Office of the Secretary Of Defense (OSD)
Defense Health Program (DHP)
Small Business Innovation Research (SBIR)
FY2011.1Program Description

Introduction

The OSD Defense Health Program (DHP) SBIR Program, in coordination with the Director of Defense Research & Engineering (Research Directorate) is sponsoring topics in the Biomedical technology area in this solicitation.

The Army is participating in the OSD SBIR Program on this solicitation. The service laboratories act as our OSD Agent in the management and execution of the contracts with small businesses. The service laboratories, often referred to as a DoD Component acting on behalf of the OSD, invite small business firms to submit proposals under this Small Business Innovation Research (SBIR) Program solicitation. In order to participate in the OSD SBIR Program this year, all potential proposers should register on the DoD SBIR Web site as soon as you can, and should follow the instruction for electronic submittal of proposals. It is required that all bidders submit their proposal cover sheet, company commercialization report and their firm's technical and cost proposal form electronically through the DoD SBIR/STTR Proposal Submission Web site at http://www.dodsbir.net/submission. If you experience problems submitting your proposal, call the help desk (toll free) at 1-866-724-7457. You must include a Company Commercialization Report as part of each proposal you submit; however, it does not count against the proposal page limit of 25 pages. Please note that improper handling of this form may result in the proposal being substantially delayed. Information provided may have a direct impact on the review of the proposal. The DoD SBIR Proposal Submission Web site allows your company to come in any time (prior to the proposal submission deadline) to edit your Cover Sheets, Technical and Cost Proposal and Company Commercialization Report.

We WILL NOT accept any proposals that are not submitted through the on-line submission site. The submission site does not limit the overall file size for each electronic proposal; there is only a 25-page limit. However, file uploads may take a great deal of time depending on your file size and your Internet server connection speed. If you wish to upload a very large file, it is highly recommended that you submit prior to the deadline submittal date, as the last day is heavily trafficked. You are responsible for performing a virus check on each technical proposal file to be uploaded electronically. The detection of a virus on any submission may be cause for the rejection of the proposal. We will not accept e-mail submissions.

Firms with strong research and development capabilities in science or engineering in any of the topic areas described in this section and with the ability to commercialize the results are encouraged to participate. Subject to availability of funds, the DUSD(S&T) SBIR Program will support high quality research and development proposals of innovative concepts to solve the listed defense-related scientific or engineering problems, especially those concepts that also have high potential for commercialization in the private sector. Objectives of the DUSD(S&T) SBIR Program include stimulating technological innovation, strengthening the role of small business in meeting DoD research and development needs, fostering and encouraging participation by minority and disadvantaged persons in technological innovation, and increasing the commercial application of DoD-supported research and development results. The guidelines presented in the solicitation incorporate and exploit the flexibility of the SBA Policy Directive to encourage proposals based on scientific and technical approaches most likely to yield results important to DoD and the private sector.

Description of the OSD SBIR Three Phase Program

Phase I is to determine, insofar as possible, the scientific or technical merit and feasibility of ideas submitted under the SBIR Program and will typically be one half-person year effort over a period not to exceed six months, with a dollar value up to $150,000. We plan to fund 3 Phase I contracts, on average, and down-select to one Phase II contract per topic. This is assuming that the proposals are sufficient in quality to fund this many. Proposals are evaluated using the Phase I evaluation criteria, in accordance with paragraph 4.2 of the DoD 11.1 SBIR Solicitation Preface. Proposals should concentrate on that research and development which will significantly contribute to proving the scientific and technical feasibility of the proposed effort, the successful completion of which is a prerequisite for further DoD support in Phase II. The measure of Phase I success includes technical performance toward the topic objectives and evaluations of the extent to which Phase II results would have the potential to yield a product or process of continuing importance to DoD and the private sector, in accordance with Section 4.3.

Subsequent Phase II awards will be made to firms on the basis of results from the Phase I effort and the scientific and technical merit of the Phase II proposal in addressing the goals and objectives described in the topic. Phase II awards will typically cover 2 to 5 person-years of effort over a period generally not to exceed 24 months (subject to negotiation), with a dollar value up to $1,000,000. Phase II is the principal research and development effort and is expected to produce a well defined deliverable prototype or process. A more comprehensive proposal will be required for Phase II.

Under Phase III, the DoD may award non-SBIR funded follow-on contracts for products or processes, which meet the Component mission needs. This solicitation is designed, in part, to encourage the conversion of federally sponsored research and development innovation into private sector applications. The small business is expected to use non-federal capital to pursue private sector applications of the research and development.

This solicitation is for Phase I proposals only. Any proposal submitted under prior SBIR solicitations will not be considered under this solicitation; however, offerors who were not awarded a contract in response to a particular topic under prior SBIR solicitations are free to update or modify and submit the same or modified proposal if it is responsive to any of the topics listed in this section.

