Cardiac Safety Research Consortium
Governance Structure

13 May 2010

I. Scientific Rationale

Safety is a critical component of medical product[1] development and approval. In particular, cardiac safety has received intense focus with several high profile issues including market withdrawals. This has stimulated debate over the best way in which to measure efficacy while ensuring the protection of the public health. At the center of this debate is the balance between efficacy and safety. Importantly, rapid advances in therapeutic medical product development have yet to reach full potential, in part due to limits in our ability to understand and quantitate therapeutic balance.

Unfortunately the evaluative sciences surrounding medical product approval have not kept pace with our fundamental understanding of disease. Societal investment in research and development to improve the approval process has been lacking in contrast to the large investment, both private and public, in basic research and specific product advances. In order to improve the ability of regulatory agencies to promote and protect the public health there needs to be a fundamental investment in the evaluative sciences. Specifically, the scientific basis of our understanding of medical product safety needs to be enhanced and integrated with refined measurements of efficacy. An investment in the evaluative sciences will provide more precise scientifically-based information enabling health care professionals and patients to appropriately assess risk and benefits.

The *Critical Path Initiative* has been developed by the FDA to address many of these issues by establishing greater collaboration between regulators, academics, physicians, and scientists from industry. The spirit of this collaboration is intended to create opportunities by sharing existing knowledge and data that will facilitate the process of enhancing, refining, and ultimately improving the process used to evaluate new medical products. A central tenet to *Critical Path* is a focus on the evaluative science of the approval process, including both efficacy and safety measures.

The Cardiac Safety Research Consortium (CSRC) is a first step in bringing together key constituencies to focus on cardiac safety issues during the new medical product development process. By utilizing the principals of the *Critical Path Initiative*, the CSRC will focus on improving the evaluative sciences specifically in relation to cardiac safety.

[1] Medical Product = drugs, biologics, devices, and combination products

II. Mission Statement

To advance scientific knowledge on cardiac safety for new and existing medical products by building a collaborative environment based upon the principles of the FDA's *Critical Path Initiative* as well as other public health priorities.

III. Areas of Focus in Cardiac Safety

This consortium will address cardiac safety in cardiovascular and non-cardiovascular medical products. While the initial focus will be on the proarrhythmic risk of products, the intent of this public-private partnership is to cultivate collaborations facilitating the development of clinical research strategies, evaluative tools, standards, validated tests and cardiovascular biomarkers related to broader aspects of cardiac safety including, but not limited to arrhythmia, thrombosis, myocardial infarction, and heart failure.

IV. Key Objectives

1. To facilitate focused pragmatic research that will inform regulatory processes with regard to cardiac safety
2. To develop expert consensus around common nomenclature, standards, and key definitions, and to draft white papers in challenging areas, describing what is known, unknown, and proposing paths forward to address such knowledge gaps
3. To develop knowledge and strategies intended to improve the evaluative sciences in relation to cardiac safety and product development
4. To coordinate "think tanks" and other programs and public forums for open discussion and updates on topics in cardiovascular safety pertaining to drug and device development
5. To establish infrastructure and operational processes with the following components:
    - Transparent processes that promote dialogue
    - Assure input from all primary stakeholders (e.g. FDA, industry, academics, NIH)
    - Involve all Consortium contributors (those private partners that contribute annually to fund the overarching Consortium activities) in the decision-making and project development process
    - Leverage resources and expertise from multiple public and private partners
    - Create an open and efficient mechanism for submitting potential projects and their objective evaluation
    - Facilitate and, where appropriate, orchestrate mechanisms for the continuance of ongoing cardiac safety research programs
    - Involve broader public or patient groups in the process as appropriate
    - Encourage cross-sector interaction and problem solving

- Leverage previously conducted and ongoing clinical studies, research infrastructure and databases
- Preserve proprietary interests

V. Governance Structure

Consortium Membership

The CSRC will be organized into a number of committees drawn from members of the CSRC and the FDA. CSRC membership will include representatives from the major stakeholders including, but not limited to, academia, the pharmaceutical industry, biologics industry, device industry, professional societies, trade organizations, contract research organizations, core laboratory organizations, patient advocate groups, and interested regulatory agencies. These major stakeholders will not be limited to United States representation, but may include participation from international groups.

