REPORT FROM THE COMMITTEE TO REDEFINE THE SPECIALIZED CENTERS OF RESEARCH PROGRAMS

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BACKGROUND

Specialized Centers of Research (SCOR) programs were initiated by the NHLBI in 1971 in high-priority areas to encourage research to translate basic science findings to the clinic. SCORs require both basic and clinical research projects focused on diseases and clinical problems relevant to the mission of the Institute. The interactions between the basic and clinical projects are intended to enhance transfer of fundamental research findings to the clinical setting and to help focus fundamental research investigations on issues of major clinical importance. The Institute currently supports the following SCOR programs:

- Acute Lung Injury
- Airway Biology and Pathogenesis of Cystic Fibrosis
- Cellular and Molecular Mechanisms of Asthma
- Hematopoietic Stem Cell Biology
- Hemostatic and Thrombotic Diseases
- Ischemic Heart Disease in Blacks
- Molecular Genetics of Hypertension
- Molecular Medicine and Atherosclerosis
- Neurobiology of Sleep and Sleep Apnea
- Pathobiology of Fibrotic Lung Disease
- Pathobiology of Lung Development
- Pediatric Cardiovascular Disease
- Ischemic Heart Disease, Heart Failure, and Sudden Cardiac Death
- Transfusion Biology and Medicine

In 1993, based on a recommendation from the National Heart, Lung, and Blood Advisory Council, the Institute established a process of inviting extramural experts to conduct a formal evaluation of each SCOR program early in its second funding period to advise the Institute on continued relevance and future directions. Unless a continued need is identified, a sunset provision limits a SCOR program to 10 years of continuous funding. For both of the recently reviewed programs, the Acute Lung Injury SCOR (October 2000) and the Pediatric Cardiovascular Disease SCOR (January 2001), the reviewers noted their excellent scientific productivity, but commented that direct contributions to clinical care were not clear, and that there was little evidence of productive collaborations between basic and clinical investigators as indicated by the paucity of joint publications or other evidence of collaboration.

These comments have raised concerns that the SCOR mechanism may not be fulfilling its intended translational research function, and thus may not be distinguishable in practice from the Program Project Grant mechanism. In response to these findings, an NHLBI extramural staff SCOR Reinvention Committee was convened by the Director, NHLBI, and charged with reviewing the SCOR mechanism, discussing its strengths and weaknesses, and developing recommendations to enhance the clinical focus and utility in SCOR programs. This report reflects the results of that Committee's efforts.

NEED FOR SCOR PROGRAM

The Committee began its deliberations by addressing the fundamental question of whether to recommend that the SCOR program be continued in any format. The Committee considered several viewpoints, but It was agreed unanimously that the SCOR program offers a unique

mechanism for producing collaboration between basic and clinical researchers that would otherwise be unlikely to occur. Furthermore, the SCOR program provides an excellent tool to further the Institute's goals of translating bench findings to the bedside. The SCOR mechanism provides for teams of researchers to take an interactive multidisciplinary approach to basic and clinical aspects of a disease or condition. In addition, the SCOR program provides a natural venue for broad training of investigators to think in terms of both basic and clinical research aspects of clinically-relevant problems.

COMPONENTS OF A SCOR

There was clear consensus that, for progress to continue in translating laboratory findings to the bedside, SCOR applications should propose hypothesis-driven research focused on questions relevant to the clinical condition(s) under study. The analytic tools and scientific acumen have now reached a sufficient critical mass to forge ahead with research programs capable of linking molecular genetic discoveries to their implications for pediatric and adult public health. The next generation of SCORs should begin to answer, among other questions, what proportion of a given disease is due to mutations in a particular gene, and how genotype affects therapeutic outcome. The Committee members agreed that, in the past, the clinical questions posed in the SCOR have not been as well-developed as the basic science research. For the next iteration of the SCOR mechanism, clinically relevant questions should provide the central theme. It was recognized, however, that in order to answer these questions, SCOR researchers will need to draw on molecular, animal, and clinical research in varying proportions depending on the specific hypotheses under consideration.