For Phase II, no separate solicitation will be issued and no unsolicited proposals will be accepted. Only those firms that were awarded Phase I contracts, and have successfully completed their Phase I efforts, may be invited to submit a Phase II proposal. Invitations to submit Phase II proposals will be released at or before the end of the Phase I period of performance. The decision to invite a Phase II proposal will be made based upon the success of the Phase I contract to meet the technical goals of the topic, as well as the overall merit based upon the criteria in section 4.3 of the DoD 11.1 SBIR Solicitation. DoD is not obligated to make any awards under Phase I, II, or III. DoD is not responsible for any money expended by the proposer before award of any contract. For specifics regarding the evaluation and award of Phase I or II contracts, please read the front section of this solicitation very carefully. Every Phase II proposal will be reviewed for overall merit based upon the criteria in section 4.3 of the DoD 11.1 SBIR Solicitation, repeated below:

a. The soundness, technical merit, and innovation of the proposed approach and its incremental progress toward topic or subtopic solution.
b. The qualifications of the proposed principal/key investigators, supporting staff, and consultants. Qualifications include not only the ability to perform the research and development but also the ability to commercialize the results.

c. The potential for commercial (defense and private sector) application and the benefits expected to accrue from this commercialization.

In addition, the OSD SBIR Program has a Phase II Plus Program, which provides matching SBIR funds to expand an existing Phase II contract that attracts investment funds from a DoD acquisition program, a non-SBIR/non-STTR government program or Private sector investments. Phase II Plus allows for an existing Phase II OSD SBIR contract to be extended for up to one year per Phase II Plus application, to perform additional research and development. Phase II Plus matching funds will be provided on a one-for-one basis up to a maximum $500,000 of SBIR funds. All Phase II Plus awards are subject to acceptance, review, and selection of candidate projects, are subject to availability of funding, and successful negotiation and award of a Phase II Plus contract modification. The funds provided by the DoD acquisition program or a non-SBIR/non-STTR government program must be obligated on the OSD Phase II contract as a modification just prior to or concurrent with the OSD SBIR funds. Private sector funds must be deemed an "outside investor" which may include such entities as another company, or an investor. It does not include the owners or family members, or affiliates of the small business (13 CFR 121.103).

The Fast Track provisions in section 4.0 of this solicitation apply as follows. Under the Fast Track policy, SBIR projects that attract matching cash from an outside investor for their Phase II effort have an opportunity to receive interim funding between Phases I and II, to be evaluated for Phase II under an expedited process, and to be selected for Phase II award provided they meet or exceed the technical thresholds and have met their Phase I technical goals, as discussed Section 4.5. Under the Fast Track Program, a company submits a Fast Track application, including statement of work and cost estimate, within 120 to 180 days of the award of a Phase I contract (see the Fast Track Application Form on www.dodsbir.net/submission). Also submitted at this time is a commitment of third party funding for Phase II. Subsequently, the company must submit its Phase I Final Report and its Phase II proposal no later than 210 days after the effective date of Phase I, and must certify, within 45 days of being selected for Phase II award, that all matching funds have been transferred to the company. For projects that qualify for the Fast Track (as discussed in Section 4.5), DoD will evaluate the Phase II proposals in an expedited manner in accordance with the above criteria, and may select these proposals for Phase II award provided: (1) they meet or exceed selection criteria (a) and (b) above and (2) the project has substantially met its Phase I technical goals (and assuming budgetary and other programmatic factors are met, as discussed in Section 4.1). Fast Track proposals, having attracted matching cash from an outside investor, presumptively meet criterion (c). However, selection and award of a Fast Track proposal is not mandated and DoD retains the discretion not to select or fund any Fast Track proposal.

Follow-On Funding

In addition to supporting scientific and engineering research and development, another important goal of the program is conversion of DoD-supported research and development into commercial (both Defense and Private Sector) products. Proposers are encouraged to obtain a contingent commitment for follow-on funding prior to Phase II where it is felt that the research and development has commercialization potential in either a Defense system or the private sector. Proposers who feel that their research and development have the potential to meet Defense system objectives or private sector market needs are encouraged to obtain either non-SBIR DoD follow-on funding or non-federal follow-on funding, for Phase III to pursue commercialization development. The commitment should be obtained during the course of Phase I performance, or early in the Phase II performance. This commitment may be contingent upon the DoD supported development meeting some specific technical objectives in Phase II which if met, would justify funding to pursue further development for commercial (either Defense related or private sector) purposes in Phase III. The recipient will be permitted to obtain commercial rights to

any invention made in either Phase I or Phase II, subject to the patent policies stated elsewhere in this solicitation.

Contact with DoD

General informational questions pertaining to proposal instructions contained in this solicitation should be directed to the topic authors and point of contact identified in the topic description section. Proposals should be electronically submitted. Oral communications with DoD personnel regarding the technical content of this solicitation during the pre-solicitation phase are allowed, however, proposal evaluation is conducted only on the written submittal. Oral communications during the pre-solicitation period should be considered informal, and will not be factored into the selection for award of contracts. Oral communications subsequent to the pre-solicitation period, during the Phase I proposal preparation periods are prohibited for reasons of competitive fairness; however, to obtain answers to technical questions during the formal solicitation period, please visit http://www.dodsbir.net/sitis. Refer to Section 1.5 of the DoD 11.1 SBIR Solicitation for more information and dates that SITIS is open.