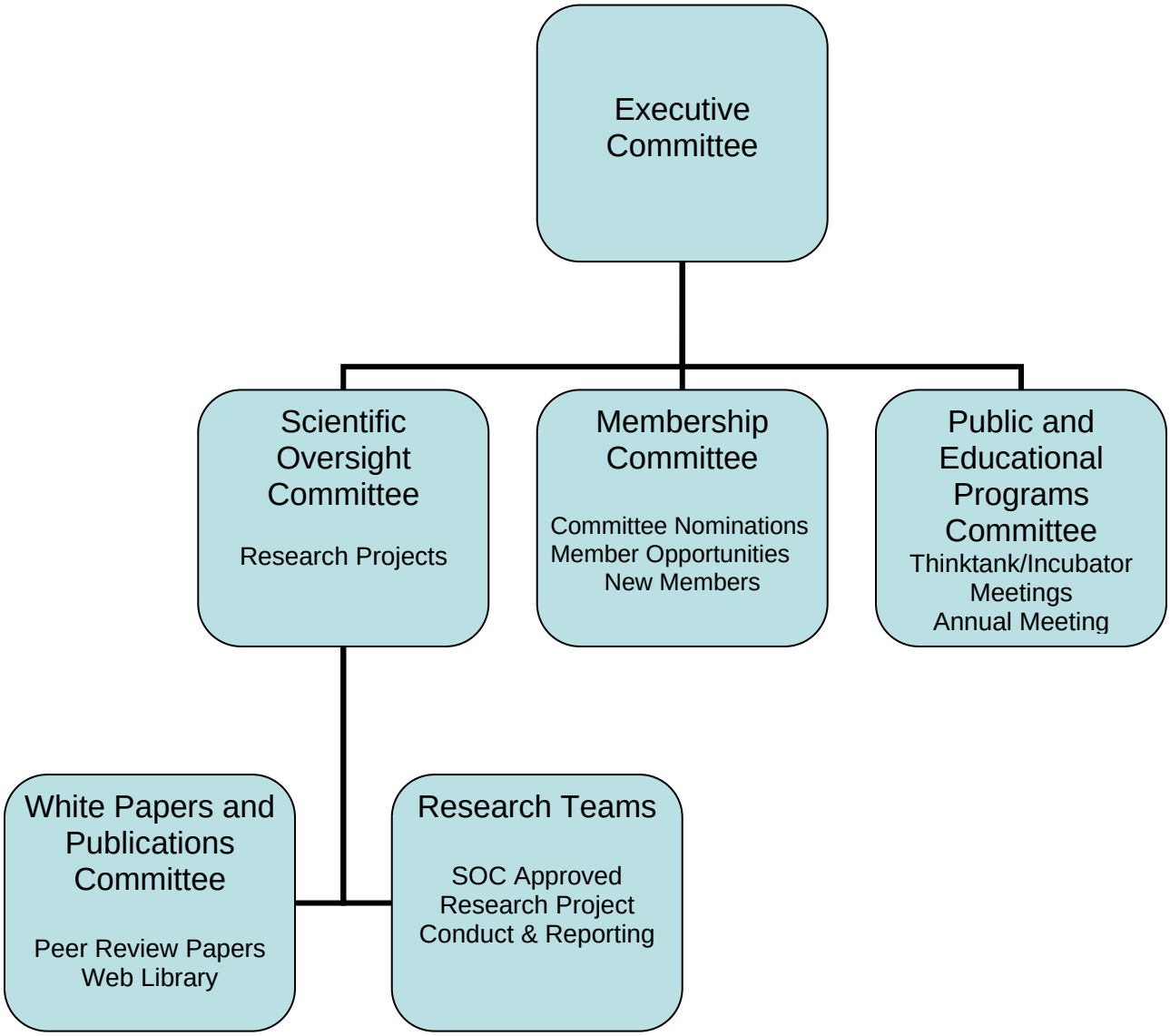
The CSRC seeks broad participation in its activities through the participation of its members in the mission and activities of the organization. Criteria for membership require meaningful contribution although the specifics of the contribution of each member will vary, as detailed in the CSRC Membership Charter. Members from private industry are expected to make some financial contribution, as also described in the Membership Charter. All members are expected to make contributions-in-kind including data, technology, organizational and operational manpower, or other resources. CSRC members are eligible to participate in the different committees of the CSRC as described below.