A general approach to more clinically oriented research in the SCOR mechanism is as follows. A SCOR should consist of well-integrated basic and clinical projects that are all related to a common theme and test hypotheses of clinical relevance to the mission of the NHLBI. The pertinent research questions should emanate from clinical needs and issues that lend themselves to physiological, biochemical, pharmacological, immunological, and genetic analyses, using *in vivo* as well as molecular and cellular approaches. Understanding well-characterized animal models permits genotype-phenotype studies in humans. Information gained in clinical inquiries in turn will provide leads for hypothesis-driven experiments of keen clinical relevance in animal models. Success of therapy may vary by genotype, which can be further investigated in both animal and clinical models.

To reflect this increased clinical emphasis, the Committee recommends a new title: Specialized Centers of Clinically Oriented Research (SCCOR). The acronym is rooted in the original program, but with an additional "C" to emphasize the centrality of clinical research.

Definition of Clinically Oriented Research

After agreeing that the SCOR mechanism should be retained with a new title and modified format, the next issue with which the Committee grappled was how to define patient-oriented research in the new **SCCOR** mechanism. The NIH Director's Panel on Clinical Research adopted the following definition of clinical research in 1995: patient-oriented research is research conducted with human subjects (or on material of human origin such as tissues, specimens, and cognitive phenomena) for which investigators interact directly with human subjects. This area of research includes: development of new technologies, mechanisms of human disease, therapeutic interventions, and clinical trials. This definition has been adopted

for use in grant mechanisms including the Mentored Patient-Oriented Research Career Development Award (K23). The Programs of Excellence in Gene Therapy (PEGTs) adopted another definition of clinically oriented research, which is simply a Phase I or Phase II clinical trial. (Phase III trials are clearly clinical research, but are not included as part of the PEGTs.)

Based on these examples, and its own discussions, the Committee recommends the following definition of clinically oriented research for the new NHLBI **SCCOR** Programs:

> **Clinically oriented research is defined as research conducted with human subjects with whom the investigator has interacted directly. Clinical investigations can include studies of subjects with the disease of interest as well as normal healthy subjects.**

It is expected that the requirement for investigator interaction with the study participants will eliminate research involving archived tissue, but there may be very rare circumstances where this would be acceptable. In addition, it is not the intention of the **SCCOR** Program that Phase III trials would be performed. However, results from **SCCOR** research may very well provide the basis of subsequent Phase III clinical trials.

Examples of clinically oriented research that can bridge basic science knowledge to the practice of medicine include but are not limited to:

- Phase I/II trials of novel therapeutic interventions
- mechanisms underlying the etiology and pathophysiology of human disease
- identification of biomarkers of disease
- study of assay systems for diagnostic or therapeutic purposes
- use of devices for screening or therapeutic purposes
- genetic variability influencing outcome of therapy
- genetic variability and its role in the cause and progression of disease

Clinically oriented research projects, whether on human subjects or human specimens, will be subject to the standard NHLBI policies and procedures regarding human subjects monitoring.

Requirements for Clinical Projects

Although each SCOR award is currently required to have at least one clinical project, in general those projects have not been as well-developed as the basic science research. In order to redefine the new **SCCOR** mechanism as more clinically relevant, and to distinguish it further from program projects, the Committee recommends changing the balance between basic science and clinical science. Therefore, in addition to strengthening the definition of clinically oriented research, the Committee has the following recommendations for the clinical projects in a **SCCOR** program.

Recommendations:

1. Each awarded NHLBI **SCCOR** must consist of three or more projects, all of which are directly related to the **SCCOR** program topic.

2. The number of clinical projects in each awarded NHLBI **SCCOR** must be greater than or equal to the number of basic science projects, both at the time of award, as well as throughout the non-competing grant period. A core will not be counted as one of the clinical projects. One or more of the clinical projects can be proposed as a collaborative project among the other **SCCOR** awards in a particular **SCCOR** program, but this will not be required. Commitment to such collaboration must be clearly demonstrated.

3. **SCCOR** applicants should provide a detailed data and safety monitoring plan for the clinical research proposed, which will be considered as part of the peer review of the application. This plan should address informed consent, recruitment, reporting of adverse events, oversight of clinical issues in the protocols, storage and analysis of confidential data, and dissemination of any research results. There may be isolated cases when the Institute may wish to convene a DSMB to oversee the clinical projects in a **SCCOR** program.

Centralized Resources and Shared Services

Bench to bedside translation requires not only expanded clinical research, but also investment in dedicated resources to achieve this goal. One example is the need for large databases encompassing clinical and genetic information on affected patients and their families, structured to permit access by researchers in other institutions. Other types of dedicated resources include tissue repositories, additional animal models of human disease, sophisticated imaging centers for detailed characterization of animal models to permit detailed morphological and physiological assessment, genomic and proteomic centers, and multi-site recruitment of patients under a common protocol.

One approach discussed by the Committee would be to have administrative, basic, or clinical cores that would serve all sites within a **SCCOR** program, such as a mouse phenotyping facility that would serve all investigators in the entire Pediatric Cardiovascular Disease **SCCOR** Program. However, this would require a common approach in projects within a **SCCOR** program, which may not exist among the applications that are ultimately successful. Most of these dedicated resources are the type of undertaking typically found in the core projects of individual **SCCORs**. It is reasonable for the Institute to expect that certain resources that are shared across projects in an individual **SCCOR** award may also be shared between awards within a **SCCOR** program whenever feasible.

One such area where a core that serves all sites within a **SCCOR** program may be feasible is a clinical core. Functions of such a clinical core could include development and maintenance of infrastructure for clinical research, such as a patient database, blood and specimen repositories for applicable clinical projects, administration of data and safety monitoring plans, and skills development programs for clinical researchers (see discussion in section on Skills Development).

Another way to foster translational research is to link the **SCCOR** programs with existing programs, such as General Clinical Research Centers (GCRCs) funded by the National Center for Research Resources (NCRR), NHLBI Clinical Research Networks, the Programs for Genomic Applications, the NHLBI Proteomics Initiative, and the Programs of Excellence in Gene Therapy, in order to improve scientific efficiency and realize economies of scale. For example, the Programs of Excellence in Gene Therapy, through their National Cores, offer

preclinical and clinical vector production (adenoviral and retroviral vectors), cell morphology analysis, and hematopoietic stem cell processing at no cost to NHLBI-supported investigators. In addition, relatively large populations of well-characterized patients are recruited for various protocols within the NHLBI Clinical Research Networks. **SCCOR** researchers (as well as other extramural investigators) could benefit from having access to DNA and other biological specimens from these patients, and translational research could be facilitated by identifying, for example, prognosis for patients with similar diseases caused by different known genetic mutations.

Recommendations:

1. Administrative and scientific cores should remain part of the **SCCOR** program. The RFA should stipulate that the resources represented by cores and any materials developed in them (e.g., biological specimens) are expected to be shared widely within the **SCCOR** program. Outside requests for specimens, data, and other materials should be reviewed and prioritized by a committee of **SCCOR** investigators or by an External Scientific Panel composed of extramural scientists.

2. One of the things that should be considered for each **SCCOR** program announced is whether a collaborative clinical core would be beneficial to the particular disease area(s) under consideration. If so, the RFA should require that applicants propose a Clinical Core that would serve all of the successful applicants in a given **SCCOR** program. Applicants should outline which activities they propose to be shared and describe how the Clinical Core would function. These Clinical Core proposals should be reviewed as discrete elements of the applications, with separate numerical scores assigned as for the research projects. The Institute would then choose the successful Clinical Core proposal based on this review.

3. Language should be included in the RFAs to encourage **SCCOR** applicants to make use of existing programs, such as GCRCs or NHLBI Clinical Research Networks, as resources for facilitating the proposed clinical research.

REVIEW ISSUES

In order to achieve the goal of increased clinical emphasis and relevance, the Special Emphasis Panels (SEPs) reviewing the **SCCOR** applications must have the appropriate composition and specific directions. With an increased clinical emphasis, successful applicants will have to incorporate strong clinical projects within the overall program, but also will be required to integrate clinical research with the basic science research.

Recommendations:

1. The responsiveness of new **SCCOR** applications should be evaluated rigorously prior to review, particularly in the area of clinically oriented research. Applications that are submitted without the requisite proportion of clinical to basic science projects will be judged to be non-responsive.

2. The Request for Applications should stress the primacy of a clinical focus as the basis for the integration of the basic and clinical research in each **SCCOR** application. The SEPs that review the NHLBI **SCCOR** programs should be instructed that integration of the basic and clinical research has a very high priority and is essential to a successful application.

3. The SEPs should have expertise in clinical research commensurate with that in the basic sciences. Depending on the subject area, this could include expertise in Phase I/II clinical trial design, biostatistics, pharmacology, and ethics. In addition, the SEPs should include clinicians with current experience treating patients in the particular subject area, such as hypertension, congenital heart disease, acute lung injury, blood dyscrasias, or sleep disorders.

4. The SRA should convene a conference call of SEP members and program staff before the review to stress the Institute's emphasis on the increased importance of clinical research in **SCCOR** applications, and to reiterate that the number of clinical projects in each awarded NHLBI **SCCOR** must be greater than or equal to the number of basic science projects.

5. All scientific cores should be evaluated and scored by the SEP using the same numerical criteria used for projects. Only the administrative core would continue to be evaluated on a "pass-fail" basis.

6. In selecting which **SCCOR** applications to fund, a major factor guiding the Institute will be the strength of the clinical projects and their integration with the basic science projects. Applications with weak clinical projects will be unlikely to be funded, regardless of the overall priority score. Standard criteria such as program balance and available funds, also will be factored into the decision. This approach, which should be well-publicized prior to review, may mean that **SCCOR** applications will not be funded strictly in order of priority score.

SKILLS DEVELOPMENT

One of the strengths of the **SCCOR** mechanism is the rich opportunity it affords for interdisciplinary career skills development. The Committee is strongly in favor of incorporating a Skills Development component in **SCCOR** programs, both to train clinical scientists and to provide cross-disciplinary training for both basic and clinical scientists. The Institute currently is examining strategies to incorporate skills development in multi-component grant mechanisms, such as Program Project Grants and **SCCOR** programs. Results of this deliberation will be reflected in RFA language for individual **SCCORs**.

Recommendations:

1. The principles developed for Skills Development for Program Project Grants would guide the Skill Development activities in the new **SCCOR** mechanism. If needed, additional administrative guidelines would be developed to assist applicants in the preparation of a Skill Development component for a **SCCOR** application.

2. A budget beyond the **SCCOR** budget cap should be allocated to a Clinical Core for skills development. Allowable costs could include salary support for the Core Leader and other investigators and staff, travel costs for new investigators, costs for courses, seminars, workshops and other activities directly related to the Core, and related supplies and equipment. Salary support for the new investigators could be requested in the specific research project within the **SCCOR** where their research will be conducted.

3. Regardless of the format of a Skills Development component, innovative strategies also should be proposed in **SCCOR** applications for cross-disciplinary career development, to achieve the goal of having basic scientists conversant with clinical issues relevant to their research, and vice versa. Examples include a program of seminars focusing on scientific topics that include an integration of both basic and clinical studies, or an "exchange" program where clinicians spend time in basic science labs, and basic scientists spend time in clinical situations such as rounds.

ADMINISTRATIVE ISSUES

The Committee discussed a number of administrative issues pertaining to the new **SCCOR** program.

Recommendations:

1. The funding period should continue to be five years. Extending the length to seven years was discussed, but the consensus was that seven years was too long between peer reviews, especially given that the program will be reconfigured.

2. Current sunset provisions should be retained, accompanied by review by an outside Evaluation Committee mid-way through the second funding period.

3. The budget cap for individual **SCCOR** awards should be increased, possibly beyond the level of the P01 cap, to accommodate the increased expense associated with the increased amount of clinical research now required. It is recognized that this recommendation is likely to result in a decreased number of centers; the Committee believed that this trade-off was worth making in order to achieve the goals of the new **SCCOR** mechanism.

4. The provision that at least 50% of the components of a **SCCOR** award should be at one institution should be retained. In addition, one of the clinical projects must be at the primary **SCCOR** institution.

5. Site visits should be considered, primarily for the clinical projects.

SUMMARY

The goal of the proposed changes in the NHLBI **SCCOR** mechanism is to refocus the research toward clinical questions. The principal changes proposed are to incorporate a rigorous definition of clinical research, require an increased proportion of clinical projects, encourage

coordination of clinical research with other **SCCOR** centers as well as with existing clinical research resources, and provide the option of adding a skills development component focusing on cross-disciplinary training as well as specific skills development for clinical scientists. A corollary of these changes is that review criteria for the clinical component must be strengthened; that careful attention must be paid to the composition of the SEPs for the SCORs; that strong, integrated clinical projects will be required for funding; and that the priority score will not be the sole determinant of funding. Finally, consideration should be given to increasing the **SCCOR** budget cap to accommodate the increased proportion of clinical research.