

Introduction to the Breast Cancer Family Registry

The Breast Cancer Family Registry (B-CFR) is an international research infrastructure for investigators interested in conducting population- and clinic-based interdisciplinary studies on the genetic and molecular epidemiology of breast cancer and its behavioral implications. The B-CFR was developed by a multidisciplinary, international team of investigators as a consortium of six field centers and an informatics support center (ISC). The six field centers are the Northern California Cancer Center, Cancer Care Ontario, the University of Melbourne, Columbia University, Fox Chase Cancer Center, and the University of Utah. The ISC is housed at Research Triangle Institute (RTI) in North Carolina.

A central goal of the B-CFR is the translation of this research to the clinical and prevention setting for the benefit of registry participants and the general public. The B-CFR has information and biospecimens contributed by more than 15,300 families across the spectrum of risk for breast cancer and from population-based or relative controls.

Of particular interest are:

- Identification and characterization of cancer susceptibility genes
- Definition of gene-gene and gene-environment interactions in cancer etiology
- Translational, preventive, and behavioral implications of research findings

Special features include:

- Population-based and clinic-based ascertainment
- Systematic collection of validated family histories
- Epidemiologic risk factor data
- Clinical and follow-up data
- Biospecimens (including tumor blocks and Epstein-Barr virus (EBV)-transformed cell lines)
- Ongoing molecular characterization of the participating families

The resources collected by the B-CFR are open to the scientific and medical community for collaborative research projects. To date more than 220 manuscripts have been published on projects that utilized the B-CFR research infrastructure. To make the resources collected by the B-CFR centers available to the research community and to ensure they are utilized for projects with significant scientific and/or medical interest, the B-CFR has developed a unique system of scientific review of potential projects. This application and review process is described below.

Breast-CFR Application and Review Process

Investigators interested in pursuing collaborative research projects using Cancer Family Registries (CFR) resources must submit an application for access to the available data and biological materials. These applications are reviewed with careful consideration given to their scientific merit, their overlap with ongoing CFR studies, and the impact of the proposed study on the inventory of biological materials.

Applications follow two different review paths depending on the types of resources being requested. They typically take 6 weeks to process from submission of the full application to final notification. Applications only requesting access to data resources follow an expedited review track. These “Data Only” applications are evaluated on a rolling basis and can be processed in approximately 3 weeks from submission of the full application to final notification.

Review Process for General Applications (Not Data Only)

The CFR application process can be divided into three phases: Phase I, the project initiation and collaboration phase; Phase II, the Steering Committee (SC) review phase; and Phase III, the Advisory Committee (AC) review phase. These phases of the application process are described in detail below. See Figure 1 for a flow diagram of the general review process.

Phase I—Project Initiation and Collaboration Phase

The first step in the application process is the submission of a “Concept Description.” The Concept Description is a short (1 to 2 pages) description of the proposed research project. This description briefly explains the hypotheses, design, and methods of the study. It lists the CFR sites and external investigators with whom the applicant wishes to collaborate. The Concept Description also describes the types of resources being requested and concisely defines the study population(s).

The applicant submits the Concept Description through an online submission form in the Online Application Tracking System (OATS) hosted by the CFR Informatics Support Center (CFR-ISC).

Step-by-Step Instructions for Submitting a Concept Description to the OATS

- 1) Go to the following URL: <https://www.cfrisc.org/isc/viewATSgeneralinfo.do>
- 2) When you get to the web page, click the link New Application under the “New Submissions” heading.
- 3) You will be asked whether or not you have an ISC Website account. If you already have an account, click the appropriate link and skip to Step 6. If you do not have an account, click the appropriate link and you will be directed to a page where you can fill in basic account information.
- 4) Click the Login link in the upper right-hand corner and log in using your account credentials.
- 5) You will then be brought to the home page of the CFR ISC portal. Under “Links” on the left-hand side of the page, click New Application and skip to Step 7.
- 6) Click the New Application link under “New Submissions.”
- 7) Select the B-CFR registry and click the [Select Registry] button.
- 8) You will then be taken to the Concept Description web form. While you are filling out this form, you can save your progress without submitting. When you are ready to submit the completed Concept Description, click the [Finalize] button. After finalizing, you will not be able to edit the submitted Concept Description.

