Stanford | Environmental Health & Safety

Administrative Panel on Biosafety (APB) Policy

Review of APB Protocols

Date: October 2024

Policy on APB Protocol Review

APB Policy allows three methods of APB review: (a) Full Committee Review (FCR) by a convened quorum of the members of the APB as supported by Biosafety Staff, (b) Designated Member Reivew (DMR) by one or more APB members or Biosafety Staff, or (c) Administrative Review by Biosafety Staff. Regardless of the review method, biosafety activities can only be initiated after a proposed research protocol has been fully approved.

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- Protocols considered for FCR
    - All Basic Research Protocols will be considered for FCR unless they meet the requirements for DMR and are not selected for FCR or meet the requirements for Administrative Review.
    - All Clinical Research Protocols will be considered for FCR unless they meet the requirements for Administrative Review. Currently, Clinical Protocols are not eligible for DMR.
    - The following Clinical Research Protocol Reports are required to be presented at FCR.
        - Phase 1: All Adverse Events (AEs) / series adverse events (SAEs) at least possibly related to the Investigational Produce (IP) by the Sponsor or Principal Investigator (PI) and at or above Grade 3 (reported by PI in real time).
        - Phase 2 and 3: All Serious Adverse Events (SAEs) at least possibly related to the IP by the Sponsor or PI and at or above Grade 3 (reported by the PI as annual summary).
- FCR Process
    - Principal Investigator (PI) submits protocol in eProtocol.
    - Biosafety Staff check for completeness, determine if protocol meets criteria for FCR, DMR or Administrative Review, and assign protocol to a panel meeting.
    - Biosafety Staff assign protocol to a Primary Reviewer, generally a member of the Biosafety Staff, but may also include consultants or APB members. Secondary reviewers are assigned on an as needed basis.
        - If a protocol is assigned to more than one designated reviewer, the reviewers must be unanimous in any decision. They must all review identical versions of the protocol and, if modifications are requested by any one of the reviewers, the other reviewers must be aware of and agree to the modifications.
        - Primary Reviewer status may be reassigned in the case of unexpected or planned long-term staff outages to facilitate timely review and approval. If a new Primary Reviewer is assigned, they are responsible for reviewing all comments and responses from the previous Primary Reviewer and determining if the issues have been adequately addressed or need to be sent back to the PI.
    - Reviewers review protocol.

- Questions or comments are noted in eProtocol and routed to the PI. The PI responds to comments. Comment-response cycles continue until questions and comments are sufficiently addressed.
- If comment-response cycles are continuing at the time when the APB agenda is being formalized (generally 1 week prior to the APB meeting), and if the PI has not responded to significant questions by the requested response date, the Primary Reviewer will contact the PI by email to request a response and provide a final deadline. If the PI continues to not respond, the Primary Reviewer has the discretion to determine if the protocol can continue to be assigned to that month's APB meeting, or if it should be Moved to the following month's APB meeting. If a protocol is Moved, this is done in eProtocol such that notification is sent to the PI.

- Protocol is confirmed for the assigned meeting and added to the agenda that will be emailed to the APB members, generally 1 week prior to the APB meeting. All protocols and comments/responses are available to APB members through eProtocol.
- APB members review protocols and comments/responses prior to convened APB meetings.
- Primary Reviewer presents protocol at convened APB meeting.
- APB discusses and votes on the protocol.
  - The protocol vote outcome may result in:
    - Approved
    - Tabled
    - Conditionally Approved
      - APB determines if protocol needs to continue with FCR, subsequent DMR, or subsequent Administrative Review
    - Not Approved
- Reviewer sends result of protocol vote outcome to the PI through eProtocol.
  - If protocol is Tabled, Conditionally Approved, or Not Approved, the Reviewer sends, through eProtocol, any comments or modifications required for further review.
  - If FCR of the revised protocol is selected:
    - The Biosafety Staff will notify the PI in writing of any requested modifications.
    - The revised protocol will undergo the usual procedure for FCR.

- Once all requested modifications to the protocol have been made, the Biosafety Staff will assign the revised protocol to a convened APB meeting agenda.
- See below for DMR subsequent to FCR process, or Administrative Review subsequent to FCR process.