Representation from the FDA

The participation of the FDA will be guided by the Memorandum of Understanding executed between the FDA and the DCRI (September, 2006). The FDA will appoint Federal liaisons to the Executive Committee of the CSRC and, as needed, to the other Committees, Advisory Boards and Research Teams. Such Federal liaisons will not have any fiduciary roles in the CSRC and will be non-voting (see Appendix A for roles and responsibilities of FDA representatives).

Members of other Federal agencies (NIH, CMS, CDC etc.), as well as members of interested regulatory agencies from outside of the United States, are welcome to participate as members of the CSRC.

Figure 1: Committee Structure



Committee Structure and Governance (Figure 1)

Executive Committee

The Executive Committee will primarily maintain the CSRC organization in concert with its Charter mission. The Executive Committee will provide oversight of all CSRC Committee activities, based primarily through review of each Committee's recommendations to the Executive group. The Executive Committee will retain final decision making responsibility for all CSRC activities and processes. The Executive Committee will also retain final responsibility for providing all in-kind and fiscal resources, or strategies and support for obtaining such resources, needed to facilitate each Committee's activities on behalf of the CSRC.

Composition

- The Executive Committee will consist of a total of 11 voting members (including the two co-chairs) at least 5-8 representatives from Pharmaceutical/Biologics, Device or other related industry and 3-6 from academia.
- Co-Chairperson will consist of one member from academia and one member from industry
- FDA will sustain at least 3-9 Advisors to the Executive Committee, including 1-3 from each of the Center for Drugs, Center for Devices, and Office of the Commissioner
- The Executive Committee may change its size or composition as needed beyond the above through formal modification of this Governance Charter
- Open voting seats on the Executive Committee will be filled through an ad hoc nominations committee coordinated by the Membership Committee chair
- Open Advisory seats from FDA will be filled by FDA selection
- The Executive Committee may invite experts and advisors to Committee meetings as needed

Responsibilities

- Ensure that all activities are commensurate with the CSRC Mission through oversight of all committee activities
- Ensure development of operational infrastructure in order to orchestrate and facilitate CSRC activities and committees
- Form ad hoc advisory groups or committees as needed

Eligibility and Expectations for Participation

- Must be a Founding or Sustaining Member (as defined in the Membership Charter)
- Regular (>50%) participation in conference calls (anticipate 2 hours / month)
- Attend at least 1 face-to-face meeting of Executive Committee each year
- If Executive Committee member can not fulfill these expectations then the member may be asked to step down by consensus of the co-chairs

Scientific Oversight Committee (SOC)

The SOC will provide the primary intellectual repository for the solicitation, review, and ongoing oversight of all CSRC scientific projects and programs, and will make recommendations on all such directly to the Executive Committee. To execute this mission, the SOC will develop and facilitate Research Teams specifically dedicated to each of the approved research programs.

Composition

- Chair: Must be a full member of CSRC with at least 1 year prior membership
- Co-chair: May be Advisory or Associate Member in select cases
- Committee size not to exceed 11 voting members (not including non-voting Advisors)

- Membership to include at least one academic, one member from industry, and one member from Regulatory
- Membership to include at least one representative from each Research Team
- Membership to include at least the Chair of the White Papers Committee

Responsibilities

- Solicit and review scientific project proposals
- Recommend project proposals to the Executive Committee for final approval
- Form and manage Research Teams specific to implementation of approved projects
- Provide ongoing oversight and facilitation of Research Team activities, timelines and deliverables
- Support and facilitate leadership and activities of the White Paper Writing Committee
- Liaise with other CSRC Committees as needed to coordinate related efforts

Eligibility and Expectations for Participation

- Meetings as required primarily by teleconference, face-to-face if needed
- Regular (>50%) participation in conference calls (anticipate 2 hours / month)
- If SOC Committee member can not fulfill these expectations then the member will be asked to step down based on consensus by the co-chairs
- Research Team leaders will be full members with at least 6 months membership in CSRC. Research Team composition will be determined on a specific project-related basis by the SOC.
- All specific Research Teams executing programs that involve CSRC resources or CSRC funding mechanisms will include CSRC Project Leader from DCRI.

White Papers and Publications Committee

The White Papers and Publications Committee will organize and provide logistical support for all CSRC sponsored publications. Although this committee is separate from other committees, it is intended to work in an integrated fashion to ensure that appropriate topics are raised to the SOC for consideration from the various CSRC groups. This group functions as an oversight committee to review proposals for white papers or similar publications in which the CSRC is involved. Specifically, the committee focuses on topics which either emerge from or would likely catalyze other sustained efforts such as research projects or public meetings and programs. The White Papers and Publications Committee then assists in forming specific writing and reviewer groups as needed to provide direction, guidance, administrative support, communications, and involvement with other facets of the CSRC. Membership of this committee will consist of industry, academia, regulators and patient advocacy groups. The White Papers and Publications Committee will report through the SOC.

Composition

- Chair: Must be a full member of CSRC with at least 1 year prior membership
- Co-chair: May be Advisory or Associate Member in select cases

- Membership to include at least one academic, one member from industry, and one member from Regulatory
- Members of the actual White Paper writing group should all be members of the CSRC. However, if there are circumstances whereby expertise for a publication is needed and the person is not a member of the CSRC the issue may be brought to the Scientific Oversight Committee for review.

Responsibilities

- To develop writing and reviewer groups which will draft white papers in challenging areas, describing what is known, unknown, and proposing paths forward to address such knowledge gaps

Eligibility and Expectations for Participation

- Regular (>50%) participation in conference calls (anticipate 2 hours / month)
- If committee member cannot fulfill these expectations then the member will be asked to step down by the chair(s)

Membership Committee

The Membership Committee will be the primary center of activity to sustain the vitality of the CSRC through recruiting new members and through ensuring that members have opportunities to participate and contribute to the CSRC organization at every level. The Membership Committee will also serve as the organizational center for determination of membership status of new applicants (according to stipulations of the Membership Charter). The Membership Committee will also provide means for replacement of Committee leadership positions through the formation of ad hoc nominations processes when needed.

Composition

- Chair: Must be a full member of CSRC with at least 1 year prior membership
- Co-chair: May be Advisory or Associate Member in selected cases
- Committee size not to exceed 11 voting members (not including non-voting Advisors)
- Membership to include at least one academic, one member from industry, and one member from Regulatory

Responsibilities

- Develop and maintain CSRC informational materials for potential new members
- Solicit, provide support and outreach for potential members
- Evaluate (approve/reject) applications for CSRC membership
- Determine level of membership (Founding/Sustaining/Principal/Associate)
- Provide information on and facilitate new members opportunities within the CSRC
- Liaise with other CSRC Committees as needed to coordinate related efforts
- Develop annual evaluation of membership status for all members

Eligibility and Expectations for Participation

- Regular (>50%) participation in conference calls (anticipate 2 hours / month)
- If SOC committee member can not fulfill these expectations then the member will be asked to step down by the chair(s)

Meeting Planning and Public Forums Committee

The Public Meeting Committee will organize and provide logistical support for all CSRC sponsored public meetings. Although this committee is separate from the SOC and other committees, it works in an integrated fashion to ensure that appropriate topics are raised to the Executive Committee for consideration from the various CSRC groups. This group functions as an oversight committee to review proposals for annual meetings, think tanks, or other public forums in which the CSRC is involved. Specifically, the committee focuses on meetings which would likely catalyze other sustained efforts such as white papers and research projects. The oversight committee then assists in forming specific working groups as needed to provide direction, guidance, administrative support, communications, and involvement with other facets of the CSRC. Membership of this committee will consist of industry, academia, regulators and patient advocacy groups.

Composition

- Chair: Must be a full member of CSRC with at least 1 year prior membership
- Co-chair: May be Advisory or Associate Member in selected cases
- Committee size not to exceed 11 voting members (not including non-voting Advisors)
- Membership to include at least one academic, one member from industry, and one member from Regulatory
- All program planning teams will include direct participation of CSRC project leadership from DCRI to ensure appropriate financial planning

Responsibilities

- Identify and prioritize topical themes for thinktank/incubator meetings, in addition to the Annual Meeting
- Ensure the Annual CSRC meeting
- Develop meeting planning teams for each specific meeting
- Provide oversight and facilitate the activities of each specific Meeting Planning Team
- Meeting Planning Teams will be chaired by a full member with at least 6 months membership in CSRC, along with a co-chair who may be an Associate member or Advisor in selected cases
- Composition of specific Meeting Planning Teams will be determined by the Public Programs Committee
- Liaise with other CSRC Committees as needed to coordinate related efforts.

