International Severe Acute Respiratory Infection Consortium (ISARIC)

GOVERNING FRAMEWORK

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1. ISARIC Governing Principles

1.1 Vision

The vision of the International Severe Acute Respiratory Infection Consortium (ISARIC) is to change the approach to global collaborative patient-oriented research between and during epidemics of severe acute respiratory infections and other rapidly emerging public health threats in order to generate new knowledge, maximise the availability of clinical information, and thereby save lives.

1.2 Mission

ISARIC is a multi-regional collaboration of research networks with a focus on investigator-led clinical studies in adults and children. ISARIC's mission is both to conduct world-class clinical research in the inter-pandemic influenza period and to provide a collaborative platform through which clinical studies could be undertaken rapidly in response to the emergence of a novel respiratory pathogen or other new infectious disease outbreak.

1.3 Objectives

The aim of the Consortium is to establish a sustainable federation of research networks with global geographic coverage, including a strong focus on middle- and low-resource settings, that facilitates and coordinates international studies on severe acute respiratory infection (SARI) and emerging threats and liaises with national and supra-national public health authorities. The Consortium aims to conduct studies designed to elucidate pathogenesis, observational studies including registries, and interventional clinical trials in patients with SARI of all ages during the inter-pandemic periods, and with the flexibility and capacity to respond quickly to the range of plausible rapidly emergent threats. While it is anticipated that most participating networks will be hospital-based, other ones that can quickly access SARI patients will be included.

The key objectives of the Consortium are:

- To develop a more comprehensive understanding of human and pathogen factors contributing to SARI and disease severity across all ages;
- To define and validate optimal clinical management approaches adapted to the range of resource settings globally;
- To develop operational readiness to conduct essential clinical research to characterise and respond to new epidemic or pandemic infectious disease threats and to inform and guide evidence-based optimal clinical management;
- To develop capacity to undertake research in under-resourced areas;
- To undertake global clinical research for SARI and other threats in a timely, efficient, targeted and coordinated manner in order to maximise the information from studies and thereby save lives.

The overall role of the Consortium is to facilitate the work of investigators and networks and, when appropriate, to conduct cross-Consortium studies and assist with the solicitation of funding. Ownership of data, samples and publications resulting from Consortium-endorsed activities remains with the individual investigators and networks.

1.4 Funding of the Consortium

1.4.1 Funding sources

It is expected that funding for the day-to-day operation of ISARIC and any activities carried out on behalf of the Consortium will come from a variety of public and private sources (not-for-profit and for-profit). Funding applications for financial or in-kind support for specific research projects in the name of ISARIC and for ISARIC's core operation have to be endorsed

by the Consortium's Executive Committee. Funding applications to for-profit organisations have to be endorsed by the Council of ISARIC. Funding applications for specific ISARIC research projects should include in their budget an appropriate contribution to the operational costs of the Secretariat and the Regional Hubs.

1.4.2 Collaboration with for-profit organisations

While ISARIC encourages active collaboration with for-profit organisations (e.g. with the pharmaceutical industry), any such collaboration has to be approved by the Council.

Funding obtained from for-profit organisations for ISARIC-endorsed activities must be governed by a contract that is ratified by the Executive Committee, and must be unrestricted according to the guiding principles detailed in the Consortium's policy on relations with for-profit entities (see separate document).

The Council will endorse and revise these guiding principles as appropriate.

2. Structure of the Consortium

The Consortium is formed of the Council of ISARIC, Executive Committee, Secretariat, Stakeholder Advisory Board, Independent Data Access Committee and Working Groups. In addition to these organs, there are Regional Hubs in each geographic region involved in the Consortium's activities. A schematic outline of the Consortium structure is depicted in Figure 1 below (Appendix I).

2.1 Council of ISARIC

2.1.1 Role of the Council

The scientific direction and overall leadership of ISARIC is provided through the Council which is formed of representatives from research networks and individual investigators. Responsibilities of the Council include selection of Executive Committee members, endorsement of study protocols and other documents generated by the Working Groups for public posting, and for modifications to the ISARIC Governing Framework, Policy on Relations with For-Profit Entities. ISARIC Data-Sharing and other core ISARIC documents. The Council is responsible to and representative of the member organisations of ISARIC, and holds the Executive Committee responsible for the operation of the Consortium.