- The approval date of the protocol is the date of the assigned APB meeting, but approval is not granted until all conditions are sufficiently met, as determined by either FCR or DMR. The date on which conditions are met will be stated in the approval notes.

APB Designated Member Review

- Protocols considered for DMR
  - DMR may take place for Basic Research Protocols that meet the following conditions:
    - Protocols that have reached the end of their 3-year approval cycle (or 1-year cycle for BSL-3 level protocols) and have been cloned and resubmitted as "Continuing New" protocols, if no substantive modifications have been made in agents, procedures, or risk, as determined by Biosafety Staff review and in consultation as needed with the APB Chairs or Biosafety Officer.
    - New protocols that contain only viral vectors.
      - NOTE: Viral vector work with (a) novel viral vectors, (b) novel envelope proteins, or (c) novel work with transduced cells must go to FCR. Novel, in this instance, is defined as things not, at the time of review, commonly or widely seen in APB protocols, or for which the Primary Reviewer feels that the risk assessment of the work is generally higher than that normally seen with similar agents, processes, or procedures. This can be determined as needed in consultation with the APB Chairs or Biosafety Officer.
    - New protocols that contain only prion-like protein (PLP) work.
      - NOTE: Novel PLP work must go to FCR. Novel, in this instance, is defined as things not, at the time review, commonly or widely seen in APB protocols, or for which the Primary Reviewer feels that the risk assessment of the work is generally higher than that normally seen with similar agents, processes, or procedures. This can be determined as needed in consultation with the APB Chairs or Biosafety Officer.
  - Clinical Research Protocols are not eligible for DMR at this time.

- Conditions to Conduct DMR
    - Protocols are reviewed in full by the DMR Process.
    - All members of the APB must be given an opportunity to call for FCR for each individual protocol. A list of eligible DMR protocols is sent to all APB members prior to a scheduled APB meeting, along with information on how to call for FCR of a given protocol.
    - DMR may result in approval, a requirement for modifications (to secure approval), or referral to the full committee for review. DMR may not result in withholding of approval.
    - If, and only if, no member requests FCR, the protocol may be approved by the assigned Primary Reviewer or Reviewers.
- DMR Process
    - Principal Investigator (PI) submits protocol in eProtocol.
    - Biosafety Staff check for completeness, determine if protocol meets criteria for FCR, DMR or Administrative Review, and assign protocol to a panel meeting.
    - Biosafety Staff assign protocol to a Primary Reviewer, generally a member of the Biosafety Staff, but may also include consultants or APB members. Secondary reviewers are assigned on an as needed basis.
        - If a protocol is assigned to more than one designated reviewer, the reviewers must be unanimous in any decision. They must all review identical versions of the protocol and, if modifications are requested by any one of the reviewers, the other reviewers must be aware of and agree to the modifications.
        - Primary Reviewer status may be reassigned in the case of unexpected or planned long-term staff outages to facilitate timely review and approval. If a new Primary Reviewer is assigned, they are responsible for reviewing all comments and responses from the previous Primary Reviewer and determining if the issues have been adequately addressed or need to be sent back to the PI.
    - Reviewers review protocol.
        - Questions or comments are noted in eProtocol and routed to the PI. The PI responds to comments. Comment-response cycles continue until questions and comments are sufficiently addressed.
        - If comment-response cycles are continuing at the time when the APB agenda is being formalized (generally 1 week prior to the APB meeting), and if the PI has not responded to significant questions by the requested response date, the Primary Reviewer will contact the PI by email to request

a response and provide a final deadline. If the PI continues to not respond, the Primary Reviewer has the discretion to determine if the protocol can continue to be assigned to that month's APB meeting, or if it should be Moved to the following month's APB meeting. If a protocol is Moved, this is done in eProtocol such that notification is sent to the PI.