Proposal Submission

Proposals shall be submitted in response to a specific topic identified in the following topic description sections. The topics listed are the only topics for which proposals will be accepted. Scientific and technical information assistance may be requested by using the SBIR/STTR Interactive Technical Information System (SITIS).

It is required that all bidders submit their proposal cover sheet, company commercialization report and their firm's technical and cost proposal form electronically through the DoD SBIR/STTR Proposal Submission Web site at http://www.dodsbir.net/submission. (This applies to both Phase I and Phase II proposal submission.) If you experience problems submitting your proposal, call the SBIR Help Desk (toll free) at 866-724-7457. You must include a Company Commercialization Report as part of each proposal you submit; however, it does not count against the proposal page limit of 25 pages. Please note that improper handling of this form may result in the proposal being substantially delayed. Information provided may have a direct impact on the review of the proposal. The proposal submission Web site allows your company to come in any time (prior to the proposal submission deadline) to edit your Cover Sheets, Technical and Cost Proposal and Company Commercialization Report. We **WILL NOT accept any proposals not submitted through the on-line submission site.** The submission site does not limit the overall file size for each electronic proposal, only the number of pages is limited. However, file uploads may take a great deal of time depending on your file size and your internet server connection speed. You are responsible for performing a virus check on each technical proposal file to be uploaded electronically. The detection of a virus on any submission may be cause for the rejection of the proposal. We will not accept e-mail submissions.

The following pages contain a summary of the technology focus areas, followed by the topics.

Defense Health Program Biomedical Technology Focus Area

The Department of Defense is aggressively pursuing unified Force Health Protection and Deployment Health strategies to protect Service members and their families from health hazards associated with military service. Toward that end, DoD is undertaking technology development programs that save lives and promote healthy individuals, units and communities while improving both force morale and warfighting capabilities.

The operational force is exposed to health threats throughout the operational continuum, from CONUS fixed facilities (garrison, base, ashore) through deployment, employment, and redeployment. DoD is developing policy and procedures to assess occupational and environmental health threats for all locations.

When Force Health Protection capabilities are fully implemented, commanders will have a more complete view of potential health threats. Integration of assessments from health databases and other assessments from intelligence (e.g., about land mines, directed enemy fire, fratricide) and safety (e.g., about injuries, vehicle accidents, explosives, aviation mishaps) will provide a framework for identifying future medical technology capabilities necessary for Force Health Protection.

Ensuring the health of the force encompasses several key capabilities:

- To mobilize, deploy and sustain medical and health support for any operation requiring military services;
- To maintain and project the continuum of healthcare resources required to provide for the health of the force;
- To operate in conjunction with beneficiary healthcare; and
- To develop training systems which provide realistic rehearsal of emergency medical and surgical procedures and unit-level medical operations.

These capabilities comprise an integrated and focused approach to protect and sustain DoD's most important resource—its Service members and their families—throughout the entire length of service commitment.

The Office of the Secretary of Defense believes that the small-business community can be effective in developing new technology-based approaches to needs in force health protection. Five broad capability areas of particular interest are the focus for the 2011 Defense Health SBIR Program. They are described in detail below:

Health Surveillance Planning and Decision Support Tools: Tailorable and targeted software applications that are integrated into the Military Health System's backbone of installed information systems are the essential enabling technology for surveillance. Applications in the areas of decision support tools, data and knowledge management, information visualization technologies including geospatial tools, and artificial intelligence-based appliqués for essential analyses are needed. It is expected that the applications would produce a comprehensive system of risk based assessments, predictions, and courses-of-action utilizing epidemiological, intelligence, environmental exposure, and health information concerning deployed forces. The applications should also allow for predictive modeling of medical readiness scalable from individuals to the aggregated Force, given such data streams as reported real and somatic symptoms.

New Methods to Monitor Health Status and Clinical Laboratory Data: Monitoring of health status during deployments is necessary to determine etiologic factors of deployment related health change. Data and information analysis tools are needed to collect and harmonize disparate data and information sources

and to provide health status surveillance pre- or post-injury to medical information consumers within and outside of military medical channels. Health monitoring should be for a limited set of indicators, and should yield an unambiguous interpretation of health status. Projects are required to have a strong biological basis and be sensitive to changes in health status based on either real-time measurements from warfighters in an operational environment, clinical laboratory data sources, and/or recorded in-patient or out-patient or trauma registry data.

Medical Training and Learning Tools: Developing and maintaining skills among the personnel of the Military Health System is an important aspect of deployment health. Advanced distributed learning, simulation-based training and other computer-based training technology should enable all health-care personnel to plan, respond and manage the future medical missions, and should assist medical professionals to maintain clinical knowledge, skills, and certifications. Tools that can be extended to use by the general military population for proactive preventive medicine are desirable. Tools should be based on existing medical and allied health knowledge, should be universally accessible, should allow for unlimited practice, and should be SCORM-compliant in content and in delivery modalities.

