MEMORANDUM OF UNDERSTANDING BETWEEN THE PARTNER MEMBERS, AS SET OUT IN APPENDIX 1 IN RESPECT OF THE INTERNATIONAL RARE CANCERS INITIATIVE

This document is a memorandum of understanding among the organizations that initiated and intend to continue to work together to encourage the development of clinical trials in rare cancers through participation in a joint program known as the International Rare Cancer Initiative, the IRCI.

Mission

The mission of the IRCI is to make clinical trials in rare types of cancer practicable through international collaborations.

Functions of the IRCI

The IRCI…

1. …brings together international experts in rare cancers and member organizations that have the capacity to perform clinical trials across national boundaries.
2. …is a forum for member organizations to prioritize global rare cancer strategies.
3. ...coordinates discussion of clinical trials in cancers that otherwise lack international organizing infrastructure.
4. …facilitates review of concepts and protocols by member organizations.
5. …works to lower barriers to performance of international clinical trials in cancer.
6. …provides a common voice for academic clinicians to approach industry for worldwide collaboration in rare cancer clinical trials.

Rationale

The member organizations have undertaken this initiative because:

1. Some cancers are so rare that accrual from individual networks would not provide enough patients to perform meaningful clinical trials. One important way to make progress in these cancers is to merge the accrual base of several organizations.
2. Rare cancer trials are resource-intensive, but the burden can be spread among multiple collaborators.
3. Long trial duration is a common reason for trial failure and also a major determinant of trial cost. International accrual may shorten trials and allow more rapid development of treatments.

4. Aside from the benefit of studying rare cancers in their own right, it is likely that the exploration of rare cancers will provide insight into mechanisms applicable to other diseases.
5. The linkages and joint processes developed in this initiative may facilitate international collaboration in more common cancers and in biologically-defined subsets of those cancers, which may increasingly become the focus of future trials worldwide.

Participation

International and national organizations with the capacity to participate in international cancer clinical trials and associated funding bodies are welcome to join the initiative, with the expectation of contributing to support the core operation of this initiative and subject to consensus approval by the existing membership as set out in Appendix 1

Expectations

IRCI member organizations intend to…

1. Meet at least twice each year to review ongoing trials, consider additional trials or diseases, and to discuss administrative issues.

2. Contribute to the success of this joint effort by:

    a. Providing financial or other support* to the initiative to enable central administrative support based at CR-UK and provision of travel assistance to its own members to attend related meetings and conferences.

    (*EORTC intends to support a full time IRCI project manager after 2012)

    b. Providing in kind assistance to the initiative in the form of contributing scientific and regulatory expertise and hosting of face-to-face meetings on a revolving basis.

    c. Actively participating in the solicitation and review of trial concepts and protocols for rare cancer clinical trials.

    d. Working to minimize overlap in rare cancer portfolios, and to prioritize diseases that are of common interest to multiple collaborators.

    e. Following the processes outlined below.

Processes

Governance

The IRCI is intended to be a relatively informal group, with emphasis less on its own administration than in making international rare clinical trials happen. Nonetheless, some structure is desired to cement the association together and to keep it functioning smoothly.

1. The IRCI should be governed by a board of directors (BOD).

a. Each member organization should appoint one member to the IRCI BOD. To do this, an appropriately empowered individual within the member organization should send a letter of appointment to the chair of the IRCI BOD. There is no term limit for BOD members, and the appointing organization can change their BOD member at any time. The duty of a BOD member is to actively participate in BOD meetings. BOD members may invite additional people from their organization to attend a BOD meeting.

b. The IRCI should have three officer positions, with specific duties. Any member of the BOD can be nominated to this role, and election is by majority of the BOD members present at a BOD meeting. Elections should be held every two years. At least one officer should be present at all meetings related to the IRCI.

   These officer positions are:

   i. Chair: Responsible for strategic and scientific leadership of the initiative, overall organization and continuity of projects. The Chair should be identified as the primary contact for the initiative to external parties.

   ii. Vice-Chair: The Vice-Chair should assist the Chair in any manner the Chair requests.

   iii. Secretary: The primary responsibility of the secretary is to maintain documentation and administrative coordination of the initiative.

c. Board Procedure: The intention is that BOD meetings avoid formal procedure whenever possible. To obviate detailed bylaws specific to the IRCI, BOD procedures may default to Robert's Rules of Order, unless these are superseded by this document.

Meetings

1. BOD members should receive notification of upcoming BOD meetings at least three months in advance.

2. Every effort should be made that BOD members receive notification of other meetings or teleconferences.

3. The IRCI should archive minutes and supporting documents on the IRCI website.

4. Records of the IRCI should be placed in the public domain as far as possible, with the exception of information covered by confidentiality agreements with

third parties and information that a member organization is not permitted to release according to applicable law or regulation.