- If, at any time, the Primary Reviewer determines that the criteria for assigned FCR, DRM or Administrative Reivew are not met, they will reassign the protocol to appropriate FCR, DMR or Administrative Review.
- Protocol is confirmed for the assigned meeting and added to the DMR protocol list that will be emailed to the APB members prior to the meeting, generally 1 week prior to the APB meeting. All protocols and comments/responses are available to APB members through eProtocol.
- APB members review protocols and comments/responses prior to convened APB meetings. Any member may call for FCR of any protocol.
- If no APB member calls for FCR prior to or during the convened APB meeting to which the protocol is assigned, the Biosafety Staff may approve the protocol without APB presentation, discussion and voting.
- The approval date of the protocol is the date of the assigned APB meeting, but approval is not granted until all questions and comments are sufficiently met, as determined by the Primary Reviewer, in consultation as needed with the APB Chairs or the Biosafety Officer. The date on which conditions are met will be stated in the approval notes.

- DMR Process Subsequent to FCR
  - If the APB determines that a protocol being discussed at a convened meeting lacks substantive information necessary for approval, the APB may require additional modifications or clarification from the Principal Investigator (PI) in order to secure approval. In such situations, the APB can:
    - Vote to return the protocol for FCR at a future convened meeting (see above process), or
    - Employ DMR, or
    - Employ Administrative Review by Primary Reviewer (see below process).
  - If DMR subsequent to FCR is selected:
    - Any protocol requiring substantive modifications to secure approval will be available to any APB member via eProtocol.
    - The Biosafety Staff will notify the PI in eProtocol of any requested modifications.

- The revised protocol will undergo the usual procedure for DMR by one or more designated members of the APB or Biosafety Staff that the APB Chairs or Biosafety Officer has designated to conduct the review.
- Any member of the APB may, at any time, see the revised protocol and/or request FCR.
- As long as no member requests FCR before or during the assigned APB meeting, the revised protocol becomes eligible for approval by the DMR process.

APB Administrative Review

- Protocols considered for Administrative Review
  - Ongoing (previously approved) Basic Research APB protocols if all proposed changes by the PI meet the following conditions. For each modification, the Biosafety Staff will review the change and associated requirements by the APB (see below). If any proposed change is not included on the list below, the protocol will be considered for FCR or DMR (see above).
    - Addition, removal or modification of personnel, including associated changes with training or biological agent/personnel table.
    - Addition or removal of funding sources.
    - Addition or removal of other panels provided any updates to the relevant biosafety work meets requirements for Administrative Review.
    - Addition or removal of location.
    - Addition or removal of Biosafety Cabinet (BSC).
    - Addition, removal or modifications to description provided no significant changes are made to existing methods.
    - Addition or removal of a viral vector to a protocol that already contains viral vectors. This will be limited to common viral vectors (see list below) with common pseudotyped envelopes (see below), and limited to non-novel work with viral vectors (Novel, in this instance, is defined as things not, at the time of review, commonly or widely seen in APB protocols, or for which the Primary Reviewer feels that the risk assessment of the work is generally higher than that normally seen with similar agents, processes, or procedures. This can be determined as needed in consultation with the APB Chairs or Biosafety Officer.)
      - Common viral vectors:
        a. Retroviruses, including Lentivirus, Murine retrovirus, Simian immunodeficiency virus, Equine infectious anemia virus

b. Adenovirus, Canine adenovirus
c. Adeno-associated virus
d. Herpes simplex virus, Pseudorabies virus as an amplicon only
e. Rabies virus
f. Sendai virus
g. Other vectors as determined by Biosafety Staff in consultation with APB Chairs or Biosafety Officer

- Common envelopes
  a. Amphotropic envelope
  b. Vesicular stomatitis virus G protein (VSV-g)
  c. Other envelopes as determined by Biosafety Staff in consultation with APB Chairs or Biosafety Officer

- Addition or removal of synthetic nucleic acids (sNA) to a protocol that contains similar sNA.
- Addition or removal of strains of an already approved agent, provided the risk profile of the new strain is not higher than that of the already approved agent. Risk profile includes risk group category, sensitivity or resistance to treatment options, host range, pathogenesis, virulence, transmission, etc.
- Addition or removal of cell lines, provided the added cell line does not contain a new agent or pose a higher risk than the cell lines currently listed on the protocol, as determined by the Primary Reviewer in consultation as needed with the APB Chairs or Biosafety Officer.
- Addition or removal of removing animal species, provided the species is similar to an already approved species and procedures and housing can be provided at the appropriate biosafety level.

o Ongoing (previously approved) Clinical Research APB protocols if all proposed changes by the PI meet the following conditions. For each modification, the Biosafety Staff will review the change and associated requirements by the APB (see below). If any proposed change is not included on the list below, the protocol will be considered for FCR (see above).