Traumatic Brain Injury (TBI) and Post Traumatic Stress Disorder (PTSD): TBI and PTSD are important priorities for casualty care in the DoD Medical Health System. Improved understanding of the etiology, identification, assessment, and treatment of TBI and PTSD is essential to force health protection.

For PTSD, research is needed to close gaps in knowledge about; 1) the epidemiology of PTSD, including the incidence, factors important in susceptibility and recovery and its impact on the function of the patient, families and caregivers; 2) basic neurobiology and genetic factors associated with PTSD; 3) prevention of PTSD, including development of methodologies for screening, detection, and diagnosis.

For TBI, research is needed to increase knowledge about the mechanism of injury in both closed and open head injury and to develop assessment methodologies for understanding the field epidemiology and blast physics related to brain injury, outcome metrics for the treatment and clinical management of all severity levels of TBI, neuroprotection and repair strategies, and effective approaches to rehabilitation/reintegration.

Tools or other products with commercial potential and systems that help to address these gaps in monitoring and assessing can substantially advance the DoD program to prevent and treat TBI and PTSD.

Acute and Rehabilitative Management of Traumatic Extremity and Eye Injury: With the successful implementation of body armor, extremity injuries have grown in its contribution to morbidity and mortality in the combat casualty. Eye injuries are also commonly associated with blast as well, with both direct damage to the eye and damage to the optic nerve and visual cortex playing a role. As a result, improved methodologies are sought in both the acute and rehabilitation phases of the clinical management of extremity and eye injuries, particularly as a result of blast. Technologies directed at repairing/restoring nerve, muscle and tendon damage that may occur as a direct result of the traumatic injury or due to secondary mechanisms of damage such as compartment syndrome are of interest as are improvements in rehabilitative strategies for recovery of normal limb function. Improvements in limb prosthetic devices are also sought.

OSD-DHP SBIR 11.1 Topic Index

The Defense Health Program Biomedical Technology topics are:

OSD11-H01	Artificial Vaccines Based on DNA Origami
OSD11-H02	Statistical Model Development in Epidemiological Research
OSD11-H03	Non-Radiological Imaging Devices for Combat Casualty Care Associated with Burn
OSD11-H04	Enhancing the User's Experience in an Amputee Virtual Environment Support Space

OSD SBIR 11.1 Topic Descriptions

OSD11-H01 TITLE: Artificial Vaccines Based on DNA Origami

TECHNOLOGY AREAS: Chemical/Bio Defense, Biomedical

OBJECTIVE: To build artificial antibodies using DNA origami

DESCRIPTION: Currently most vaccines are designed to mimic as closely as possible a natural infection process. Live attenuated virus vaccines are often used to produce a very low grade infection that leads to protective immunity. Many diseases have been successfully controlled using live attenuated vaccines, saving lives.

However, there are problems with using attenuated infectious agents as vaccines. Many infectious diseases for which successful vaccines have not yet been developed are those where recurrent infection does not prevent subsequent re-infections. Examples include parasitic diseases and certain viral diseases, with the most common example being the Human immunodeficiency virus (HIV).

A huge effort has gone into making extremely safe attenuated virus vaccines. Today's vaccines are extremely safe. However, accidents can still occur. In the 1950s, 200,000 people were inadvertently injected with live virulent polio virus during routine immunizations. 70,000 people became ill as a result of the vaccine, 200 of which were permanently paralyzed. Ten people died. An artificial vaccine would completely eliminate the possibility of inadvertent infection.

There has been work on developing artificial vaccines. Much of the work has been in the area of antigenic epitopes. An antigenic epitope is a portion of a given antigen that is recognized by the immune system. The majority of antigenic epitopes are conformational epitopes where the interaction with antibodies are based on the structure and charge distribution of the interacting species. Epitopes are generally extracted from the pathogen which they are designed to mimic.

In the case of parasites, outer surface proteins are often used in the production of vaccines. However, these outer surface protein based vaccines also have potential problems. For example, the LYMErix vaccine, developed to combat Lyme disease, may have caused significant autoimmune side effects to hundreds of vaccine recipients.

A completely artificial vaccine could eliminate the need to store and produce attenuated pathogens or parasites. Artificial vaccines could also provide vaccines against diseases where attenuated pathogens-based methods have been shown to be ineffective. For example, it is very unlikely that a vaccine for HIV based on an attenuated virus could ever be made to work. The goal of this effort is to examine DNA origami based methods as a possible mechanism for producing artificial vaccines.

The folding of single- and double-stranded DNA is a chemically well-understood and controllable process. DNA is generally associated with the storage of genetic information. However, in many ways, it is also an ideal building material. DNA's sequence dictates its shape and structure. Recently, progress has facilitated cheap and easy manufacturing of DNA strands with custom sequences. The use of self-assembled DNA sequences is thus a very attractive approach in the search for artificial vaccines. The science of DNA origami has recently progressed to the point that it is now possible to design and manufacture complex structures using DNA folding techniques. Much of the science of DNA origami is centered on producing better design software. The ability to produce better design software is a critical component of the controlled design and production large complex structures using DNA origami.

PHASE I: Conduct a feasibility study of producing artificial epitopes using DNA origami. Methods should be developed to design structures with predetermined shapes and functions. Methods for manipulating the physical properties of the self-assembled structures should also be examined. In particular, methods should be developed to manipulate the charge on the surface of a DNA self-assembled nanostructure. Also, the production of controlled hydrophobic and hydrophilic surfaces should be examined using DNA origami methods. A preliminary design should be made to produce structures using DNA origami that will function as epitopes. Where possible, target

antibodies related to biological warfare agents or simulants should be used to test the epitopes and determine selective affinity.

PHASE II: Fabricate artificial epitopes using DNA origami. Test the affinity of the epitopes to known antibodies. Based on the results of the tests, refine the design of the epitopes. Examine methods for incorporating the new artificial epitopes into vaccines or vaccine-like structures.

PHASE III DUAL USE COMMERCIALIZATION: Further research and development during Phase III efforts will be directed toward refining final deployable designs for artificial vaccines. Design modifications based on results from tests conducted during Phase II will be incorporated. Manufacturability specific to U.S. Army CONOPS and end-user requirements should be examined. Artificial vaccines will have numerous commercial applications, particularly in the field of medicine. It is expected that commercialization will accelerate once the artificial epitopes become less expensive and easier to use. It is the goal of this effort to produce affordable, stable vaccines that can be reliably mass-produced for battlefield applications.

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KEYWORDS: Biological Detection, artificial antibodies, DNA origami, self-assembled nanostructures

OSD11-H02 TITLE: Statistical Model Development in Epidemiological Research

TECHNOLOGY AREAS: Biomedical, Human Systems

ACQUISITION PROGRAM: Office of the Principal Assistant for Acquisition, USAMRMC

OBJECTIVE: To develop statistical data modeling software for epidemiology statistical analysis that enables users to develop a suitable model according the data structure and research hypothesis, to correct bias, to set proper modeling as well as to interpret the results.

DESCRIPTION: Epidemiological studies are used to identify risk factors for diseases and to determine optimal treatment approaches in clinical practice. Many investigations depend upon statistical analysis to draw conclusions. The data collected is often longitudinal and complex; hence there is a need to develop efficient analysis technique and software that result in unbiased, least-dispersed estimations. Research findings based on accurately analyzed data will identify the causation of disease and determine optimal treatments that will benefit both individuals and society. Improper modeling of data is often insufficient leading to questionable analysis and hampers the assessment of the strengths of the study. Little literature has been found for bias correction on epidemiology data analysis, hence we will study statistical challenges with longitudinal data analysis including: bias identification and correction, correlated data inference, issues with measurement errors or missing values.

This proposal will study the following:
1. Bias is the incorrect assessment of the association between an exposure and an effect in the target population in which the estimated expectation does not equal the true value. This occurs often in a variety statistical applications. Selection bias, information bias and confounding bias are common in epidemiological studies (Hill & DG Kleinbaum, 2005). The development of approaches to correct for these biases is a current challenge in epidemiological research and necessary for researchers to make correct conclusions. Few existing software can handle the bias correction and discussion.
2. Measurement errors and missing values have adverse effects on epidemiologic research. It has long been known that error of measurement increases variance and brings correlation coefficients closer to zero. Consequently, if error of measurement differs from one time to another, any statistical procedure based on either variances or correlation coefficients (Kraemer, 1992) will be affected by those varying errors of measurement. It is important in designing a study to minimize error of measurement in order to have greater accuracy of estimation and therefore greater power in testing. An additional crucial issue in longitudinal studies is whether the measurement error or missing values are similar for all time points during the time span of interest. The development of statistical methodology to address the problems of measurement error and missing values will advance longitudinal regression methods in epidemiological studies.
3. Data in longitudinal studies is often correlated and has been traditionally dealt with using general estimation equation (GEE) that compensate for the dependence within individuals and the intra-class and serial correlations. However, longitudinal survey data collected may be multi-level, involving further variation of dependence across the sampling units or clusters. Thus the estimation of the association between health outcomes and the various determinants of health also depends on the underlying variation of the dependency. Appropriate analyses of these correlated longitudinal data must account for variance of dependency. Few studies have dealt with this issue. It is difficult to distinguish the effects of correlated factors (Nunn and Lerou 2002) on outcomes, even without considering the variation of correlations, when using classical models in the most commonly used software. Deleting or ignoring correlated factors, which is commonly done, may lead to a biased conclusion. Identifying and correcting the co-linearity is a current and challenging statistical problem.
4. Complex probability sampling designs involving clustering and stratification are one of the major sources of data for a variety of studies (You and Rao, 2002). The data may not contain sufficient sample size for "small areas".