2.1.2 Composition of the Council

The Council includes Independent External Advisors, members of the Executive Committee, members with observer status and one representative from:

- each research network that is a member of ISARIC
- each Regional Hub (in the first instance only with observer status)
- each Working Group

2.1.3 Membership criteria for research networks

The Consortium aims to be inclusive and welcomes existing research networks as long as they are:

- Independent and founded, led and run by academic investigators (i.e., not led by industry)
- Scientifically active, with scholarly contributions that are attributable to the network and in research areas relevant to the Consortium
- Multicentre
- Have ready access to patients with SARI for enrolment into studies

- Supportive of ISARIC's vision and mission in terms of data-sharing and contributing to joint publications
- Governed by practices consistent with the mission and vision of ISARIC.

All of these criteria are required for membership and voting rights. Representatives from other networks or institutions may be invited as observers on the Council at its discretion but do not have voting rights on the Council.

Prospective Council members are asked to declare in writing that they agree to abide by the principles and operating procedures set out in the ISARIC Governing Framework, including a specific agreement on data sharing (to be drafted), before participating. No membership fees are levied.

Member networks are expected to nominate a new representative to the Council if their current representative is elected to sit on the Executive Committee as a voting member.

2.1.4 Independent External Advisors

Independent External Advisors to the Council should be senior individuals with international standing in the field of public health or another scientific field related to the Consortium and who provide a representation of the different regions contributing to the Consortium. Their term of office is for two years in the first instance and begins at the start of the next calendar year following their endorsement by the Council. Independent External Advisors may be nominated by any member of the Consortium and are endorsed through a majority vote (i.e. > 50% of all members) of the Council. They may resign from office at any time by giving notice in writing to the Executive Committee. If it serves the best interest of the Consortium, they may be removed by a two-thirds majority vote of the Council.

2.1.5 Members with observer status

In the first instance, members of the Council with observer status will be: Regional Hub representatives, a WHO representative, and a funder representative (the latter two through their non-voting membership of the Executive Committee). The Council reserves the right to accept further members with observer status at a later stage. Council members with observer status may also be invited to sit it on Executive Committee meetings.

2.1.6 Voting rights

Independent External Advisors, the Chair and Vice-Chair of the Executive Committee, and the Head of the Secretariat have one vote each on the Council. Research networks have one vote through their representative to the Council. Each Working Group elects by a majority vote a representative to the Executive Committee who also has one vote on the Council to reflect the interests of the Working Group. Members with observer status do not have voting rights.

2.1.7 Meetings of the Council

The Council meets in person on an annual basis and, via teleconference, on a semi-annual basis. Additional meetings (in person or via teleconference) will be scheduled as required.
Meetings of the Council are presided over by the Chair of the Executive Committee. Minutes of each meeting of the Council are distributed to all member organisations and are submitted to the Stakeholder Advisory Board if requested.

2.2 Executive Committee

2.2.1 Role of the Executive Committee

Executive responsibility for ISARIC activities lies with the Executive Committee. The Executive Committee steers the Consortium and provides general supervision of its

activities, reports to the Council, is advised by the Stakeholder Advisory Board, and line-manages the Secretariat.

2.2.2 Composition of the Executive Committee

The Executive Committee is drawn from within the Council and includes:

- An elected Chair and two elected Vice-Chairs
- Head of the Secretariat
- A single representative from each of the Working Groups (currently four in number)
- Non-voting observers (WHO, InFACT, funder representative).

At any given time, each research network should have no more than one voting member on the Executive Committee. InFACT should nominate a representative as a non-voting observer to the Executive Committee, except if an InFACT investigator already holds the position of Chair or Vice Chair.

2.2.3 Selection procedures and responsibilities

Chair and Vice-Chairs

The Chair and Vice-Chairs are elected for a two-year term by a majority vote (i.e. > 50% of all members) of the Council. If not specified otherwise, the election will be held at the annual meeting of the Council. Terms of office begin at the start of the calendar year following the election. If it serves the best interest of the Consortium, the Chair and Vice-Chairs may be removed by a two-thirds majority vote of the Council. The Chair and Vice-Chairs may resign from office at any time by giving notice in writing to the Chair of the Stakeholder Advisory Board and Head of the Secretariat. To ensure balanced representation of the various ISARIC participants and geographic regions, an individual may not serve more than two consecutive or non-consecutive two-year terms as chair or two consecutive or non-consecutive two-year terms as Vice-Chair. Where an individual fills a vacancy for Chair or Vice-Chair, if less than one year is served this will not count as a term, but if more than one year is served, this will count as a term. An individual who has served for two consecutive terms as Vice-Chair remains eligible to become Chair of the Executive Committee.

The Chair's responsibilities are to preside over Council and Executive Committee meetings; to conduct the elections; to line-manage the Head of the Secretariat; and to report to the Stakeholder Advisory Board on a semi-annual basis, and when called upon to do so. The Vice-Chairs assist the Chair with these responsibilities. In the absence of the Chair, the Vice-Chairs preside over meetings, conduct elections, and report to the Stakeholder Advisory Board.

Working Group representatives

Each ISARIC Working Group has the right to elect by a majority vote one representative to the Executive Committee to reflect the interests of the Group.

Observers

Observers have no voting rights and are appointed by the Council (see section 2.2.2). In the first instance there will be three members with observer status: a WHO representative, an InFACT representative, and a funder representative selected by the Stakeholder Advisory Board. The Council reserves the right to allow further members with observer status at a later stage.

2.2.4 Meetings of the Executive Committee

The Executive Committee meets in person at the annual meeting of the Council, and on at least a bi-monthly basis via teleconference. Additional meetings (in person or via teleconference) will be scheduled as required.

Minutes of each meeting of the Executive Committee are kept and are submitted to the Council and Stakeholder Advisory Board as soon as they are prepared and, again, immediately after they have been ratified at the next meeting.

2.3 Secretariat

2.3.1 Role of the Secretariat

The ISARIC Secretariat coordinates the daily activities of the Consortium and supports the activities of the Executive Committee, Working Groups, and their project teams by maintaining communications and accurate recordings of meetings, contributing to the development of funding proposals, and by providing assistance with Consortium-wide data sharing and with communications between the Regional Hubs. Depending on the nature of the projects, the Secretariat may also be involved in the implementation of study protocols. The Secretariat is led by the Head of the Secretariat and a Senior Programme Manager who is responsible for the coordination of the Consortium's day-to-day activities and the support of Executive Council and Working Group activities.

2.3.2 Secretariat posts

The Head of the Secretariat and the Senior Programme Manager are selected by the Executive Committee, and recruited and employed by an academic institution (currently the University of Oxford through their Human Resources department). Other positions could be added in future as needed and as funding permits.

2.3.3 Location of the Secretariat

In the first instance the Secretariat will be based at the Centre for Tropical Medicine, Nuffield Department of Medicine, University of Oxford. Administrative support is provided by the Nuffield Department of Medicine.

2.4 Stakeholder Advisory Board

2.4.1 Role of the Stakeholder Advisory Board

The Stakeholder Advisory Board identifies funding opportunities, helps to develop the strategic vision of the Consortium, and provides advice to the Executive Committee to ensure that progress is in accordance with the mission and objectives of the Consortium.

2.4.2 Composition of the Stakeholder Advisory Board

The Stakeholder Advisory Board is formed of six to eight members, including a representative from the institution where the Secretariat is located (currently the University of Oxford), and representatives from the funding organisations providing direct support to the Consortium (maximum of six). The Chair of the Stakeholder Advisory Board is nominated on a rotational basis from among its members and at a two-year interval.

Funding organisations that provide financial or in-kind support to the Consortium can each name one representative. The tenure of the representative is at the discretion of the funding organisation. Governmental agencies and not-for-profit organisations that fund specific protocols of the Consortium are eligible. Pharmaceutical industry groups that might provide funding or materials for study are not eligible. The tenure of the representative from funding organisations is at the discretion of the individual organisation. In future, if more than eight organisations provide support and nominate representatives, the Stakeholder Advisory Board will establish a suitable process of rotating membership every two years.

The institutional representative to the Stakeholder Advisory Board (currently Oxford University) is nominated by the institution housing the Secretariat and approved by the Stakeholder Advisory Board. The tenure of the representative from the institution is at the discretion of the institution housing the Secretariat.

The Chair of the Executive Committee may sit in on Stakeholder Advisory Board meetings as an observer. If appropriate, further members of the Council (e.g. the Head of the Secretariat) can be invited by the Stakeholder Advisory Board to attend its meetings as observers.

2.4.3 Voting rights

Each member of the Stakeholder Advisory Board has one vote. Representatives of funding organisations are expected to recuse themselves and abstain from voting on matters that concern activities in which they have potential conflicts of interest (e.g., involvement as investigators). Any real or potential conflict of interest should be declared at the outset of any meetings.

2.4.4 Meetings of the Stakeholder Advisory Board

The Stakeholder Advisory Board convenes in person at the annual meeting of the Council and, via teleconference, on a semi-annual basis. Additional meetings (in person or via teleconference) will be scheduled as required.

2.5 Regional Hubs

2.5.1 Role of the Regional Hubs

Regional Hubs are a critical component of ISARIC. It is their role to strengthen the Consortium's global approach to collaborative research by ensuring that low- and middle-income countries and their member networks are represented adequately on the Council and the Working Groups by facilitating regular communication between networks in the various regions through close interactions with the Secretariat; and by integrating activities of the Working Groups and their project teams at the regional level.

2.5.2 Regional Hub status

Regional Hubs are identified at the discretion of the Executive Committee and endorsed by the Council. The Council can formally assign Regional Hub status to the existing operations or communications centres of a member networks that represent certain regions. If it serves the best interest of the Consortium, Regional Hub status can be revoked by a majority vote of the Council. Member networks may relinquish their Regional Hub status at any time by giving notice in writing to the Chair of the Executive Committee.

2.5.3 Regional Hub representative

Each Regional Hub nominates a representative to the Council who is responsible for maintaining effective communication between the Council and member networks in their region.

2.6 Independent Data Access Committee

2.6.1 Role of the Independent Data Access Committee

Any external requests to access and use data generated by ISARIC investigators and on behalf of the Consortium have to be submitted to the Secretariat. For any requests in which an initial survey of involved investigators finds possible cause for not sharing data, the request will be referred to an Independent Data Access Committee for review. Decisions of the Committee are based on whether a request meets the criteria laid out in the ISARIC data access guidelines (see separate document – to be drafted) and on requirements of the local ethics committees where the relevant study was conducted. Decisions made by the Independent Data Access Committee can be appealed by any member of the Consortium and can be overruled by a two-thirds majority vote of all members of the Council.

2.6.2 Composition of the Independent Data Access Committee

The Independent Data Access Committee is composed of independent external experts selected to cover the full range of expertise including statistics and ethics required to

critically evaluate requests and achieve ISARIC's data access objectives. These individuals may come from institutions outside or represented in the Consortium but they may not be investigators in Consortium-related studies or members of the Consortium's other governance bodies. Members are nominated by the Council or Executive Committee and ratified by the Stakeholder Advisory Board.

2.6.3 Meetings of the Independent Data Access Committee

The Independent Data Access Committee meets via teleconference as required. If necessary, face-to-face meetings can be arranged by the Secretariat. Minutes of each meeting of the Independent Data Access Committee are kept and are submitted to the Executive Committee and to the Stakeholder Advisory Board if requested.

2.7 Working Groups

2.7.1 Role of the Working Groups

ISARIC Working Groups are investigator-led and represent the constituent units of the Consortium. They generate ideas, concepts, study protocols and related documents, including applications for funding for specific projects. In the first instance, the Consortium is expected to include the following four Working Groups:

- Working Group 1: "Inter-pandemic clinical trials"
- Working Group 2: "Global data collection and collation"
- Working Group 3: "Genomics, Pathogenesis and Pharmacology"
- Working Group 4: "Changing Clinical Research paradigms for rapidly emerging public health threats"

The scope of planned activities for these four Working Groups is outlined in Appendix II. Within a Working Group, individual project teams are responsible for the delivery of these activities, including the development of specific protocols to be submitted to funding agencies. The number and topic focus of Working Groups is expected to change as the Consortium evolves. The Council or Executive Committee can propose the establishment of additional Working Groups. New Working Groups or major changes in their terms of reference have to be ratified by the Executive Committee before activities on behalf of ISARIC can commence. Working Groups can be disbanded by a majority vote (i.e. > 50%) of its members or by a majority vote (i.e. > 50% of all members) of the Council. In the latter case, Working Groups retain the right of appeal against this decision.

2.7.2 Composition of the Working Groups

Each of the Working Groups includes members, a Chair and Vice-Chair, a representative to the Executive Committee (who has one vote on the Council, and who may also be the Chair or Vice-Chair), and project team leads. For efficient working the anticipated size of the Working Groups will be approximately 10-20 members. The size of project teams will be at the discretion of the Working Group members.

Members

Working Groups are composed of ISARIC research network representatives, as well as invited investigators who are not affiliated with a particular ISARIC member network. Invitations to individual investigators can be issued by the Chair of the Working Group or the Head of the Secretariat upon recommendation by the Working Group and endorsement by the Executive Committee.

Unless specified otherwise, Working Group membership will remain open and individuals will be able to become a member or leave a Working Group at any stage. If it serves the best interest of the Consortium, any member may be removed by a majority vote of the Working Group but retains the right to appeal to the Council. No investigator should be member of

more than two Working Groups at any one time, and no research networks should provide more than three representatives across the four Working Groups.
All members have the freedom to carry out other research projects, and ISARIC membership does not limit any other activity outside of the Consortium.

Chair and Vice-Chair

Each Working Group has a Chair and Vice-Chair who are elected by a majority vote of the Group and accountable to the Executive Committee. The Chair leads the Working Group, organises and runs its meetings, and assigns and coordinates activities within the Group. The Vice-Chair will perform these activities in the absence of the Chair or as requested by the Chair.
The term of office for the position of Chair and Vice-Chair is for two years in the first instance and renewable once. The Chair or Vice-Chair may resign from office at any time by giving notice in writing to the Working Group and the Head of the Secretariat. If it serves the best interest of the Consortium, the Chair or Vice-Chair may be removed by a majority vote of the Working Group.

Representatives to the Executive Committee and Council

Each Working Group has a voting representative on the Executive Committee and Council who is elected by a majority vote of the Group. The representative is responsible liaises with the Working Group Chair and Vice-Chair to maintain an overview of the activities within the Group, provides regular progress reports to the Executive Committee and Council, and represents the interests of the Group at meetings of the Executive Committee and Council. The representative to the Executive Committee and Council may be the Chair or Vice-Chair of the Working Group or a project team leader.
The term of office for the position of representative to the Executive Committee and Council is for two years in the first instance. The representative may resign from office at any time by giving notice in writing to the Working Group and the Head of the Secretariat. If it serves the best interest of the Consortium, the representative may be removed by a majority vote of the Working Group.

Project team leads

Project team leads are responsible for leading individual project team activities within a Working Group. They are accountable to and appointed by the Working Group based on their specific expertise and contributions to developing individual projects and protocols.
The tenure of project team lead is determined by the project requirements and is not time-limited. Project team leads may resign at any time by giving notice in writing to the Working Group. If it serves the best interest of the Consortium, the project team lead may be removed by a majority vote of the Working Group.

2.7.3 Conduct of business and accountability

Each Working Group project team establishes its own rules for conduct of business and work plan (including goals, objectives, timelines, critical milestones, monitoring and evaluation plans). In the absence of a contrary provision by the Executive Committee, a majority (i.e. > 50%) of all members of each Working Group present at a Working Group meeting constitutes a quorum for the transaction of a business.
Working Groups are accountable to the Executive Committee and Council. They report to the Executive Committee and the Council through their representatives and to the rest of the Consortium through a semi-annual report. Progress of Working Group activities is monitored by the Executive Committee and the Stakeholder Advisory Board. Working Group Chairs and representatives may be invited to report directly to the Stakeholder Advisory Board.

2.7.4 Endorsement of Working Group outputs and outward-facing activities

Protocols, documents for public posting, and manuscripts for publication generated by a Working Group need to be ratified formally by the Executive Committee in order to qualify for official endorsement as ISARIC output. At the discretion of the Executive Council, a publishing subcommittee can be formed to review manuscripts to be submitted in the name of ISARIC, and to address authorship questions.
Any documents submitted by a Working Group for ratification will be circulated to all members of the Council for comments. The decision of whether or not to ratify a submitted document will take into consideration those comments received in timely fashion from members of the Council. It is expected that the time from submission to initial feedback by the Executive Committee will be no longer than 4-6 weeks. Only outputs ratified by the Executive Committee can be published in the name of an ISARIC Working Group or the Consortium as a whole.
Any other outward-facing activities proposed by a Working Group (e.g. scientific colloquia, workshops) need to be formally ratified by the Executive Committee in order to qualify for official endorsement as ISARIC activity.

