

Terms of Reference

Scientific Advisory Board for Homocystinurias

I. Specific Responsibilities:

- Work with the HCU Network Australia and HCU Network America (herein called “HCUNAs”) to develop research strategy and identify key priorities for funding.
- Provide non-binding but informed guidance on matters specific to HCUNAs research and funding strategies, including opportunities for new programs or clinical trials.
- Provide peer review for applications submitted to HCUNAs for funding and provide recommendations on specific projects to be funded.
- Support any grant applications submitted by HCUNAs to other funding bodies.
- Participate in periodic reviews of HCUNAs Research Strategy.

II. Duty and Values:

- Members of the SAB agree to act in the best interests of the HCUNAs and patients with homocystinuria in good faith and in a transparent, honest, professional and courteous manner.
- It is expected that any potential conflicts of interests will be communicated by SAB members and the SAB chair will then determine whether the member must be recused from specific discussion or decisions, or if other actions need to be taken to manage the potential conflict. According to the report of the USA Institute of Medicine (IOM) Committee on Conflict of Interest in Medical Research, Education, and Practice a conflict of interest is:

“a set of circumstances that creates a risk that the professional judgment or actions regarding a primary interest (i.e. promoting and protecting the integrity of research, the welfare of patients, and the quality of medical education) will be unduly influenced by a secondary interest (i.e. financial interests)”.

- A primary focus in consideration of conflict of interest must be to avoid any potential harm to patients that could occur due to conflicts that could potentially affect the ability to make decisions that are in patients’ best interest.
- Industry is not expected to participate in any SAB discussions or decisions, and industry funding will not be solicited or accepted to support research under the purview of the SAB. If industry requests information on any SAB discussion pertaining to relevant research they may be conducting or considering, it is the decision of the SAB Chair whether to share high level conclusions on a specific mechanism without divulging any specific opinions of SAB members.

III. Membership:

- The SAB will consist of a Chair, a Vice-Chair and up to 8 scientific/clinical members, with the heads of HCU Network Australia and HCU Network America serving as non-voting members to represent patient interests.
- The members of the SAB are individuals, external to HCUNA, who have scientific knowledge, experience and expertise relevant to HCUNAs and/or associated research disciplines. The majority will be active in research.
- The board should include a significant number of non-beneficiaries, and beneficiaries should not be present when decisions are made on funding for projects they are directly involved in.
- For stand-alone meetings, SAB members will be reimbursed for their expenses associated with travel to the meeting. For meetings scheduled in conjunction with scientific or other congresses, SAB members will be reimbursed for incremental

expenses associated with their participation in the meeting (e.g. hotel costs for additional night if needed to participate in meeting).

- SAB members are appointed for a three-year term, after which they can at the request of the chair be re-elected immediately for an extension term of 2 years. Over time, the SAB will seek to stagger terms in order to avoid disruption if several members were to end their terms in the same year.
- Potential new SAB members will be nominated by the Chair of the SAB, current members of the SAB or the heads of HCUNAs (who may, for example, recommend additional members to achieve an appropriate balance of expertise or perspectives.) Reliance on one person to nominate individuals should be avoided.
- The current members of the SAB will vote to approve any new members being asked to join the SAB.
- All SAB members will be asked to complete a declaration of all potential conflicts of interest and updates will be requested before each review meeting.
- A SAB member may retire or resign his/her office at any time and is requested to provide written notice to the Chair of the SAB and the heads of HCUNAs of his/her decision to do so.

IV. Nomination of the Chair and Vice-Chair of the SAB:

- The heads of HCU Network Australia and HCU Network America will appoint the initial chair of the SAB. The Chair will serve a 3-year term, after which they can at the request of the heads of HCUNAs be re-elected immediately for an extension term of 2 years.
- The Heads of HCUNAs will request input from all SAB members and the current chair prior to reelecting or appointing a new chair.
- The Chair of the SAB will appoint a Vice-Chair to stand-in whenever the chair is not available for a specific meeting or for a specific time period, or when the Chair declares a conflict of interest on a particular matter.

V. Role of the Chair:

- Contribute to development of the agenda for meetings, with input from heads of HCUNAs.
- Chair meetings of the SAB and take reasonable steps for the proper functioning of the SAB, including ensuring proper conduct of meetings, facilitating an appropriate level of discussion, ensuring that every member's views are considered, and where possible seeking consensus amongst the members.
- Take reasonable steps regarding the adequate flow of relevant information to, and from, the SAB and the heads of HCUNAs.
- While the Chair should be eligible for funding during their tenure, as it is unfair to penalize a researcher involved in the field for taking on this role, extra care must be exercised to avoid a real or perceived conflict of interest. If an area of research in the chair's area of expertise is considered a priority by the SAB, and/or if a specific RFP is issued requesting grant proposals in the chair's area of expertise, the Vice-Chair will step in at meetings or during off-line discussions where an application by the Chair is being considered.

VI. Meetings

- The SAB will conduct a minimum of one meeting per year (either in person or by teleconference), in addition to any ad hoc teleconferences or meetings as necessary. The intent will be to schedule meetings at conferences where the majority of SAB members plan to be in attendance.
- All members must declare any conflicts of interest should they arise during the meeting.
- There must be a quorum of voting members available (50% with a minimum of 4) to schedule a meeting.