Combining information from multiple data sources, potentially improves estimation in small areas, and is an alternative choice for data analysis and needs to be validated.
5. Statistical Software for Epidemiology Research (SSER): Epidemiologists require statistical analysis software in the conduct of research. Correct study design and model selection are problematic for researchers conducting epidemiological studies. Much of epidemiology research is observational-case control, cross section, coherent or conventional. Reporting observational studies is often insufficient quality including, improper statistical model for the actual data, such as in-distinguishable matching and un-matching of controls, confusing interaction terms and confounding, mishandling of quantitative variables, simple deletion of missing records, improper explanation of the results. Poor reporting hampers the assessment of the strengths and weakness of the study and the generalizability of the conclusions. Most software has no functionality for model selection, bias correction and result explanation. This project will seek to develop a software tool that allows research investigators to conduct hypothesis-driven, model selection and data exploration based on data type, study design and hypothesis. It will help investigators improve the quality of epidemiology statistical analysis.

The software should have the following characteristics:
1) Easily enter data, to include data from Excel, comma separated files, or directly entered into the software.
2) It automatically checks the data type and data distribution, missing values.
3) It can describe the bias, which may occur in analyses and address bias effect and potential correction.
4) It can check for confounding and co-linearity.
5) It can handle quantitative variables in the analyses: linear or nonlinear, the ways grouping the data correctly.
6) It can handle longitudinal data.
7) According to the data structure (case-control, cross section, coherent or conventional) and the hypothesis of the study, it will use raw or summary data to perform suitable analyses.
8) It will do sensitivity analyses.
9) It will analyze data and get professional and understandable results.
10) It will provide a variety of statistical procedures to choose from, including common statistics.
11) It can interact with some commonly used statistical software, such as SAS or S-plus or stata.
12) It will explain the hypothesis tested and walk investigators though the decision making process leading to the most appropriate.
13) It will provide graphical results.
14) It will show how to report the conclusions on many of the procedures.
15) It will include a diagram in the manual to help select the correct procedures to analyze data.
16) It will provide sample write-ups using scientific format to describe the results.

PHASE I: Four statistical subtopics in developing new approaches to epidemiology data analysis are proposed. In Phase I the contractor will study the four proposed topics. Two topics will be selected for work in Phase I and II, according to their potential ability and knowledge of statistical modeling. A proposed detailed plan to include initial pilot studies for SSER will be prepared through study the four topics. The following should be accomplished in Phase I:
1. Identify the research questions.
2. Compare the currently and commonly used statistic approaches for the selected two subtopics.
3. State the advantages and disadvantages of the currently used methods to model longitudinal data.
4. Develop an initial novel concept and a statistical design.
5. Determine the expected direction of developed methods and statistics.
6. Design the pilot studies for the developed methods and statistics.
7. Establish the performance goal and testing criteria.
8. Layout the basic steps and approaches in detail.
9. Report the results from initial works.
10. Prepare for SSER: Investigate and summarize the existing statistical models for observational studies including the longitudinal analyses, outline the basic steps for developing software for basic epidemiological studies, and outline the algorithm for model selection and setting based on data structure and hypothesis.

PHASE II: In Phase II, novel and developed methods should be proposed, and proved to be better than classical models with mathematical proofs and/or simulation. The developed method should be validated using simulation data and actual data. Research findings and application products should be presented in professional conferences. At least, one statistical manuscript for each area should be submitted to a professional statistical journal. Two or

three manuscripts for each area applying the developed method on data should be accepted by or submitted to professional journals. Research in other areas not initially selected in Phase I may begin. The software of SSER should be applicable for investigators. The basic statistical model, such as logistic, general linear, conditional logistic, ANOVA, MANCOVA, repeated measurements, survival analysis, Poisson analysis as well as basic descriptive analysis etc. should be available. A critical statistical modeling for bias correction need exist to the software for the new developed method. This tool must be flexible and user-friendly for researchers to be able to directly analyze data.

In Phase II, the following will be completed:
1. Compare the developed method with currently used methods with simulated and existing data.
2. Determine if the developed method is supported by mathematical statistics, and if so, give the proof in detail. If it cannot be proved with mathematical statistics, it must be validated by simulations.
3. Find the properties of the developed method and the mathematical statistics.
4. Present findings and applications at professional conferences.
5. Publish the manuscripts related to developed methods and applications in professional journals.
6. Develop a statistical procedure or software for the developed methods.
7. Develop the statistical software for SSER.
8. Finalize the statistical software.

PHASE III: In Phase III, the contractor will continue to refine products developed in Phase II, especially for the software SSER. The contractor may need to improve those products based on feedback from various sources. If funded from non-SBIR government sources, the contractor can start to develop methods and statistics for other areas and continue to improve and complete the software tool of SSER that allows investigators to conduct hypothesis-driven research with auto model selection and conduct epidemiology statistical analysis.

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KEYWORDS: Statistical Software for Epidemiology Research, Model selection, Result explanation, Bias Correction, Missing Data, Longitudinal Data, Small Area Data Combining

OSD11-H03 TITLE: Non-Radiological Imaging Devices for Combat Casualty Care associated with Burn

TECHNOLOGY AREAS: Biomedical, Human Systems

OBJECTIVE: Develop novel imaging technologies utilizing non-ionizing radiation to predict burn depth and boundaries. The goal is to investigate portable, non-invasive approaches leading to new methods for burn assessment as alternatives to visual inspection and painful biopsy.