After submitting a Concept Description, applicants will receive an application tracking ID number, application materials, and instructions via e-mail.

Phase II—Draft Application and Steering Committee Review Phase

After submitting the Concept Description and receiving the application materials, an applicant develops a full “Draft Application.” The Draft Application is a complete application that is submitted to the SC for review and comment. A complete Draft Application consists of the following components:

- 1) A completed CFR application (filled out through an online Web form)
- 2) A National Institutes of Health (NIH) biosketch of the application’s Principal Investigator (PI) (if external) and all external collaborators listed in the application (PHS 398 form preferred)
- 3) A completed NIH Resources form (PHS 398 form preferred)

The Draft Application is submitted online through OATS. After submitting a Concept Description, an applicant can access the full application Web forms through the task list on the CFR-ISC Web site. A hyperlink to this task list is included in the e-mail notification containing the application ID number and materials. NIH biosketches and NIH Resources forms should be completed, saved, and uploaded in the “Study Design” section of the online application (.DOC and .PDF formats are preferred). Step-by-step instructions for submitting a Draft Application through the OATS are provided below.

The Scientific Liaison—Proposals submitted by external investigators are assigned a Scientific Liaison. The Scientific Liaison is an internal CFR investigator who is familiar with the application process and with the resources available within the registry. An applicant should receive contact information for the assigned liaison within 2 weeks of submitting a Concept Description. External applicants are strongly encouraged to contact their liaisons and discuss their projects before submitting their full applications.

The main roles of the Scientific Liaison are to assist the applicant in developing a Draft Application and to act as a liaison between the applicant and the CFR site principal investigators. The Scientific Liaison can help an applicant understand what resources are currently available and assess whether a project is feasible given the available resources. The liaison may also bring potential concerns to the attention of appropriate CFR personnel, such as the SC, the NIH Project Officer, and the Scientific Review Coordinator.

Examples of areas in which external investigators may need guidance from the Scientific Liaison include, but are not limited to:

- Identifying the most appropriate CFR sites with which to collaborate
- Exploring what characterizations have already been conducted (or are currently being conducted) on CFR participants
- Identifying which data and biospecimens are available
- Understanding how requests are translated into a tangible list of data elements
- Exploring how studies can be designed to minimize overlap with existing projects
- Fostering collaborations between the applicant and other CFR investigators when appropriate

The Breast-CFR Site Principal Investigators—Each CFR site has a designated PI and one or more Co-PIs. After establishing which sites they are interested in collaborating with (i.e., receiving resources from), applicants should contact the PIs and/or Co-PIs of those sites. The site PIs are the investigators with the most intimate knowledge of the data and materials collected for the CFR at their institutions and can provide valuable insights relevant to most CFR projects. These interactions also provide an opportunity to foster truly collaborative studies between external investigators and CFR personnel. The PIs and Co-PIs of each site are listed in Table 1 below.

Table 1. Contact Information for Breast-CFR Site Principal Investigators

Australian Breast Cancer Family Registry		
John Hopper, Ph.D.	PI	j.hopper@unimelb.edu.au
Melissa Southey, Ph.D.	Co-PI	msouthey@unimelb.edu.au
Family Risk Assessment Program at Fox Chase Cancer Center		
Mary Daly, M.D., Ph.D.	PI	mary.daly@fccc.edu
Andrew Godwin, Ph.D.	Co-PI	andrew.godwin@fccc.edu
Metropolitan New York Registry		
Mary Beth Terry, Ph.D.	PI	mt146@columbia.edu
Ruby Senie, Ph.D.	Co-PI	rts15@columbia.edu
Regina Santella, Ph.D.	Co-PI	rps1@columbia.edu
Northern California Cooperative Family Registry for Breast Cancer		
Esther John, Ph.D.	PI	ejohn@nccc.org
Dee West, Ph.D.	Co-PI	dwest@nccc.org
Alice Whittemore, Ph.D.	Co-PI	alicesw@stanford.edu
Ontario Cancer Genetics Network (Cancer Care Ontario)		
Irene Andrulis, Ph.D.	PI	andrulis@mshri.on.ca
Julia Knight, Ph.D.	Co-PI	knight@mshri.on.ca
Norman Boyd, M.D., D.Sc.	Co-PI	boyd@uhnres.utoronto.ca
Utah Cooperative Breast Cancer Registry at Huntsman Cancer Institute		
Saundra Buys, M.D.	PI	saundra.buys@hci.utah.edu
David Goldgar, Ph.D.	Co-PI	david.goldgar@hsc.utah.edu