Interaction with Industry

1. It is intended that all trials undertaken by the IRCI members preserve the following principals of independence of academic research:

    a. Concepts should undergo transparent peer review.

    b. Trial databases should remain in the hands of academic trial organizations.

    c. Except for correlative studies that do not compromise the primary endpoint, trial results should not be released until publication of primary endpoints.

    d. Trial databases should not be shared until primary analysis is complete.

2. Exploratory discussions with industry by any member are fine, but any proposal or agreement in the name of the IRCI should be issued by the IRCI BOD through its officers.

3. All trials undertaken by the IRCI should strive to support participation of all members.

4. Neither IRCI nor IRCI members should permit industry to impose or otherwise place restrictions or constraints on data or results publication.

Disease / Trial Selection

1. New trials can be brought into the IRCI portfolio in one of two ways – the IRCI BOD can agree to prioritize a disease and call through its members for corresponding proposals, or a member organization can approach the IRCI for collaboration when it knows of a suitable trial evolving within its own ranks. Preferably, new trial designs will be developed jointly through the IRCI.

2. Solicited diseases

    a. After BOD members consult with their respective organizations, the BOD may identify specific diseases for emphasis, and organize a working group of experts to consider background information, the current landscape, and potential trial opportunities.

    b. When a disease is selected for development, each member organization should search for experts within its constituency.

    c. An expert Disease Chair may be appointed to a disease working group by the IRCI BOD. The IRCI may organize the initial meeting for the working group, but an administrative officer can organize follow-on meetings. The Disease Chair may liaise with the BOD, providing updates about progress.

d. The BOD may review progress of each working group on a biyearly basis, providing feedback to the group after each evaluation. If there is no immediate prospect of a trial, the BOD may designate a disease as inactive, and no further follow up should occur unless the BOD is approached with new information.

Clinical Trial Development

1. The IRCI serves as a central forum for development of new international clinical trials in rare cancers, and investigators are urged to reach consensus in this forum. However, the IRCI itself does not approve trials on behalf of its member organizations. A clinical investigator developing a new concept should submit the concept to his/her respective member organization through normal review channels. That organization is the "trial lead" organization and may approve, disapprove or request modification of the concept, per its standard procedures.

2. Once the trial lead organization has endorsed a concept, the concept should be forwarded to other member organizations that have expressed interest. Typically, this takes place prior to protocol development. The other organizations should follow their own review procedures, but for the sake of efficiency, may opt to accept the review of the trial lead organization. Rapid feedback on the concept should be channeled to the study investigator, with the intention of informing protocol development.

3. Protocols should be developed according to the style of the trial lead organization. Collaborating organizations may prepare organization-specific appendices to override portions of the common protocol according to their own requirements. The trial lead organization should assure that the organization-specific appendices do not conflict with the overall protocol.

4. The trial lead organization may or may not have structural capacity to run a particular clinical trial. In such a case it may rely on a different structure to effectively run the trial under its scientific overview and supervision. In such case, the trial lead organization should privilege partnerships with member organizations within IRCI having adequate infrastructure to execute the required activities. Such a partnership may be established by approaching an IRCI member of the choice of the trial lead organization or through an open call. This condition should be made clear for industrial partners (if any) from the very beginning.

5. It is preferable to develop a common protocol, but in exceptional circumstances, the IRCI may permit implementation of parallel protocols, stipulating that each protocol be independently powered for a self-contained primary endpoint, and that the statistical section describe a planned meta-analysis referencing the external protocol. This latter model is deprecated based on past experiences where individual studies have diverged, confounding the meta-analysis.

6. Prior to the launch of a trial, collaborating organizations should designate sub-principal investigators. A trial management group should be constituted from the principal investigator (PI), sub-PIs, and trial operations personnel from member organizations. This trial steering committee should meet as required to maintain coordination across the involved organizations.

7. Collaborating organizations should work together to minimize the number of trial amendments.

8. A clinical trial can be badged as an IRCI initiative as long as two member organizations agree to conduct the trial.

9. An IRCI project manager should ensure optimal coordination between the various participating groups and coordinating offices once a project is entering development and activation.

Results and Publication

1. IRCI members intend that results of all clinical trials performed under this initiative should be published in a timely manner in a peer-reviewed, open access journal, regardless of whether the trial was successful or negative, or whether the result was statistically significant. Similarly, results from correlative studies using biological material obtained in an IRCI trial should be published in a similar manner.

2. Publications should conform to the CONSORT guidelines and to the International Committee of Medical Journal Editors guidelines on authorship.