DESCRIPTION: Medical imaging techniques such as magnetic resonance imaging (MRI), computed tomography (CT) and ultrasonography (US) have improved medical outcomes for cancers, neurodegenerative diseases, and trauma. These imaging modalities are also used routinely in the hospital to aid in the prevention, detection and treatment of disease and injury. The techniques offer assessments of tumor volumes, early indications of tissue

pathology associated with trauma and response to surgical or pharmaceutical intervention. Medical imaging also offers the capabilities to evaluate the early stages and longitudinal progression of disease through functional imaging techniques such as positron emission tomography (PET) (1). The ability to identify injured regions of interest through imagery provides essential indicators for intervention planning of trauma.

Assessment of burn generally doesn't take advantage of these techniques. Burn assessment is typically accomplished via visual inspection to predict wound depth. The accuracy of visual assessments for predicting wound depth ranges between 60 and 80%. Tissue perfusion is intricately related to burn depth and a number of tools including dyes, thermal imaging and laser doppler imaging (LDI) can capture this information. All of these techniques are under study to investigate burn depth. Other methods such as optical measurement and ultrasound are also under investigation and show promise (2). While LDI is widely appreciated for its ability to predict wound depth, it is far from widespread acceptance (3). Diverse patient populations have not been studied. Additionally, the roles of critical parameters such as room temperature, patient positioning and respiratory rate remain under-investigated. Other techniques such as active dynamic infrared thermal imaging (ADT) and near infrared spectroscopy (NIRS) also show promise, but suffer from similar challenges as related to LDI. Much of this work also does not account for the multilayered and diverse structure of human skin, which is primarily divided into the dermis and epidermis, with epidermal substructures.

This topic seeks out methods which can non-invasively and accurately detect and diagnose burn depth. Methodologies must ultimately demonstrate ease of use, be robust and require little to no reagents. Proposed methods should describe the phenomenological nature of their measurements and how they will account for the heterogeneous structure of the skin in terms of proposed measurement. Additional discussion should outline controls for variables such as burn temperature, evaporation at the wound site and patient positioning. A strong knowledge of burn imaging should be presented as part of the proposal.

Methods suitable for this topic are envisioned to include, but are not limited to, optical imaging and ultrasound. Advances in existing methods, such as LDI, are also encouraged.

PHASE I: Phase I of this request for proposals is intended to take advantage of an already existing concept or prototype. This phase shall define and determine basic performance characteristics of the instrumentation with respect to native tissue. As part of this basic performance assessment, variables such as probe positioning, skin temperature and room temperature shall be evaluated. The minimal performance metric here will be whether or not the probe can accurately discern between the dermis and epidermis. The work shall not be done with burn. The proposed research shall describe how these performance variables will be assayed with their model and shall suggest a more comprehensive list based on the literature for their respective techniques.

PHASE II: This phase is intended to refine system performance. In vivo models of burn must be used to assess the accuracy of this tool to predict burn depth. Studies of full thickness and partial thickness wounds shall be conducted. It is anticipated that a burn expert will be recruited as part of the team of engineers developing this concept. The modeling from phase I is expected to benefit these studies. Comparison with histology and visual assessment by burn experts is required as part of this proposal. This work would be conducted in conjunction with efforts to boost portability and reduce size of the working prototype. This phase shall culminate in FDA approval of the device ahead of large-scale clinical trials.

PHASE III: Burn injuries occur on both battlefield and domestic settings. Approximately 2.4 million burn injuries are reported within the US each year (4). Accurate burn depth assessment is required in order for the surgeon to determine how much tissue to resect in a great many of these cases. Outcomes from Phases I and II of this request would be put to use in a large-scale clinical trial of the emerging technology. A diverse patient population must be considered as part of this study. The endpoint of this work would show that the prototype device can objectively and accurately predict wound depth. Integration of debridement technologies at this phase shall be considered.

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KEYWORDS: Burn Assessment, Burn Depth, Imaging, Non-invasive measurement, Infrared, Optical, Ultrasound

OSD11-H04 TITLE: Enhancing the User's Experience in an Amputee Virtual Environment Support Space

TECHNOLOGY AREAS: Biomedical, Electronics

OBJECTIVE: In a Phase II FY10 Advanced Army Medical Technology Initiative (AAMTI) effort, "Amputee Virtual Environment Support Space (AVESS)," a virtual world environment is being created on the Second Life Enterprise ® platform to allow for remote peer support group environment. We seek to enhance this virtual world experience by adding features to further engage users in the environment.

DESCRIPTION: Overall, we are looking to enhance the user experience in AVESS by improving upon the following areas:

• Non-Verbal communication - Currently, the AVESS environment will support both textual and verbal real-time communication. While this is extremely beneficial to the amputee population in allowing for peer support, the environment is missing the key components of real-time body language, gestures, and facial expressions. By adding actual, real-time, non-verbal communication to the synchronous communication, users could feel more immersed in the environment.