The Steering Committee Review—Full Draft Applications are distributed to the SC for review and comment. Applications requesting access to biological materials are also distributed to the chairperson of the Biospecimen Working Group (BWG). Other CFR investigators or committees may be asked to review specific applications on an ad hoc basis if the SC chairperson deems their expertise necessary to evaluate an application.

The specified committees review and comment on the proposal. The issues they carefully consider include the following:

- The availability of requested resources
- The impact of the biospecimen requests on the inventory of resources
- Feasibility of the project considering available resources
- Potential overlap with ongoing CFR projects

During this review phase the applicant may be contacted by members of the reviewing committee(s) and/or the Scientific Review Coordinator requesting clarification of specific issues. After the review is complete, the reviewing committees make recommendations and comments. These recommendations and comments are forwarded to the applicant before the applicant submits a Final Application for review by the scientific AC.

Step-by-Step Instructions for Submitting a Draft Application to the OATS

- 1) After the Scientific Liaison is assigned you will receive an email with the liaison information and notifying you that the full application is available. This email will contain a link to your OATS task list. Click that link and login using your account credentials. (You can also go to the CFR-ISC homepage (<https://www.cfrisc.org/isc/welcome.do>), login using the Login link in the upper right hand corner of the page, and then click the Task List link in the menu bar, on the left hand side.)
- 2) In your task list click the Create/Edit Draft Application link for the application you wish to submit.
- 3) You will be brought to a page with links to the 5 sections of the full application along the top of the page: General Information, Collaborators, Resources, Research Attributes, and Study Description.
- 4) Fill out the online form for each section of the application. Changes will be saved automatically when moving from one section of the application to another. The sections can be filled out in any order. After saving you can logout of OATS and return later to complete the application. Login and then click the Task List in the menu bar. Find your pending application and click Create/Edit Draft Application.
- 5) After completing each section of the application click the Finalize link. You will be taken to a summary page which will display all of the submitted application information. Review this page. If it is satisfactory hit the [Finalize] button at the bottom of the page and the application will be submitted. If you wish to make changes you can go back to each section and make appropriate edits. You will not be able to edit your application after finalizing it.

Phase III—Final Application and Advisory Committee Review Phase

Applicants are notified that the SC/BWG reviews are complete via e-mail. They can view the comments made by the reviewing committees, respond to these comments, and can submit edits to their applications. The comments from the SC/BWG review, the applicant's responses to those comments, and the revised Final Application are all distributed to the AC for consideration during its review.

During its review the AC considers the comments and recommendations from the SC/BWG review as well as the applicant's responses to these comments and subsequent revisions to the application. The AC evaluates applications based on the following criteria:

- Scientific and/or medical interest of the proposal
- Appropriateness of the study design for addressing the research question
- Amounts of materials requested
- Qualifications and experience of the researchers
- Whether the proposed study could be undertaken without the research infrastructure of the CFR
- Whether the proposed study will enhance the value of the CFR and/or lead to future collaborative studies

After its review, the AC can make one of the following recommendations:

- 1) Approved
- 2) Approved With Suggestions
- 3) Decision Pending Clarification
- 4) Disapproved

In the case of "Approved" applications (or "Approved With Suggestions"), the AC also specifies a priority (low, medium, or high) indicating its level of enthusiasm for the project. Applicants receive a letter informing them of the AC's decision as well as a summary of the review.

If the application is "Approved With Suggestions," the applicant must respond to specified comments in the AC review summary and submit responses to the Scientific Review Coordinator before data or biospecimens can be dispatched. The application does not require additional review, however, and is essentially approved.

In the case of a “Decision Pending Clarification,” the applicant must respond to specified comments in the review summary. The AC then reviews the responses electronically. Based on the responses, the AC makes one of the four recommendations listed above, which can include requests for additional clarification.

If the application is “Disapproved” by the AC, the applicant will receive a letter informing him or her of the AC’s decision and a summary of the AC review, explaining the reasons why the application was not approved.

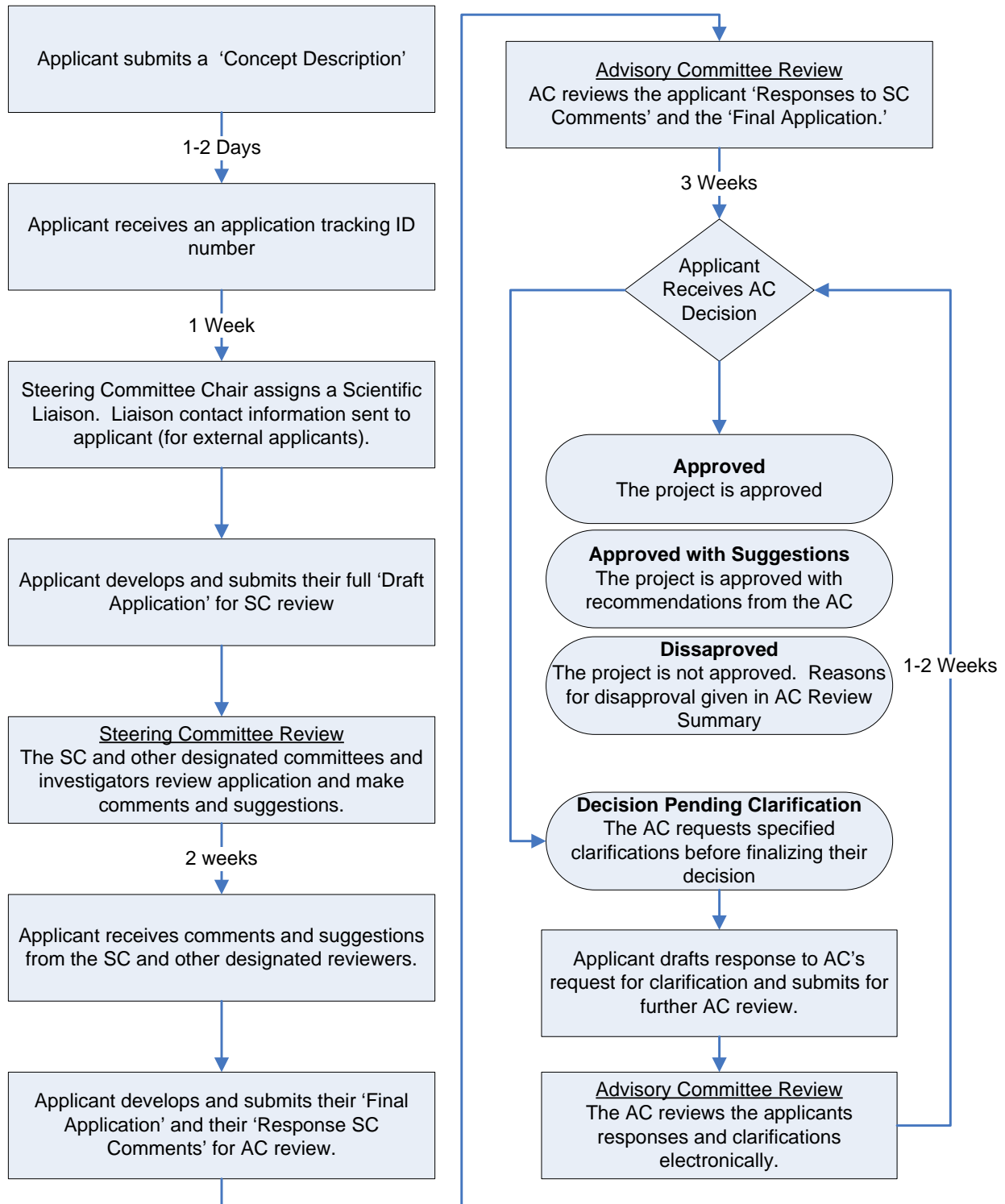


Figure 1. Flowchart describing the review process for general Breast-CFR applications.

Review Process for “Data Only” Applications

Applications requesting only data resources follow an expedited review track. This allows such applications to be reviewed in approximately 3 weeks from submission of the full application. In the expedited review the SC can approve an application during Phase II of the review process. Data Only applications approved at this stage do not require review by the scientific AC. Applications that are not approved for expedited approval by the SC can be sent to the AC for final review and approval or disapproval. This expedited review process is outlined below. See Figures 2A and 2B for flow diagrams detailing the expedited review process.

Phase I—Project Initiation and Collaboration Phase

This phase proceeds the same way as in the general application process (described above). The applicant submits a “Concept Description” and subsequently receives the full application materials and an application tracking ID number.

Phase II—Full Application and Steering Committee Review Phase

This phase of the review is similar to the general application process as well. A Scientific Liaison is assigned to the project if it was submitted by an external investigator, and the applicant develops a full application. A completed full application consists of the following components:

- 1) A completed CFR application (filled out through an online Web form)
- 2) An NIH biosketch of the application PI (if external) and all external collaborators listed in the application (PHS 398 form preferred)
- 3) A completed NIH Resources form (PHS 398 form preferred)

The full application is reviewed by the SC. Other CFR investigators or committees may be asked to review specific applications on an ad hoc basis. During the review designated members of the SC vote whether they are “In Favor” or “Not In Favor” of expedited approval of the application. If a majority of the voting members are “In Favor,” the application is approved. The applicant receives notification of the decision as well as comments made by SC members during their review.

If a majority of the voting members are “Not In Favor” (or if the votes are tied), the applicant receives notification of the SC decision as well as comments made by the SC members during their review. These comments will contain reasoning why the SC vote was “Not In Favor” of expedited approval of the application. At this point the applicant has two options. The applicant can respond to the SC comments, revise the application, and resubmit it for re-review by the SC. Alternatively, the applicant can have the application sent to the AC for review (Phase III).

Phase III—Final Application and Advisory Committee Review Phase

A “Data Only” application not approved by the SC can be sent to the AC for final review and decision. Prior to submitting the application for AC review, the applicant has the opportunity to respond to the SC comments and to revise the application. The comments from the SC review, the applicant’s responses to those comments, and the revised, final application are distributed to the AC for review.

The AC then reviews the application electronically on a rolling basis. When reviewing the application, the AC considers the SC comments, the applicant’s responses to those comments, and the revised application (if revisions were made). As with the standard application procedure, the AC can make one of the following recommendations: (1) Approved, (2) Approved With Suggestions, (3) Decision Pending Clarification, or (4) Disapproved.

If the AC votes to approve the application, the project is approved. The applicant will receive notification of approval and be given access to the requested data resources.