Eligibility and Expectations for Participation

- Regular (>50%) participation in conference calls (anticipate 2 hours / month)
- If committee member cannot fulfill these expectations then the member will be asked to step down by the chair(s)

IV. Antitrust Guidelines

(future Appendix C will contain more detailed language)

The consortium will handle all antitrust issues in compliance with federal standards (Sherman Act 15 U.S.C sect 1 *et seq)*. Specifically, any indication of improper commercial bias or facilitation of collusion (directly or indirectly) associated with the legitimate scope of Consortium activities could expose its members to antitrust risk. Issues may arise that could have antitrust implications which include but are not limited to:

1. Use of Consortium unfairly to promote a particular technology or product or exclude another for commercial reasons
2. Inappropriate sharing of confidential/competitively sensitive information of competing companies including intellectual property, pricing, production or innovative plans

All members of the consortium will need to abide by guidelines based upon federal standards to prevent such risk.

Recommended Antitrust Guidelines

1. Private partners may freely conduct activities that do not infringe on intellectual property of other members or intellectual property generated by the Consortium (see section VIII Intellectual Property, data sharing guidelines)
2. No member shall take or seek action relating to Consortium for purposes of excluding products or technology of competitors from the market or impeding research and development
3. Executive Committee must review/approve all public communication and data sharing activities

Restricted Topics

1. Pricing, pricing policies, market shares, services of private partners
2. Intentions about commercial activities, including advertising, promotion, research and development outside the Consortium, or whether to deal with specific customers (including government programs)
3. Speculation or prediction about commercial activities of private partners in response to business or legislative developments
4. Discussion of any topic of commercial significance to competitors that may involve antitrust compliance

VII. Intellectual Property Guidelines

(future Appendix C will contain more detailed language)

1. Except as authorized or required by law, no participant shall be required, by virtue of their participation in the Consortium, to grant exclusive licenses to any entity
2. Consortium participants, grantees, or contractors will not be forbidden to challenge patents or Intellectual Property of other Consortium participants, grantees or contractors including patents or Intellectual Property arising from the Consortium
3. Clear rules will govern whether, and under what circumstances, participants will be required to disclose the existence of Intellectual Property or patent applications regarding inventions relevant to Consortium activities
4. Any research data, results, or Intellectual Property collected or shared with the Consortium will be covered by written contract with the contributor in conformity with these guidelines

VIII. Data Sharing Guidelines

I. Sharing data from public and private partners is anticipated to expedite the work of the Consortium
II. Confidential scientific data may be shared by Consortium participants, subject to intellectual property, antitrust, data sharing and FDA confidentiality policies and other federal laws
III. Participants should not share data or other confidential information about commercial activities with each other, particularly restricted topics (see antitrust guidelines)
IV. Executive Committee and legal counsel of the participants should be consulted on the appropriateness of:
    a. Data sharing (FDA OCC must approve all activities associated with sponsor-data)
    b. Confidential and commercial information
    c. Subject to foregoing precautions, if unaggregated, confidential, and competitively sensitive information are collected under Consortium activities, such information should never be shared outside the project team and should be destroyed except where subject to federal regulation
V. Any data collection from private participants should include statements that info will be handled in conformity with final guidelines of the Consortium

Funding

Financial operations will be the responsibility of, and managed through Duke in conjunction with the Duke-FDA Memorandum of Understanding to conduct the CSRC Public-Private Partnership.

Funding for CSRC will be derived primarily from membership dues per the Membership Charter. CSRC membership requires annual renewal (based on meeting the requirements and expectations of membership as described above). However, organizations that join the CSRC as Founding Members prior to June 2010 or current Founding Members will have the annual renewal fee waived until 2012.

Thinktank meetings will be run on a responsible "break even" fiscal plan which may involve registration fees. Any residual from thinktank meetings will be directly re-invested into CSRC activities. CSRC thinktank meetings will not provide honoraria or other personal revenue of any kind to participants. The management of participating faculty registration fees or related expenses will be individually managed by the specific program planning team.

Ad hoc efforts to apply for, receive and manage grants may be reasonably considered by the Executive Committee, with input from any and all relevant CSRC Committees.

Appendix A: Roles and Responsibilities for FDA Federal Liaison

The activities of all FDA representatives to the CSRC will abide by Title18 U.S.C, section 208, of the criminal conflict of interest statute, which prohibits federal employees from participating in an official matter that affects the financial interest of an outside organization in which the employee serves as officer, director or trustee. The Office of Government Ethics has opined a federal employee can violate section 208 by participating in an official matter that affects the financial interest of an outside organization in which the federal employee serves as officer, director or trustee, even where the federal employee serves as an official duty activity. Therefore, section 208 prohibits federal employees from serving in their official capacity as officer, director or trustee of an outside organization, unless one of the following options has been satisfied:

- An employee may be assigned as a "Federal Liaison" to the organization, which would not implicate section 208. As a Federal Liaison to the CSRC, the employee would be the DHHS/FDA representative to the organization, and would present and receive information and views on behalf of the Department and FDA; but would not direct the organizations internal operations, or
- An FDA employee may serve in an official capacity if a federal statute expressly authorizes such service with the organization; or
- An FDA employee may serve in an official capacity if the outside organization releases the individual from all fiduciary obligations. In order for such a release to be effective, it would have to be permitted under applicable state law; or
- An FDA employee may serve in an official capacity if the individual obtains a waiver of the conflict of interest statute under section 208 from the appropriate DHHS official (see link for sample waiver); or
- An FDA employee may serve an organization in a purely private capacity, as an outside activity. An employee who engages in an outside activity as officer, director or trustee of an organization would have to recuse himself from any official matter that affects the financial interest of the organization. The employee would have to avoid any appearance of using his public office for private gain, and proper clearance must be obtained on Form HHS-520, "Request for Approval of Outside Activity."

It is recommended that each component determine whether employees in their FDA Center/Office are serving outside organizations in their official capacity as an officer, director or trustee. If it is determined that an employee is serving an outside organization as part of his official duties, action should be taken on one of the options listed above.

Appendix B: SOC Project Clearance Criteria

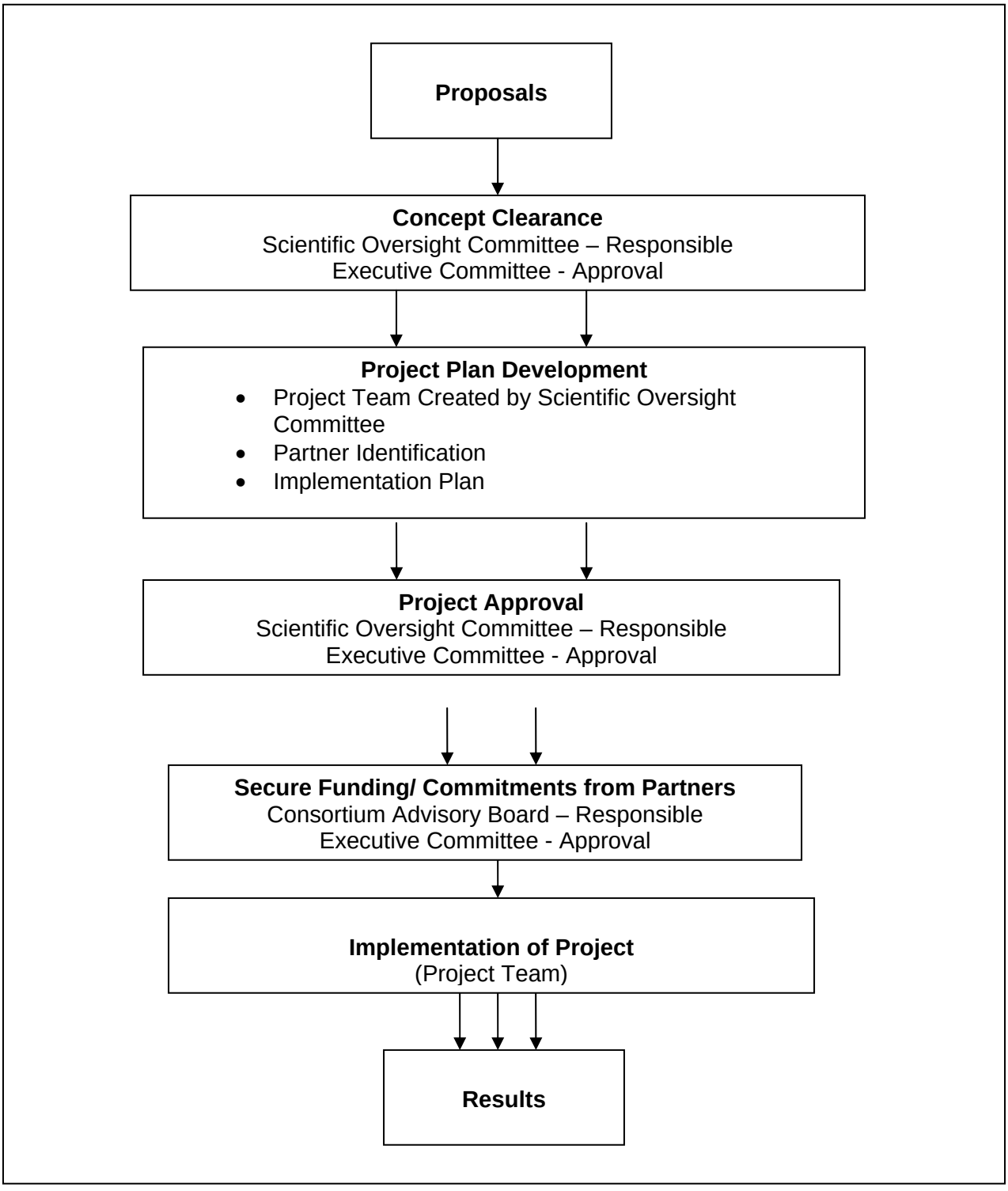
A preliminary list of criteria for the first level clearance of project proposals (prior to project plan development) includes the following:

1. **Collaborative approach:** Are the goal(s) of the project attainable through a partnership within the context of the Consortium?
2. **Scientific importance**: Will the proposed studies/projects promote the understanding of the underlying biology of disease or health?
3. **Clinical importance**: Will proposed studies/projects meet a clinical need for diagnosis; assessment of disease activity, stage, severity, or outcomes; and/or provide useful information in the conduct of clinical trials?
4. What resources are already available to address the problem and does the project offer a **unique** solution(s)? How does the proposed project fill scientific gaps?
5. **Regulatory importance**: Will biomarker development and/or qualification facilitate drug development and/or approval?
6. **Feasibility**: Is the proposed studies/projects feasible operationally, technically and financially? Does the technical platform permit the accomplishment of the study's aims? Is there a potential for development and commercialization beyond research laboratory applications? What evidence is available that the biomarkers identified are likely to be a measure of pathologic disease?
7. Does the project foster and improve opportunities among industry competitors rather than relating specifically to a particular product in the competitive sphere?
8. Do the partners express a **willingness to share data** (if applicable to the project)?
9. Do the partners express a willingness to share the results of their analyses in the public domain?
10. Have Consortium partners agreed to the **rationale and intent of the project**?
11. Are partners available to **conduct and fund the project**?

Please note that every project is not required to meet all of the criteria outlined above; the weighting of the criteria will be determined by the CSRC Executive Committee.

A chart denoting the concept clearance process is attached

Cardiac Safety Research Consortium
Proposed Concept Clearance Process



The Cardiac Safety Research Consortium (CSRC)

Project Concept Submission Form

1. Submission Date		
2. Submitter name, title, email address, and phone number		
3. Name of Submitting Organization		
4. Name(s) of Other Partner Organization(s), If Applicable	Name of Organization	Organizational Contact
5. Title of Project Concept		
6. Scientific Gap/Public Health Need addressed		
7. Technologies addressed (imaging, molecular, genetic, etc.)		
8. Has the concept received any formal review? If so by whom?		
9. What is the estimated budget for the project?		
10. What is the estimated duration of the project?		

NOTE – ALL TABLES WILL EXPAND TO ACCOMMODATE TEXT AS ADDED.

11. In lay language, state the objective of the project and its relevance to patients. *Your answer should be limited to 50 words.*

12. Briefly describe the proposed project, including any preliminary results and evidence concerning feasibility. Provide up to 5 key literature references. *Your answer should be limited to 500 words (one page) not including references*.

13. How would the project benefit from a partnership under the CSRC? *Your answer should be limited to 150 words.*

14. How will this project promote the understanding of the underlying (patho)biology of disease or health, advance public health and further the mission of the CSRC? *Your answer should be limited to 150 words.*

15. What advantages does the project have with respect to other approaches? How does the proposed project fill scientific gaps and public health needs? *Your answer should be limited to 150 words.*

16. How would this project facilitate medical product development and/or regulatory approval? *Your answer should be limited to 150 words.*

17. Is sufficient technology and data available to carry out this project? Please explain. *Your answer should be limited to 150 words.*

18. What are the prospects for development and commercialization of technologies developed in this project? *Your answer should be limited to 150 words.*

19. Is the project linked to a particular commercial product? *Your answer should be limited to 150 words.*

22. Please identify known and potential funding partners (if possible).

22. If a specific investigator or group is proposed to do the work, please provide CVs.