies and procedures was complicated by changing environmental factors, notably the change in the Connecticut medical record retention policy and the proposed USDHHS change in consent procedures. The policies and procedures will undoubtedly need to be responsive to ongoing changes in the environment before, during and after implementation.

Discussion of confidentiality and consent issues

Confidentiality and consent issues are discussed in the contractor's Final Report Sections II, III, IV, V and Appendices C, D, E and F. These issues were thoroughly discussed throughout the report and in the Attached Demonstration Project protocols and IRB applications. The consent issue is a lingering concern at the end of this project with the proposed USDHHS requirement to reconsent for use of de-identified issues. This situation is likely to be fluid which may complicate and slow future progress on either of the proposed biorepositories.

Infrastructure, IT and logistical requirements

Infrastructure, IT, and logistical requirements are discussed in the contractor's Final Report Sections II, III, IV, V and Appendices C, D, E and F, in their respective Demonstration Project Sections. The requirements stated by the contractor are limited because of other deliverables were not fully completed. It is difficult to delineate infrastructure requirements without selecting a specific housing facility. Likewise, it is difficult to determine IT needs without finalizing consent and patient codification issues, the extent to which tissue analysis tracking is required, etc. Finally, without actually doing a pilot it is difficult to fine tune logistical processes involving patient consent and clinical data retrieval, unique aspects of individual hospital participation, tissue transfer and retrieval, researcher application and fees, etc.

Cost analyses and potential for sustainability of various models

Cost analyses and sustainability are addressed in the contractor's Final Report Sections I, IV and Appendices C, D and E. Cost estimates for the various repositories were carefully formulated during the Feasibility Study, however due to the lack of implementation of the CSR and RTR demonstration projects, no actual cost data was subsequently available to further inform Connecticut's future implementation.

Projected costs and design features for a RTR were presented at Advisory Panel I. Annual expenses were estimated to be between $200,000 and $300,000 for the collection and facility to house specimens. Several years would be required to accrue a sufficient number of specimens to have a greater number than the archives of a small number of larger hospitals in the state. It was felt that at least a five year commitment to the project would need to be made at the outset for it to be productive. The potential for the development and sustainability of the RTR was subsequently significantly influenced by the discontinuation of NCI funding for RTRs.

The cost estimates for the other two repository types were also derived through careful analysis. The estimated cost of the CSR, based on existing repository data, was forecasted to be $5 to $10 million. In addition, the IT system for the CTR has a minimum of a six month delay prior to case registration and electronic reporting has not yet been widely implemented. Retrieval of data for annotation would be costly. The investigators did note that some cryopreserved biorepositories can ultimately become self-sustaining through free collection, but building the collection to the profitable point requires substantial support bridging long intervals.

ATA costs are significantly less without the need for funding a storage facility. The newer assays of FFPE tissue facilitate studies requiring a population based sampling frame or pooling patients from multiple hospital sites. The ability to analyze standard clinical specimens with the newer assays thus greatly increase the feasibility and decrease costs of these studies, and allow them to be completed in a timely and much more cost-effective manner than the CSR. The ATA costs were estimated to be $42000 for the initial set up of the master agreement, $8400 for its annual maintenance and approximately $2700 per study for IRB approvals and collection of specimens. These are not inclusive of hospital charges which would include IRB application fees at up to all 29 hospitals in Connecticut and engaging professional services of a third party to assist in the development and submission of applications. Case identification and CTR data compilation is estimated at $50 per hour.

Funding issues, including pursuit of other public and private sources, received thorough discussion at both Advisory Panels and the Sustainability Meeting. The fundamental change in the funding landscape resulted in the increased emphasis on investigating the potential use of an RTR by users in other sectors in biomedical research, including pharmaceutical or biotechnology programs in need of tumor specimens.

Oversight and governance

Oversight and governance was addressed in the contractor's Final Report Sections I, II, III, V, VI and Appendices C, D, E, F, in their respective Demonstration Project Sections. The Advisory Panel at its second meeting thoughtfully discussed these issues and identified particular challenges and possible solutions in Connecticut's environment. Oversight committees were recommended with members appointed by CTR and DPH based on recommendations from hospitals and academic institutions. Members for the ATA Committee should be drawn from cancer researchers and IRB panels whereas the

RTR Committee should primarily consist of pathologists and others familiar with Biobanking. However, again, no practical experience was gained through implementation of the Demonstration projects to further inform oversight and governance issues. Questions remain, which probably cannot be answered until further details are clarified, including sources of funding, IRB clearance of submitted protocols and procedures, establishment of a statewide Master Agreement and unique hospital needs for the ATA, and further delineating a viable business model for the RTR.

Education strategy for public and users

The implementation of the original proposed education component did not occur due to time constraints. However, the Advisors did discuss an educational component and considered it critical to reach out to the public with an education campaign in the future in order to build support in the event of a legal challenge. The Advisors noted that future educational efforts should include both providing information and a mechanism for receiving feedback from the public.