- Protocols that have reached the end of their 1-year approval cycle and have been cloned and resubmitted as “Continuing New” protocols, if no substantive modifications have been made in investigational product, procedures, or risk, as determined by Biosafety Staff review and in consultation as needed with the APB Chairs or Biosafety Officer.
  - Risk includes annual summary of all AEs at least possibly related to the IP by the Sponsor or PIand at or above Grade 3.

- All SAEs must be reported as a Clinical Research Report that is presented through FCR and are not eligible for Administrative Review.

- Addition, modification, or removal of personnel.
- Addition, modification, or removal of funding sources.
- Revisions to previously approved clinicals where no substantive modifications have been made in investigational product, procedures, or risk, as determined by Biosafety Staff review and in consultation as needed with the APB Chairs or Biosafety Officer.

- GAP protocols: If a PI fails to appropriately renew or clone/submit a protocol ("Continuing New" protocol) such that a protocol unintentionally closes/expires and the PI lacks APB coverage, a gap-coverage protocol (GAP protocol) may be created by the PI and submitted for approval by Biosafety Staff under the following conditions.
  - The GAP protocol must be an identical clone of the closed/expired protocol. The only exceptions are changes automatically made within eProtocol, such as updated training dates or updated personnel information that is automatically pulled from other Stanford systems. Any manual changes made by the PI, such as adding or removing new personnel, are not allowed.
  - No further review of the protocol is required prior to approval by Biosafety Staff, provided the PI has either submitted a second clone of the protocol or confirmed in writing that they will do this. This second clone of the protocol will undergo appropriate review through FCR, DMR, or Administrative Review as outlined within this policy.
  - Approval dates for GAP protocols are to start on the day on which coverage was last available in the closed/expired protocol, and end on a suitable short timeline, normally 3 months or 3 APB cycles after the previous coverage ended.
  - GAP protocol review and approval as outlined here supersedes the process generally outlined for Administrative Review, provided the requirements for GAP protocols are met.

- Administrative Review Considerations for Basic Research Protocols by Biosafety Staff
  - If personnel change, the review will ensure that all such personnel are appropriately identified, adequately trained and qualified, enrolled in applicable occupational health and safety programs, and meet other criteria as required by the APB.

        - If Principal Investigator changes, review will require signed acknowledgement from the transferring PI and the recipient PI regarding acceptance of responsibility for oversight of the research and personnel. At a minimum, the receiving PI must acknowledge receipt of the protocol and responsibility if the transferring PI is unavailable. Responsibility includes oversight of the work, the people performing the work, and fiscal responsibility for the work as determined by both PIs.
    - If locations change, review will ensure that appropriate signage is provided, and as needed, a visit to the location is conducted.
    - If BSC is updated, review will ensure appropriate information (make, model) is provided and that the BSC is current in certification.
    - If description is changed, review will ensure adequate and appropriate information on summary, methods, precautions, and all associated other protocol sections, are complete and other criteria as required by the APB is met
    - If viral vectors are added, review will ensure adequate information on rDNA, usage, risk, training, and other criteria as required by the APB is met.
    - If sNA is updated, review will ensure adequate information on sNA usage, risk, and other criteria as required by the APB is met.
    - If agent strain is updated, review will ensure adequate information on agent, risk, training, medical surveillance and other criteria as required by the APB is met. For removal, appropriate disposal information will be provided.
    - If cell lines are updated, review will ensure adequate information on cell type and relevant usage as required by the APB is met.
    - If animal species are added, review will ensure adequate information on species, risk, training, related animal protocol (APLAC) information, medical surveillance, and other criteria as required by the APB is met. Review will also include providing zoonotic information, housing requirements, and training on working with biohazards in animals (VSC-0004) in conjunction with the Animal Research Occupational Health and Safety Program (EHS), the Veterinary Service Center, the Stanford University Occupational Health Center, and the Administrative Panel on Laboratory Animal Care (APLAC).
- Administrative Review Considerations for Clinical Research Protocols by Biosafety Staff
    - If personnel change, the review will ensure that all such personnel are appropriately identified.
        - If Principal Investigator changes, review will require a new Informed Consent Form (ICF) and ensure all subjects know there is a new PI.

  - If associated documents, including but not limited to Investigative Brochure, Clinical Protocol, FDA documentation, ICF, or other documents, are updated, all changes will be reviewed to determine if product, procedures or risk has changed. Primary Reviewer may determine protocol needs to move to FCR or can remain Administrative Review.
- Conditions to Conduct Administrative Review
  - All modifications to a protocol must meet a category of changes allowed for Administrative Review. If any individual modification does not meet a category allowed for Administrative Review, the protocol must be assigned to FCR or DMR as appropriate.
  - Administrative Review may result in approval, a requirement for modifications (to secure approval), or referral to FCR or DMR. Administrative Review may not result in withholding of approval.
- Administrative Review Process (except GAP Protocols)
  - Principal Investigator (PI) submits protocol in eProtocol.
  - Biosafety Staff check for completeness, determine if protocol meets criteria for FCR, DMR or Administrative Review, and assign protocol to a panel meeting.
  - Biosafety Staff assign protocol to a Primary Reviewer, generally a member of the Biosafety Staff, but may also include consultants or APB members. Secondary reviewers are assigned on an as needed basis.
    - If a protocol is assigned to more than one designated reviewer, the reviewers must be unanimous in any decision. They must all review identical versions of the protocol and, if modifications are requested by any one of the reviewers, the other reviewers must be aware of and agree to the modifications.
    - Primary Reviewer status may be reassigned in the case of unexpected or planned long-term staff outages to facilitate timely review and approval. If a new Primary Reviewer is assigned, they are responsible for reviewing all comments and responses from the previous Primary Reviewer and determining if the issues have been adequately addressed or need to be sent back to the PI.
  - Reviewers review protocol.
    - Questions or comments are noted in eProtocol and routed to the PI. The PI responds to comments. Comment-response cycles continue until questions and comments are sufficiently addressed.

- If, at any time, the Primary Reviewer determines that the criteria for assigned FCR, DRM or Administrative Reivew are not met, they will reassign the protocol to appropriate FCR, DMR or Administrative Review.
- Once all questions and comments are considered sufficiently addressed, and if the protocol still meets criteria for Administrative Review, the Biosafety Staff can approve the protocol.
- The approval date of the protocol is the date on which the Biosafety Staff send the approval notice through eProtocol.

- Administrative Review Process Subsequent to FCR
  - If the APB determines that a protocol being discussed at a convened meeting lacks substantive information necessary for approval, the APB may require additional modifications or clarification from the Principal Investigator (PI) in order to secure approval. In such situations, the APB can:
    - Vote to return the protocol for FCR at a future convened meeting (see above process), or
    - Employ DMR (see above), or
    - Employ Administrative Review by Primary Reviewer.
  - If Administrative Review subsequent to FCR is selected:
    - Any protocol requiring substantive modifications to secure approval will be available to any APB member via eProtocol.
    - The Biosafety Staff will notify the PI in eProtocol of any requested modifications.
    - The revised protocol will undergo the usual procedure for Administrative Review by one or more members of the APB or Biosafety Staff that the APB Chairs or Biosafety Officer has designated to conduct the review.
    - If the Biosafety Staff have questions or concerns on the appropriateness of the response regarding required clarifications or modifications, they will consult with the APB Chairs or the Biosafety Officer, who can advise Biosafety Staff or determine if the protocol needs to move to FCR or DMR.
    - If the Biosafety staff determines that all modifications, questions, and comments are sufficiently addressed, they can approve the protocol.
    - The approval date of the protocol is the date of the assigned APB meeting, but approval is not granted until all questions and comments are sufficiently met, as determined by the Biosafety Staff, in consultation as needed with the APB Chairs or the Biosafety Officer. The date on which conditions are met will be stated in the approval notes.