All members are free to publish without official endorsement any documents that encompass their own data and are not in the name of ISARIC. Likewise, outward-facing activities not endorsed by the Consortium are not limited by ISARIC membership.

2.7.6 Authorship on Working Group publications

Group authorship is the preferred form of authorship for manuscripts submitted in the name of the Consortium, for example:

- "The Inter-pandemic Trials Working Group on behalf of ISARIC"
- "Investigators of the ISIG study/project team", with contributions from individual ISARIC investigators and member networks acknowledged.

Ownership of samples and results remain with the individual investigators and networks.

2.7.5 Meetings of the Working Groups

Working Groups meet in person or via teleconference as required, but at least on a bi-monthly basis. Minutes of each meeting of the Working Groups are kept and are submitted to the Executive Committee. The Stakeholder Advisory Board can request to view these minutes if this is in the best interest of the Consortium.

Appendix I – ISARIC structure

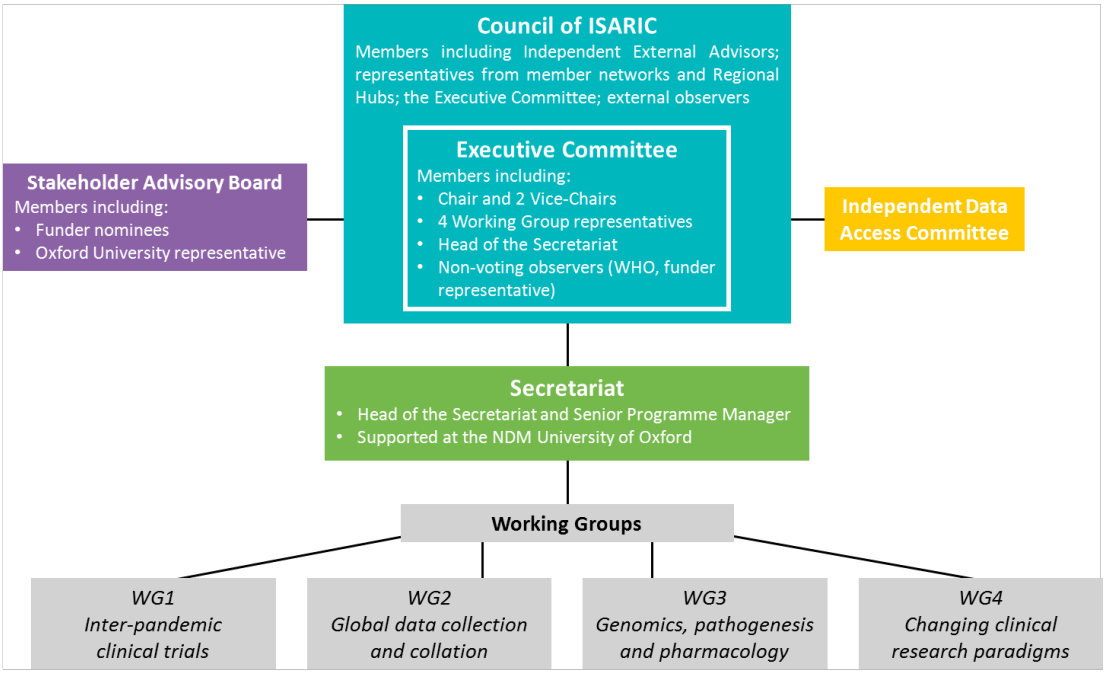

Figure 1: Structure of ISARIC.

Council:

- Steer the Consortium by providing scientific direction and overall leadership
- Hold the Executive Committee responsible for the operation of the Consortium

Executive Committee:

- Hold executive responsibility through the Chair
- Report to the Council
- Liaise with the Stakeholder Advisory Board
- Line manage the Secretariat

Secretariat:

- Coordinate the daily activities of the Consortium
- Support activities of the Executive Committee and Working Groups

Stakeholder Advisory Board:

- Help develop strategic vision
- Provide advice
- Identify funding opportunities

Independent Data Access Committee:

- Review and regulate external data requests

Working Groups:

- Generate ideas, concepts and study protocols

Appendix II – Working Groups

Working Group 1 – Inter-pandemic clinical trials

Description: This Working Group will develop candidate cross-Consortium studies based on both novel and traditional clinical trial designs that can be implemented in the inter-pandemic period.