• Immersion into the Environment - The AVESS environment allows for users to interact with their peers through virtual representations of themselves, or avatars. The avatars are driven by the user with mouse and keyboard, which makes it seem more game-like than an immersive and useful tool for interaction. Therefore, we are seeking to allow the user to feel more immersed into the virtual environment than is currently supported.

• Physical Therapist Support - While the current goal is to improve patient outcomes and quality of life by providing remote peer support, it is missing the important component of provider and patient interaction. Specifically, we would like to allow the physical therapists to engage with their patient in AVESS. For example, if a patient is completing physical therapy exercises, it would be useful for the PT to demonstrate, modify, collect data on, and watch the patient complete, these PT exercises. The exercises could also be enhanced by allowing for haptic input and output while completing resistance-based activities. This support, if proved effective, could also be a reimbursable expense for healthcare.

All of these technologies could potentially improve patient quality of care and access to care. By allowing the amputee patients to interact and boost their self-efficacy through education about their injuries, the length of time needed for both physical and psychological care could be decreased and, in turn, save time and money. Likewise, all of these technologies would be commercializable as add on modules for Second Life and similar virtual environments.

The war in Iraq is the largest and longest sustained combat operation by the U.S. military since the Vietnam War. It is estimated that nearly two million U.S. military personnel have been deployed for Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF) (Peterson et al., 2008). Dr. Chuck Scoville (COL ret.), Director of the Armed Forces Amputee Patient Care Program, stated that 937 war fighters have suffered an amputation as a result of a battle injury as of November 2009. As warfighters return from OEF/OIF with a traumatic amputation and often concomitant injuries such as Traumatic Brain Injury (TBI) and Post Traumatic Stress Disorder (PTSD), they face

long term care and recovery. Throughout the recovery process, peer support has been noted as a significant factor in improving outcomes in quality of life post injury (Richie et al. 2004). A recent study by Brenner et al. (2009) found that social support was one of the most significant "protective factors" against suicidality in returning veterans with TBI, which is often a co morbidity of traumatic amputations.

While peer support might be readily available immediately post injury at the Military Treatment Facilities (MTFs) such as Walter Reed Army Medical Center or Brooke Army Medical Center, many veterans will move back home to a location that is not within reasonable distance to one of these MTFs and will likely be isolated from their peers with similar injuries and life experiences. A report from the Veterans Affairs Office of Policy and Planning found that as of August 2009, many OEF/OIF veterans were located within significant distance from the MTFs and military bases. Therefore, a virtual world environment support group would allow these veterans with traumatic amputations to remain engaged with their peers and not become isolated.

Through their avatar in the virtual world, a sense of personal space is created by the virtual representations of themselves. Virtual World environments such as Second Life are a social space, and it is that platform's success in meeting the need of people to come together that has driven its success and popularity. "Despite the relative immaturity of the technology, virtual worlds are clearly compelling to a large and growing number of visitors. At any given moment, more than 50,000 people from countries across the globe are actively engaged in Second Life, and that number is growing steadily (Johnson 2008)". Virtual Reality Environments can provide a sense of togetherness — that sense of being in the same place doing the same things, coupled with people's increasing desire to gather with friends via the network is why virtual worlds matter.

While the AVESS environment is being explored in a FY10 Phase II AAMTI-funded effort, the improvements being proposed in this SBIR effort would allow the amputee veterans to be more fully immersed in the AVESS environment and would allow them to feel more engaged in the AVESS. The improvements could allow a greater feeling of presence among the avatars than there might be in a disembodied chat room or even utilizing the current Second Life platform (Gorini et al. 2008). This would also make it easier to facilitate the clinical communication process, positively influence group processes, and provide cohesiveness in group based therapies. Amputees could participate in live lectures to learn new rehabilitation techniques, learn about new prostheses, or for other educational purposes. In terms of physical therapy, rather than seeing or watching the techniques or new prostheses in action, they would be completely immersed in the environment for an overall sense of "being there" which is the ultimate goal of virtual reality technology.

PHASE I: During Phase I, the following objectives must be met:
• Identify the appropriate technology to improve communications in world.
• Identify the appropriate technology to allow for a more immersive experience.
• Identify the appropriate technology to allow for Physical Therapist and Patient interaction in world.
• Determine the technical feasibility of the proposed technology.
• Develop an initial concept design and model key elements.
• This Phase will demonstrate the feasibility of producing a demonstration of the proposed technology within the Second Life environment and will outline demonstration success criteria.

PHASE II: During Phase II, the following objectives must be met:
• Based on Phase I modeling, design and develop a prototype(s).
• Demonstrate the prototype(s) in accordance with the demo success criteria developed in Phase I.
• Validate the immersive technology.
• Provide a plan for practical deployment of the proposed technology.

PHASE III: Move the prototype from the laboratory into production and the marketplace. Develop, provide and execute a training program that will support the proliferation of the new devices to all appropriate patients. Provided the immersive technology meets phase I and phase II requirements, it may be applied to the current AVESS environment and utilized for remote peer support groups for military amputee patients, as well as remote physical therapy, as applicable.

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KEYWORDS: Amputee, Virtual World, Virtual Reality, Peer Support, Support Group, Physical Therapy