For the RTR, it was recommended that an education committee include pathologists, technical experts and persons with financial expertise. Ethicists and IRB panelists might be important if a long term RTR approach is adopted. The Advisors suggested various coordinators for public meetings; cancer survivor groups, local Health Departments and the American Cancer Society/CT Cancer Partnership. A comment period should be provided. A parallel outreach effort should be made to IRB panels and pathologists to review the project's design. For the ATA, the outreach would not need to be as extensive since tissues will remain at the home institutions. Hospital IRB panels should be consulted about the need for public outreach. It was also recommended that ATA representatives meet with IRB panels to discuss the ATA procedures. For the CSR, outreach could be less intensive since informed consent will be in place. It would be important, however, to educate pathologists to enhance participation. IRB panel involvement is important since an initiative to harmonize surgical consent form was recommended by Advisors.

Recommendations for the set up and operation of a statewide biorepository for research purposes

A key component of the Final Report was to recommend a model by which to set up and operate a statewide biorepository for research purpose. In its Final Report, the contractor recommended developing a virtual statewide biorepository by obtaining clearance under two scenarios: 1) determining that the project is not considered human subjects research, or 2) obtaining approval of an ATA Master Agreement by all hospitals in the state. IRB applications incorporating these approaches were submitted to the regional IRB , CICATS, in order to operationalize the concept of a virtual program (Final Report Appendix C). The contractor recommended a phased approach. First, a "virtual" statewide biorepository would be developed by obtaining clearance under a determination that the project is not human subjects research or approval of an ATA Master Agreement by all hospitals in the state. Once the ATA is operational, the second step would be to implement a one year collection of tissues for an RTR that would provide population based tumor tissues for common malignancies. As use of the ATA program increases, and the need for and sustainability of an RTR emerges, further development of a broader based RTR should be periodically reconsidered.

More specifically, the recommendations in the Final Report included

a) An ATA repository should be implemented with phase in of partner hospitals as funding permits. Funding sources that should be considered include State or private sources and individual investigators via an add-on aim of a traditional investigator initiated research application.

b) A one year collection of tissues for an RTR that would provide population based tumor tissues for common malignancies. If sufficient demand for tissues is demonstrated by the ATA repository, and a viable plan for sustainability of an RTR emerges, further consideration should be given to the development of a broader based RTR
c) Instead of developing a central CSR in Connecticut, development of biorepositories of cryopreserved tissues are best left to individual hospitals and research consortia as funding allows.
d) Legislative avenues should be pursued to support the ATA or RTR programs such as harmonizing surgical consents, reversal of the recent regulation lowering the record retention to 10 years and various options of the ATA Master Agreement.

Evaluation of Demonstration Project Success

Essentially, none of the components of the Demonstration Project was fully implemented. Therefore, project outcomes were limited to cost estimates; planning and design considerations; and development of general protocols, procedures and clearance documents, some of which were components of the Feasibility Study. All projects fell short of securing participation and IRB approvals of other hospitals, including any required hospital specific modifications of the general protocols and procedures. The CSR and RTR projects fell short of implementation of specimen collection and transfer. The components of the Common Agreement White Paper for a Statewide Virtual Biorepository were largely completed near the end of the project. The process, however, deviated from the proposed work plan in which a special team of expert authors from multiple disciplines was to draft an interim paper with subsequent period for further comment prior to final submission to DPH. The Advisory Panel discussions informed the content, however, a separate work group was not established. Notably, the protocols, procedures and IRB applications were developed in parallel with the Advisory Panel discussions instead of following their completion. The principal investigators were the primary authors of the component documents and final content. The Advisory Panel also had a period of only eight days to review the Final Report including components that were to be included in the White Paper.

It was ultimately decided to leave elements of the **CSR** project to individual hospitals and research consortia as their funding allows. This decision was appropriate and informed by survey findings and Advisor input indicating the cryopreservation is rare and would probably not increase. In addition, costs would be significant with no evident source of funding. Although human subjects exemption was granted for the **ATA** project, IRB applications are still under review. In the Final Report, the investigators recommended appropriate next steps in the implementation of the preferred ATA repository, emphasizing the need for establishment of a statewide Master Agreement and the involvement of Yale RCA to assist with the more specific hospital requirements. They also proposed a one year implementation of the **RTR** that included collecting tissues that would be available for population level research. The decision to pursue future funding would be informed by the demand for tissues through the ATA. Although, combining the large patient database data from the CTR with the new methods for analysis of FFPE holds great promise for cancer research and improved care, numerous questions remain regarding the demand for the repository, required consent, physical housing, financial sustainability and other maintenance issues. PDA considers the justification for the establishment of this one year pilot project to be weak, even for a smaller RTR focused on population level research. The costs would be considerable, even for one year, with minimal evidence that specimen collection and demand would be sufficient to support requests for additional funding. In fact, the investigators themselves at one point

noted that a five year commitment to the project would need to be made at the outset for it to be productive.

Multiple steps and challenges remain in the implementation of the two remaining recommended projects, the ATA and one year RTR, most notably securing resources to continue steps toward implementation and subsequent maintenance. The endpoint of the Biorepository Project fell well short of its original goals with the Feasibility Project comprising the majority of accomplished work plan. Although funding concerns may have obviated the implementation of specimen collection and transfer in the CSR and RTR Demonstration Projects even if the contracted timeline had been followed, the ATA project could certainly have been further progressed beyond general protocol development and IRB application to further implementation and beginning educational efforts at the individual hospital level. Significant further support of DPH or other public or private entities will be required for furtherance and final implementation of this initiative.

Conclusions

Several contextual changes occurred during the study period which affected implementation and limited the viability of a future statewide biorepository. These include the NCI decision to discontinue its RTR efforts, resulting in the loss of a potential source of future funding, as well as regulatory changes and ongoing IRB challenges.

The team of investigators had significant departures from the study timeline and deliverables, which adversely affected the implementation of both studies as well as the final products. Certain deliverables were never produced, despite the fact that DPH issued two no-cost extensions for the projects.

The investigators successfully assembled an Executive Team and Advisory Panel which were representative of all important stakeholder groups and included expansive expertise. The Advisory Panel meetings were well-planned and expertly delivered. Meeting materials were expertly prepared, but more time should have been allotted for advance review of materials. However, delays in holding the Advisory Panel meetings limited the time available for members to provide feedback on materials, especially the Final Report.

The investigators developed a high-quality survey to solicit input on the different types of biorepositiories under consideration and to gauge hospitals' potential to engage in a statewide biobanking activity. Response to the survey was lower than desired, which reduces the generalizability of the survey findings. The final report does not provide enough documentation of the follow-up methodology to determine whether best practices in survey research were followed, or whether better methodology might have increased survey response.

The evaluation of the Feasibility Study finds that the study largely accomplished its objectives, despite its delayed implementation and reporting. The investigators kept abreast of the changing biorepository landscape, and repeatedly consulted with national experts. They appropriately shared current guidelines, recent publications and current and proposed regulations with the Advisors. Although the Survey response rate was modest, the investigators acknowledged that limitation, and emphasized the importance of basing any suggestions moving forward on the compendium of the project results, with significant focus on the Advisors' input.

The evaluation of the Demonstration Project concludes that essentially, none of the three components was fully implemented. All project outcomes were subsequently limited to cost estimates; planning and design considerations; and development of general protocols, procedures and clearance documents. All projects fell short of securing participation and IRB approvals of other hospitals. The components of the Common Agreement White Paper for a Statewide Virtual Biorepository were largely completed, but the process deviated substantially from the proposed work plan. Notably, the protocols, procedures and IRB applications were developed in parallel with the Advisory Panel discussions instead of following their completion. The investigators were the primary authors of the component documents and final content, and the Advisory Panel had a very limited timeframe to review the Final Report.

It was ultimately decided to leave elements of the **CSR** project to individual hospitals and research consortia as their funding allows. This decision was appropriate and informed by survey findings and Advisor input indicating the cryopreservation is rare and would probably not increase. In addition, costs would be significant with no evident source of funding.

Multiple steps and challenges remain in the implementation of the two remaining recommended projects, the **ATA** and one year **RTR**. The endpoint of the Biorepository Project fell well short of its original goals with the Feasibility Project comprising the majority of accomplished work plan. Although funding concerns may have obviated the implementation of specimen collection and transfer in the CSR and RTR Demonstration Projects even if the contracted timeline had been followed, the ATA project could certainly have been further progressed beyond general protocol development and IRB application to further implementation and beginning educational efforts at the individual hospital level. Significant further support of DPH or other public or private entities will be required for furtherance and final implementation of this initiative.

Finally, PDA considers the justification for the establishment of a one-year RTR pilot project weak. The costs would be considerable, even for one year, with minimal evidence that specimen collection and demand would be sufficient to support requests for additional funding. In fact, the investigators themselves at one point noted that a five year commitment to the project would need to be made at the outset for it to be productive.

Appendices

A. **Review of Evaluation Process**
B. **Evaluation Questions and Bios 7_28_10**
C. **Evaluation Activities 7_28_10**
D. **Progress Memo 6_17_11**
E. **Progress Memo 10_24_11**
F. **Project Call 10_3_11**
G. **Evaluation Meeting 3_22_10**
H. **Evaluation Meeting 7_28_10**
I. **Pathology Survey Feedback Memo 8_25_10**
J. **Pathology Cover Letter Feedback 8_25_10**
K. **Survey Methodology Memo 8_25_10**
L. **Advisory Panel Meeting Attendance and Discussion Content**
M. **Assessment of Advantages and Challenges of Biorepository Types**