3. Authorship:

    a. A protocol specific agreement between lead and collaborating organizations should prospectively specify the authorship policy agreed between the participating groups. Each protocol specific agreement should identify the lead data center. The lead data center is where data from each collaborating organization should be collected and coordinated.

    b. The senior author on the publication is the principle investigator from the lead organization.

    c. At least one author position should be attributed to each participating organization that contributed patients to the study.

    d. For additional co-authors or for a fixed total number of co-authors, the number of co-authors from a given organization is proportionate to the total number of patients that the organization contributed to the study.

e. In addition, two representatives from the lead data center for each project should be included as co-authors.

f. Subject to expectations regarding publication, it is intended that each collaborating organization will own data collected from its respective clinical trials network(s).

g. Representatives from the industry are generally not intended to be co-authors on publications of IRCI study results. Their contribution in name may be acknowledged with that of other scientific contributors. Deviations from this rule should be agreed by a majority of the IRCI BOD.

4. Members intend to encourage Senior Authors to abide by the following responsibilities:

   a. Writing a first draft of the publication in a timely manner for review of all co-authors, their organizations, and the IRCI BOD.

   b. Ensuring that all authors have seen and approved the final manuscript prior to submission.

   c. Submitting the final manuscript of the article to a peer-reviewed journal once it has been approved by all co-authors, their organizations, and the IRCI BOD.

   d. Reviewing the proofs of publication and answering any "letter to the editor" that the publication may have raised.

   e. The principle investigator from the lead institution is usually the senior author of the primary study publication.

5. Each collaborating organization would own data collected from its respective clinical trial network(s), but should not publish or otherwise make those data available to external parties (e.g., any institution which is not a collaborating organisation) prior to the publication of the primary trial results.

6. IRCI should be acknowledged in the title page or acknowledgement.

Public Relations

1. All public relations inquiries should be directed to the Chair of the BOD to ensure consistency of message.

2. All press releases should be approved by the IRCI member(s) named in the release.

New members

1. A new member may be accepted:

a. After sending a request to the chair (request should come from the new member's signatory or any other person having the authority to engage its organization in such an activity)

b. After consensus determination of the Board of Directors.

c. After having read the terms of this memorandum of understanding, and agreeing to be bound of it by signing the attached New Members Admission Form (Appendix 2).

d. On receipt of the signed New Members Admission Form, the Board of Directors shall nominate and authorise a Partner Member to countersign the New Members Admission Form on behalf of all the Existing Partner Members.

Amendment and Termination

This document can be revised subject to unanimous consent of all BOD members. Any member can cease cooperation under this memorandum of understanding at any time and should endeavor to give 30 days' notice to the other members. This document does not create any binding obligations. Projects and activities under the memorandum of understanding are intended to be subject to the availability of personnel, appropriated funds and other resources.

Signed on behalf of the UK National Institute for Health Research (NIHR) Cancer Research Network (UK NCRN)

_____ _____
Name Date

_____
Title

Signed on behalf of Cancer Research UK (CR-UK)

_____ _____
Name Date

_____
Title

Signed on behalf of the US National Cancer Institute (US NCI)

_____ _____
Name Date

_____
Title

Signed on behalf of the European Organisation for the Research and Treatment of Cancer (EORTC)

_____ _____
Name Date

_____
Title

Signed on behalf of Institut National Du Cancer (INCa)

_____ _____
Name Date

_____
Title

Signed on behalf of the Canadian Cancer Trials Group (CCTG)

_____ _____
Date

_____
Director, CCTG

_____ _____
Date

_____
Director, Industry Partnerships & Innovation Park
Queen's University at Kingston

Memorandum of Understanding Appendix 1

Existing Partner Members of the International Rare Cancer Initiative

1. THE UK NATIONAL INSTITUTE FOR HEALTH RESEARCH (NIHR) CANCER RESEARCH NETWORK (UK NCRN)
2. CANCER RESEARCH UK (CR-UK)
3. THE NATIONAL CANCER INSTITUTE (US NCI)
4. THE EUROPEAN ORGANISATION FOR THE RESEARCH AND TREATMENT OF CANCER (EORTC)
5. THE INSTITUT NATIONAL DU CANCER (INCa)
6. THE CANADIAN CANCER TRIALS GROUP (CCTG)

Memorandum of Understanding Appendix 2

Template New Members Admission Form

By their signature to this document the new member confirms that they have read and have understood the terms including all rights and obligations in the attached Memorandum of Understanding and agree to be bound by it. Additionally on signing this document the new member shall be treated as being a full participating member of this International Rare Cancer Initiative.

After the consensus of the Board of Directors (BOD) about the admission of the new member determined the xx/xx/xxxx and the authorisation given the xx/xx/xxx by the BOD to the Partner to sign these present Admission Form on behalf of all Existing Partners Members.

Signed on behalf of _____

_____ _____
Name Date

_____
Title

Signed by _____

for and on behalf of all the existing members listed in Appendix 1.

_____ _____
Name Date

_____
Title