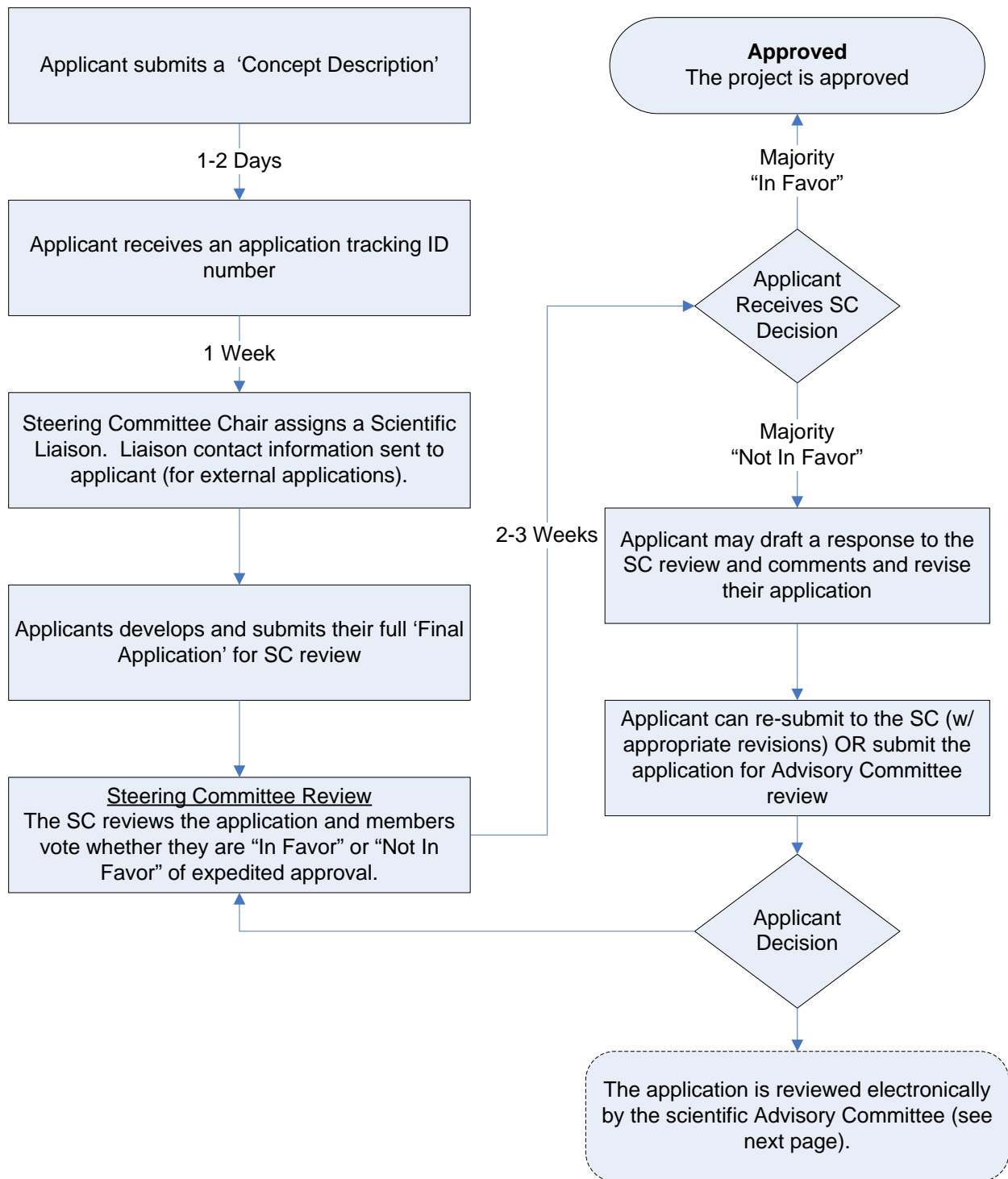


Figure 2A. Flowchart describing the review process for Data Only Breast-CFR applications.