Activities: Lead development of a minimum of three clinical trials for implementation in children and adults including low and middle income countries. Possible topics include but are not limited to: large pragmatic trials of community acquired pneumonia, immunomodulatory therapy in SARI, anti-viral therapy for influenza.

Critical Milestones: Finalisation of at least two protocols on therapeutic randomised controlled trials in SARI/community-acquired pneumonia within 18 months. Success in at least one application to major funding organisations during the first 24 months including the WT/MRC/DFID Global Health Trials, European Union, US National Institutes of Health, or Bill and Melinda Gates Foundation.

Monitoring and Evaluation Plan: The representative of the Working Group will report at least quarterly to the Executive Committee. Key funding opportunities will be tracked by the Secretariat and Executive Committee. Funding applications will be endorsed by the Executive Committee of ISARIC.

Working Group 2 – Global data collection and collation

Description: This Working Group will complete a global inventory of existing databases related to SARI and pandemic H1N1 among ISARIC and InFACT networks, undertake standardisation and harmonisation of definitions, and develop on-the-shelf pandemic/novel threat response protocols.

Activities: All partners and networks of ISARIC have agreed to share existing databases and work towards harmonisation of definitions to facilitate meta-analyses. This will include development of standards for tiered and minimal data sets that will be used for developing outbreak/pandemic protocols.

Critical Milestones: Development of an on-the-shelf, rapid- response pandemic/novel SARI threat response protocol including standard definitions, tiered datasets, and data-sharing mechanisms within 12 months. Decision on creating a clinical database for patients with SARI due to 2009 H1N1 infection within 12 months.

Monitoring and Evaluation Plan: The representative of the Working Group will report at least quarterly to the Executive Committee. The Executive Committee and Stakeholder Advisory Board will monitor progress. Pandemic protocols will be endorsed by the Executive Committee and Council of ISARIC.

Working Group 3 – Genomics, Pathogenesis and Pharmacology

Description: This Working Group will develop pathogenesis studies aimed at understanding the dynamics of host responses, host genetic factors in susceptibility, virus/host interactions, and pharmacokinetic-pharmacodynamic relationships in treated patients.

Activities: Assess existing evidence from studies in patients with SARI due to pandemic 2009 H1N1 and develop new protocols that address key questions regarding disease pathogenesis, host susceptibility, and pharmacokinetic-pharmacodynamic relationships including prevention of drug resistance.

Critical Milestones: Submission within 18 months of a protocol on host genetic studies in severe influenza; develop sample collection modules for pathogenesis and pharmacology studies to be added to both inter-pandemic and rapid-response protocols.

Monitoring and Evaluation Plan: The representative of the Working Group will report at least quarterly to the Executive Committee. The Executive Committee and Stakeholder Advisory Board will monitor progress. Funding applications will be endorsed by the Executive Committee of ISARIC.

Working Group 4 – Changing clinical research paradigms for rapidly emerging public health threats

Description: This Working Group will drive the critical evaluation of the barriers and the ethical framework required to facilitate the development of clinical research in response to a rapidly emerging health threat.

Activities: Assessing the ethics of clinical research in the context of epidemics, developing an open access module that will be part of the "*E-Research Hub*" and work towards pre-approved protocols, documents and reporting forms, and address other challenges for undertaking clinical research studies in rapidly emerging health threats. Build research capacity by assisting in the development of new and established research groups that can contribute to ISARIC studies.

Critical Milestones: Publication within 18 months of a systematic review of ethical, legal, contractual, funding, information-sharing and publication constraints to developing a rapid clinical research response. There is confirmation of the Symposium at the American Society of Tropical Medicine meeting in December 2011 that will be the formal launch of ISAIRC and a linked Symposium at the same meeting on the "*E-Research Hub*" and Open Access**.** This Working Group will convene two international workshops to address issues on ethical challenges of clinical research in the context of rapidly emerging health threats and the practical barriers to the successful implementation of clinical research in such settings.

Monitoring and Evaluation Plan: The representative of the Working Group will report at least quarterly to the Executive Committee. The Executive Committee and Stakeholder Advisory Board will monitor progress.