- The SAB may recommend suitable topics for specialised sub-committees and panels, or liaisons with outside organisations.
- The opinions and recommendations of the SAB are to be dealt with confidentially, and any official communication outside of the SAB on overall conclusions or decisions made will be agreed to by the chair and the heads of HCUNAs.
- The outcomes of research funding decisions will be publicised on the HCUNAs websites excluding any confidential information.

VII. Voting:

- While the goal of the SAB will be to reach consensus on all decisions, in the event a consensus cannot be reached a decision will be made by a:
 - (i) Simple majority of votes cast in favour by members present and eligible to vote; or
 - (ii) Resolution in writing signed by the majority of members eligible to vote.
- In the event of an equal number of votes being cast for or against a motion, the Chair (or Vice-Chair if the Chair is not present or recuses him/herself) will exercise a casting vote.
- If a member has a conflict of interest in relation to any motion, he or she must abstain from voting. This would include any grant being considered where the SAB member or their institution would receive funding.
- Decisions made by the SAB will be passed as recommendations to the Heads of HCU Network Australia and HCU Network America for final funding decisions. While the HCUNAs will make best efforts to encourage donors to fund the projects considered highest priority by the SAB, it is understood that a specific donor may choose to fund a lower priority project.

VIII. Principles of Peer Review:

- Consistent with the duty and values statement (see Section II) it is expected that HCUNAs peer reviewers:
 - are fair, accurate and honest in their review;
 - give constructive feedback;
 - act in confidence and do not disclose the content or outcome of any process in which they are involved;
 - declare all conflicts of interest and do not permit personal prejudice to influence the peer review; and
 - do not agree to participate in peer review outside their area of expertise.
- For specific projects where the SAM does not have adequate expertise to provide peer review, additional experts outside of the SAB may be called on to participate at the decision of the SAB chair.
- SAB members must declare any conflict of interest and abstain from voting or influencing on grants where such conflicts exist
- SAB members must not discuss applications with applicants and, similarly, applicants should not approach SAB members either before or after the SAB meeting. All correspondence should be made via the HCUNAs.

IX. Grant Application Process:

- The process is envisioned to include the following steps:
 - The SAB will review the recently completed global research map and strategy prior to the meeting, and the focus of discussion will be determining key priorities for initial funding by the HCUNAs at a “mechanistic” level (i.e. molecular and preclinical). The criteria suggested to guide this determination include:

- Potential risk/benefit of this approach to improve patient care;
 - Likelihood research in this area would move forward without funding by HCUNAs (e.g. a lower priority would be placed on an area if industry funding were available); and
 - Likelihood that funding a project in this area would contribute significantly to moving the research in this area forward, including potentially attaining proof of concept to motivate industry funding.
- HCUNAs will publish on their websites the areas considered highest priority for funding and potential funding levels available. A specific “Call for Proposal” will be developed and approved by the SAB Chair and published on relevant web sites (e.g. SIMD; SSIEM) and outreach will also occur to any known researchers in this area through the SAB chair and HCUNAs.
- **Expression of Interest:**
 - Researchers will be asked to submit an Expression of Interest (EOI) Application describing the proposed project at a high level and stating a potential budget range, and include in a cover letter any conflicts of interest with SAB members.
 - The SAB chair and heads of HCUNAs will do an initial review of the applications to assure the project is consistent with the stated priorities and the budget range is consistent with funding that may be available. The resultant list of EOIs for consideration will then be circulated to all SAB members with the exception of those with a conflict of interest.
 - The SAB will be asked to provide input on which EOIs they support and other considerations they would deem important, either electronically or via a teleconference. The SAB chair will be the final determinant of which EOIs to invite full applications based on the input of the SAB.

- **Full Applications**

- At least two reviewers will be asked to review each application. External reviewers may be solicited if adequate expertise is not available on the SAB, though it is preferred that at least one reviewer is an SAB member where possible.
- Grant applications, along with reviewer's comments, will be forwarded to all SAB members (except those with a declared conflict of interest) within a reasonable time period prior to a planned SAB meeting.
- A scoring matrix based on the agreed assessment criteria (scientific quality, contribution to the field, innovation and team quality and capabilities) will be provided to external reviewers and SAB members.
- SAB members with a conflict of interest will be asked to leave the meeting while those applications are discussed.
- Comments and recommendations for funding will be compiled from the SAB meeting and communicated to HCUNAs for final funding decisions by the organizations or individual donors.

- **Monitoring grant progress**

- The grant recipients must agree to provide periodic brief updates (i.e. one page summary) on progress at least quarterly to the SAB chair and heads of HCUNAs, and a final report must be provided within 3 months of the completion of work. If additional results become available over time that stemmed from the funded project, the recipient must agree to make the information available to the SAB and HCUNAs.
- If the grant is set up to deliver funding via multiple cycles (e.g. each year) then the SAB can decide not to renew funding at the recommendation of the SAB

chair and heads of HCUNAs. The timetable for such decisions must be communicated upon awarding of the grant.

- **Publication of work**

- The grant recipient must agree to make results available to the scientific community and publish the work consistent with usual practice.

Authorization

The signing of this Terms of Reference implies the HCUNAs Scientific Advisory Board Member will strive to follow the guidelines set out herein to the best of their ability to ensure a fair and equitable grant funding process.

Scientific Advisory Board Member Name:

Signature:

Date: