Developing an international network for clinical research: the Community-Acquired Pneumonia Organization experience

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Clinical research can be defined as the generation of new knowledge in the medical field by performing studies that involve patients with a specific disease. The basic steps for the development of a clinical research network are: creation of a steering committee, development of a network core study, establishment of a network coordinating center, delineation of network research opportunities and definition of the publication policy. Models for international collaborations among clinical investigators will continue to emerge as a methodology for performing research on large numbers of subjects. A well-established network is a very effective mechanism in the generation of new knowledge in a particular medical field.

Keywords: clinical research • network • pneumonia

Clinical research can be defined as the generation of new knowledge in the medical field by performing studies that involve patients with a particular disease. Since the clinical research interest of the authors is in the field of pneumonia, in this article we will describe our experience with the development of an international network for clinical research in pneumonia. However, the steps described in this manuscript can be applied to the development of a network for clinical research in other fields.

The authors are members of the Community-Acquired Pneumonia Organization (CAPO), an international network of clinical investigators in the field of pneumonia. The objective of this manuscript is to describe the basic steps for the development of a clinical research network based in our experience with the CAPO project.

Steering committee

The first step in the development of a network is to identify a core group of individuals with a common interest in clinical research in a particular field. The number and qualifications of individuals in the core group will vary depending on the scope of the project. It is advisable to include members who have a good understanding of the process of clinical research including study design, data management/analysis and medical writing. Previous experience conducting clinical studies is a necessity.

There are three major areas to explore when choosing members of the core group:

• Those with a high number of peer-reviewed publications. By choosing a core group with members who publish their work regularly, one can reasonably expect that they have a good understanding of the process of clinical research;

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- Those with a diverse background. By choosing a core group of investigators with diverse backgrounds, the projects will have access to a broader array of research questions and ideas;
- Those in geographic proximity or with ease of contact. By choosing a core group with members that are easily reachable in person or via electronic means, the likelihood of success will greatly increase. Multicenter international collaborations are now easier to perform due to the development of internet-based clinical research.

Investigators in the core group will form the Project Steering Committee. The steering committee is the main governing body of the network and provides the overall research framework for the network. One of the primary responsibilities of the steering committee is to identify and prioritize topics for investigation with the goal to define the initial core study for the network. The steering committee should evaluate proposed core studies considering the scientific merit and the feasibility according to the network capabilities.

After the core network study is implemented, the steering committee will need to evaluate any proposed core study protocol amendments, ancillary studies or secondary analyses of the core study database.

In our experience with CAPO, the original group of investigators that formed the CAPO steering committee was a selected group of the original members of the American Thoracic Society Committee for the development of national guidelines for the management of community-acquired pneumonia (CAP) [1]. It is important for members of the steering committee to be 'hubs' in their field, which involves having a great deal of research experience and contacts that will generate the social network web of information. Members of the original steering committee included:

- N Dean, University of Utah, Salt Lake City, UT, USA
- T File, Summa Health System, Akron, OH, USA
- LA Mandell, McMaster University, Ontario, Canada
- TJ Marrie, Dalhausie University, Halifax, Nova Scotia Canada
- MS Niederman, Winthrop University Hospital, Mineola, NY, USA
- A Torres, Hospital Clinic, Barcelona, Spain
- J Ramirez, University of Louisville, Louisville, KY, USA

Each one of these investigators was instrumental in giving advice regarding the initial steps in the development of the CAPO network. It was considered necessary to create an initial research protocol that would constitute the primary protocol or core study of the organization. The CAPO steering committee considered that funding from the industry could be sought to finance the initial steps of the network, as long as the funding has no impact on the selection of projects or integrity of the data.

Members of the steering committee are likely to change regularly due to time commitments. Renovation of members of the steering committee will bring new ideas to the organization.

International site selection

Another important role of each member of the steering committee is to contact members who may like to participate in the network. It is important to identify investigators for whom CAP is their primary research interest. These investigators will have a track record of publications related to pneumonia. Some of these investigators will already be in the social network of the steering committee, and others may be identified through literature searches. The ultimate goal of the international site selection is to have a network that will have a balanced global representation. This will allow maximal generalizability of study results.

Network core study

New knowledge in the field of pneumonia is considered of the highest level of evidence if data is obtained by performing prospective, randomized clinical trials. However, this type of clinical research requires considerable funding and a large time commitment on the part of the investigator and other study personnel. Since a significant amount of time and funding are unlikely during the initial steps in the development of a network, it is recommended to consider other study designs. The most cost-effective approach to generate new information is for the network to perform observational analytic studies.

The first step in identifying a core study is to develop a broad research question. A good research question will provide a concrete and measurable outcome to study. This research question forms the basis for the core study.

The CAPO steering committee agreed that the initial CAPO core study needed to have a retrospective cohort design in order to facilitate implementation of the research protocol using minimal resources at the local level. It was also important for each investigator to commit some local resources for the collection of study data. The primary resource that must be committed includes time for a local person in charge of data collection.

A full description of the CAPO study protocol, study manual and data collection form are available at the organization's website [101]. The core clinical study is entitled 'An international observational study to evaluate the current management of hospitalized patients with community-acquired pneumonia'. There are currently more than 6500 cases of hospitalized patients with CAP enrolled in the CAPO core study, representing 46 institutions from 16 countries over 9 years.

The primary objective of the CAPO core study is to evaluate the quality of care delivered to hospitalized patients with CAP. This is to be accomplished by defining current management of hospitalized patients with CAP and the proportion of patients who are managed in compliance with respective national guideline recommendations. The core study protocol and data collection form were developed with input from members of the original steering committee.

Each participating center in the CAPO project has local institutional review board (IRB) approval of the study protocol. As this is an observational study, all IRBs have waived the need for informed consent. Forms with identifying information are maintained separately from electronic files in a secure filing cabinet at each of the study sites. Participants are assigned a study identification number, and names are not used on any CAPO documentation. Data are initially collected using paper data collection forms at each participating site and then entered into a worldwide web data collection system and submitted to the CAPO network coordinating center via the study website [101]. The availability of a website for real-time reporting of data is an essential tool for increasing the reach of international research collaborations.

Network coordinating center

Every network needs to have a central place that will coordinate the project in order to maintain an organized study. This network coordinating center may have different levels of responsibilities. Minimally, the center needs to manage the administrative aspect of the project, such as the sharing of information and study materials with study sites.

The network coordinating center should also coordinate a number of other activities. It should develop and maintain the web-based programs to support internet-based clinical research, as well as the project website, which must include all party's contact information, the study protocol, case report forms and other administrative documents.

The CAPO network coordinating center was established at the Division of Infectious Diseases of the University of Louisville. At the present time the center coordinates the administrative aspects of the project, acts as a data coordinating center and as the project statistical coordinating center. The organizational structure of the center consists of a director, a project manager and eight other positions responsible for statistical support, database development and website development, as well as grant, manuscript and administrative support. The CAPO center currently supports and manages the core CAPO study as well as other CAPO-sponsored clinical research projects.

In relation to the core study, the center provides training to clinical site staff regarding data collection, data system access and remote data entry. Once a local site submits a case, the center performs quality control of the data. After all queries are appropriately addressed, the case is entered into the CAPO database.

The multidisciplinary members of the center include three part-time statisticians from the School of Public Health and Information Sciences at the University of Louisville, KY, USA, as well as one full-time data analyst within the Division of Infectious Diseases, who provide statistical support for the CAPO core study as well as for all other CAPO research projects. The primary current activities of the CAPO coordinating center include:

- Developing the study database and website
- Maintaining administrative and institutional review board documents
- Coordinating research
- Providing data quality control
- Providing data management
- Performing secondary data analysis
- Coordinating ancillary studies
- Supporting the preparation of abstracts for presentation and manuscripts for publication
- Organizing meetings for the steering committee
- Organizing the annual meeting of international CAPO investigators

Network research opportunities

The primary goal of the network is to facilitate collaboration in clinical research. To achieve this goal the network should offer investigators as many research opportunities as possible. Here we will describe possible research opportunities that a network can offer, with examples from the CAPO network.

Analysis of the CAPO network core study

The CAPO core study is evaluating the current management of hospitalized patients with CAP. Using data from the CAPO core study, investigators have evaluated different areas of the management of hospitalized patients with CAP [2,3]. Recently, Aliberti *et al.* evaluated the management of hospitalized patients with CAP in regard to duration of antibiotic therapy [4]. Investigators in a particular region have also evaluated the actual management of CAP. Under the leadership of Luna, a CAPO network was developed in Argentina to evaluate quality of care in hospitalized patients in that country [5]. More recently, under the leadership of Levy, a network was developed in Venezuela.

Unlike CAP clinical trials, participants in the CAPO observational cohort study include those patients with more complex medical problems. Patients are not excluded for participation if they are at high risk for poor outcomes. The CAPO cohort therefore more closely reflects the real-world experience of hospitalized patients with CAP as compared with many clinical trials.

Secondary analyses of the CAPO network core study

Another research opportunity is for investigators to use the CAPO database to answer research questions other than the main ones for which the data were originally obtained. Performing clinical research using existing data, defined as secondary data analysis, has the advantage of reducing the time and cost necessary to answer a research question.

Although several investigators are currently involved in the design and analysis of secondary studies utilizing the CAPO database, their numbers are not sufficient to fully explore the available data. An important way in which the CAPO project can help new investigators is by providing access to the CAPO database. Investigators with an interest in pursuing analysis of the CAPO database may contact the CAPO network coordinating center at the University of Louisville.

Two recent CAPO publications, one evaluating the role of neutropenia in the outcomes of cancer patients with CAP [6], and another evaluating the use of the pneumonia severity index as a predictor for time to clinical stability, were performed using a secondary data analysis of the CAPO database [7].

Ancillary studies to the CAPO network core study

A third research opportunity is for investigators to propose a modification of the core cohort study protocol to collect new data that will help to answer a new research question. These types of studies, defined as ancillary studies, have the advantage of being efficient and inexpensive. Proposed ancillary studies that require the addition of a significant number of variables to the core study protocol need approval by the steering committee.

These ancillary studies are defined as CAPO substudies. Investigators agreed to add an ancillary study to evaluate criteria for clinical failure and the etiology of clinical failure during the first 7 days of hospitalization for all patients enrolled in the CAPO core study [8]. Under the leadership of Bordon, the CAP HIV substudy evaluating the outcomes of HIV patients with CAP was recently completed.

• Studies of emergent pathogens using the CAPO network

The network is ready to answer questions in regard to emerging clinical challenges in the field of pneumonia. The newly recognized H1N1influenza A virus provided a near real-time opportunity to study this emerging pathogen. The CAPO network coordinating center quickly modified the case report form to include influenza-specific items and the study database was modified to accept these new fields. Within a few months of the start of the pandemic, over 300 cases of CAP due to H1N1 were entered into the database and were ready for analysis. The initial analysis of cases from Chile culminated with a recent publication in the *European Respiratory Journal* [9]. A comprehensive analysis of the H1N1 cases from different regions has been recently submitted for publication.

Combining pneumonia networks databases

A fourth research opportunity is for investigators to combine data from CAPO with another database to generate a more powerful data set. Data from CAPO regarding antimicrobial use and outcomes were recently combined with an international database of atypical pathogens in CAP. The analysis of the combined databases culminated in a manuscript describing the incidence and outcomes of atypical pneumonias [10].

Proposing new study protocols to the CAPO network

A final research option is for investigators interested in implementing a new study protocol using the current CAPO network infrastructure. Members of the steering committee will evaluate the feasibility of protocol implementation. The CAPO network coordinating center was used in a recent NIH proposal for a new study protocol using some investigators from the CAPO network. The CAPO network coordinating center will manage elements of study planning and logistics, training, monitoring and communications, online subject enrollment and randomization, data collection, data management and data analysis for this prospective randomized clinical trial of antimicrobial therapy in CAP.

Publication policy

One of the primary goals for investigators to participate in the network is to facilitate the generation of manuscripts and publications. The network should have a clear policy regarding authorship. A publication committee clarifies the order and role of each author. Some authors provide a focused contribution such as analyzing and interpreting data or drafting part of the manuscript. Others may provide a supervisory role, helping with the concept and design or critically revising the manuscript.

The CAPO publication authorship guidelines have been developed with the goal of maintaining a fair authorship distribution. The investigator with an original idea to perform an evaluation of the database and who is willing to spearhead the study will be the leading author on the manuscript. Other investigators will be invited to work on the project in various roles. This will constitute the remaining authors. The selection of investigators invited to participate in a particular project is based on the number of cases collected and entered into the CAPO database during the prior year of the study. Authors are encouraged to include, at the end of the list of authors, 'and the CAPO investigators'. At the end of the manuscript, an appendix is included with the list of all participating CAPO investigators. This mechanism allows all participating investigators to obtain credit for their work.

Maintaining an active research network

A network can be developed with the goal of studying a predefined number of patients from a finite period of time. Another model is to develop a network with the goal to conduct a longitudinal study with no predefined end point. The challenge with this type of ongoing model is that all members of the network must maintain a high level of enthusiasm. Since the primary goal for participating in the network is to generate publications, the most important factor for active participating of investigators is for the network to generate a steady flow of publications. During the initial years of the network, abstracts and posters will be the primary network output.

Some of the methods used by the CAPO network to maintain an active organization include organizing regular CAPO investigator meetings, providing educational opportunities in conducting clinical research, regularly updating the CAPO study website and generation of a monthly CAPO newsletter. The use of free web-based video conferencing software such as SkypeTM can greatly increase the possibility of communication among members of the network.

Another important aspect to maintain an active network is to facilitate the addition of new members into the network. New investigators will bring new ideas for research as well as for network advancement. To maintain growth in any research network, it is important to apply principles of social network theory. The network steering committee is usually formed by a group that is tightly connected that shares the same core information. It is important to nurture 'weak ties' to other core groups with different primary interests [11]. This will bring the necessary innovation for the networks success.

Funding a research network

In our experience with the CAPO network, the initial funding for the network was obtained from industry. After the initial budget was developed, several pharmaceutical companies were approached to have equal share of the costs. This approach was used to prevent the network from being perceived as influenced from a specific company. After the network is implemented, it is important to actively seek out new funding sources. The network will be in an optimal position to apply for industry-sponsored clinical trials in their particular area of expertise.

Once the network matures and evidence of active research is demonstrated by peer-reviewed publications, the network will be in a position to apply for funding from the NIH, CDC, or other governmental sources. One limitation of governmental sources is the fact that funding for clinical research is generally awarded to centers within the USA. Better recognition of the need and benefits of international collaboration will change public policy and increase funding for international research.

Conclusion

As the management of hospitalized patients becomes increasingly complex, studies with large numbers of patients will be necessary to answer many emerging questions. Models for international collaborations among clinical investigators will continue to emerge as a methodology for performing research in large numbers of subjects. The CAPO project represents a successful and cost-effective model of international research in the area of CAP that can be applied to other areas of clinical research. The CAPO network is fulfilling its original goal to foster international collaboration in the field of pneumonia research.

In this article, we have presented our experience with the development of an international network for clinical research. The process requires a high level of commitment and organizational capabilities, but a wellestablished network is a very effective mechanism to generate new knowledge in a particular medical field.

Future perspective

The NIH and other research organizations are recognizing the critical role of clinical research for the advancement of human health. The new science of clinical translational research is based on a close interaction between basic researchers and clinical researchers. As newly generated data from laboratory research need to be applied to a specific patient population, it is becoming more difficult to recruit the necessary number of patients to reach adequate statistical power. In the near future, international research will not be an option but a necessity as a large number of patients with a particular clinical condition will need to be studied in a timely fashion.

Executive summary

- This manuscript describes the basic steps for the development of a clinical research network.
- The first step in the development of a network is to identify a core group of individuals with a common interest in clinical research in a particular field.
- The ultimate goal of the international site selection is to have a network that will have a balanced global representation.
- The most cost-effective approach for the network core study is to perform an observational analytic study.
 Every network needs to have a central place that will coordinate the project to organize the core study and manage the
- administrative aspects of the project.
- Since the primary goal of the network is to facilitate collaboration in clinical research, the network should offer investigators as many research opportunities as possible.
- The network should have a clear policy regarding authorship.
- Development of a study website and generation of a monthly newsletter are some of the methods to maintain an active research network.
- Initial funding from pharmaceutical industries should be sought.
- Generation of an international network for clinical research requires a high level of commitment and organizational capabilities, but a well-established network is a very effective mechanism to generate new knowledge in a particular medical field.

Financial & competing interests disclosure

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Website

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