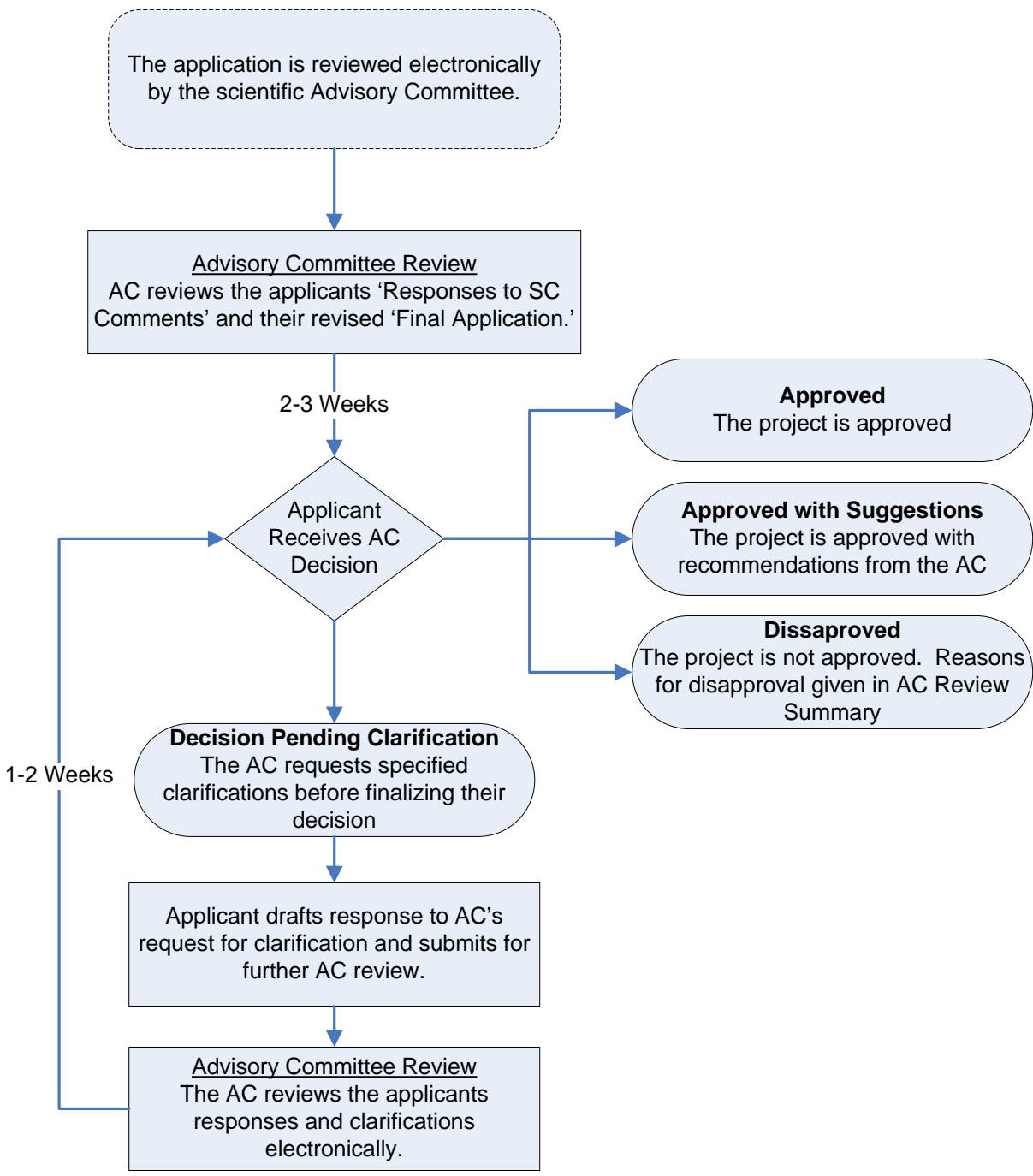


Figure 2B. Flowchart describing the review process for Data Only Breast-CFR applications submitted to the Advisory Committee after an unfavorable ruling by the Steering Committee.

Amendments and Renewals to Ongoing Breast-CFR Projects

Amendments

Approved, ongoing B-CFR projects can be modified through the submission of an amendment. These proposals undergo scientific review and approval. The types of modifications that can be implemented through the submission of an amendment include the following:

- Replacement of the lead PI
- Requests for additional biospecimen materials
- Requests for additional data resources
- Additional participant contact
- Significant changes in or additions to methodology (e.g., a new micro-array platform)
- Additional site collaborations
- Study of additional genes in molecular pathways described in the original application

Changes to an ongoing project that constitute new specific aims require the submission of a new application. Examples include the study of genes in additional molecular pathways, the study of new populations, or the study of additional environmental factors. Changes of these types cannot be enacted through an amendment.

Amendments are evaluated on a rolling basis and follow an expedited review track. Amendments that do not request additional biospecimens or patient contact follow a review process similar to that of new “Data Only” applications. It typically takes approximately 1 month to process these amendments from submission to final notification.

Amendments that request additional biospecimens or patient contact must be reviewed by the SC as well as the scientific AC (biospecimen amendments are also reviewed by the Chair of the BWG). This process is similar to the process for new applications except that amendments are reviewed electronically, on a rolling basis, and are not tied to the AC’s triannual review dates. It typically takes approximately 2 months to process these amendments from submission to final notification.

To submit an amendment, please contact the Scientific Review Coordinator, Michael R. Burgio, Ph.D. (burgiom@mail.nih.gov), for the amendment form and instructions. The amendment form is a short, two-page document describing the changes to the original application as well as any additional resources being requested.

Renewals

Breast-CFR projects are considered active for a period of 5 years from the initial approval date. If the project is not completed within 5 years, a project renewal must be submitted and approved. To initiate a renewal for a B-CFR project, please contact the Scientific Review Coordinator, Michael R. Burgio, Ph.D. (burgiom@mail.nih.gov), for the renewal form and instructions.