The warm base network

An innovative approach to selecting the best sites for your clinical trial

ecraid

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Introduction

In clinical trials time is of the essence. Patients, healthcare providers and policy makers are best served when the potential benefits of new diagnostic, treatment or preventive strategies are identified as quickly as possible. They share this interest with the pharmaceutical industry for which shorter time-to-market results in faster return on investment. While efficiency is a crucial factor in clinical research, it should go hand in hand with a focus on *quality* because reliable and solid conclusions are the ultimate goal.

One key clinical trial aspect that can have a dramatic impact on both the trial's efficiency and quality is site selection. Choosing the best sites for recruitment of patients is essential for ensuring the quality of the collected data, realising ambitious study timelines, and limiting the costs of the project. Therefore, the site selection process itself should be optimised through clear communication and considerable knowledge of the capabilities of potential trial sites.

Sites can be chosen for a trial on an ad hoc basis, or through a more structured selection process based upon detailed information on the capabilities of sites organised in a *warm base network*. A warm base network is a curated collection of trial sites focusing on specific research topics, which is continuously involved in clinical research and supported by an overarching coordinating body – a shovel-ready pharmaceutical or diagnostics trial platform.

The purpose of this white paper is to lay out the principles of a warm base network in clinical research and to showcase its advantages. It is not intended only for those who perform multi-centre clinical research themselves. We consider the insights offered here to be valuable to anyone who has a vested interest in finding the most suitable sites for their clinical trials and improving the efficiency and quality of research.

We first describe the general site selection process, as well as common issues associated with it. Subsequently, we explain the concept of warm base networks, their attributes, and advantages, and we offer advice on how to set up such a network. The paper concludes with a discussion of an existing warm base network, Ecraid's CLIN-Net.

Site selection for clinical trials

Site selection for clinical trials

Site selection is a comprehensive process which entails identifying and recruiting clinical sites and site investigators for participation in clinical trials. A site can be a hospital, research institute, clinical trial unit, general practitioner, or another entity that can include participants in a trial.

The importance of site selection

A well-designed site selection process is essential to ensure that the most suitable sites are selected for a particular clinical trial. This has a direct impact on the quality and duration of the trial, as the selected sites will determine whether: the targeted patient population can be assessed, the required number of participants can be recruited, and the study can be conducted within its budget and timeline whilst maintaining data quality and participant safety. Likewise, selecting sites which are *not* well suited for a trial's needs can lead to delays and added costs due to slow or inadequate recruitment, insufficient participant numbers, low data quality, etc.

The site selection process

Pre-selection

Site selection should be a standardised, objective, multistep procedure. It starts with pre-selection. In this phase, key selection criteria are established based upon the study protocol. These can include the patient population profile and access, staff availability and qualifications, facilities and equipment requirements, enrolment targets, regulatory and startup timelines, past performance, competition from concurrent trials, and desired geographical area.

Once a comprehensive list of selection criteria has been established, potential sites and investigators can be identified. This can be achieved through:

- The study sponsor's internal database of sites previously used;
- The use of an external database, e.g., a site network, national coordinator, local expert, or a Contract Research Organisation (CRO) within its own site network;
- Using online and offline directories;
- Publications of recent clinical trials within the studied indication;
- Postings on clinicaltrials.gov;
- Word-of-mouth references.

Feasibility questionnaire

At the end of the pre-selection phase, the site selection team drafts a list of compatible sites for the trial. Next, each person identified as a potential Principal Investigator (PI) for a site is sent an invitation for participation that assesses their initial interest in the study. If a site is interested in participating, they receive a survey that includes questions specifically tailored to the study and addresses each of the pre-defined selection criteria.

Evaluating the responses to the completed feasibility questionnaires and matching answers with the key selection criteria ensures that only the most appropriate sites are selected for participation. The feasibility questionnaire can also provide an early indication of the site's motivation and diligence while executing the trial, e.g., through the time it took for the questionnaire to be returned, or the apparent effort put into completing it.

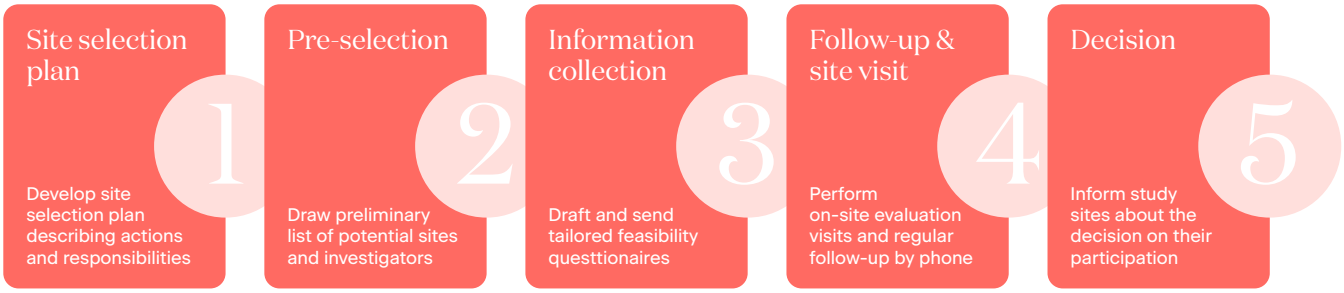
Site evaluation visits

If needed, on-site evaluation visits can then be conducted. These visits, also called site assessment or site qualification visits, are performed to verify that the site has the personnel, motivation, time, subject population, facilities, and equipment to adequately conduct the study. It is also used to establish a relationship with the PI and site staff, introduce the study in more detail, and communicate sponsor expectations. A visit is especially helpful if a site is new to the sponsor or indication, or if key site staff has changed since their last trial participation. After a visit has been conducted, a written report details all relevant findings, evaluates the site's suitability, and makes a recommendation for its inclusion.

Final decision

After all information is gathered, reviewed, and evaluated, an objective comparison can be made. The final selection is decided upon by the Sponsor of the trial, or by a Site Selection Board (SSB) which, in addition to members of the site selection team and Sponsor, can include project managers, expert advisors, or representatives of a CRO. All relevant findings based on the feasibility questionnaire and site visits are presented to the decision-maker to assist them with the final decision. Finally, the selected sites are notified of their selection status for the trial.

Figure 1. The site selection process



Common issues with site selection

Conducting a successful site selection requires considerable effort. Due to limited resources or insufficient knowledge, important elements or steps are sometimes overlooked, which can ultimately hinder patient recruitment and the ability of the trial to achieve its goals.

Frequent issues that arise during site selection can roughly be divided into three themes:

1. **Qualifications of the site**
2. **Site selection procedure**
3. **Expertise of the site selection team**

1. Qualifications of the site

— A general challenge for any site selection process is access to the right potential trial sites and investigators. Without an extensive database, it can be difficult to find sites with the appropriate expertise, staff availability and qualifications, facilities and equipment needed to carry out the study, and access to the target study population.

— Involvement and engagement of a site and principal investigator is another common challenge. While responsiveness of a potential site indicates suitability, lack of or delayed response is often a sign of insufficient time or motivation. Potential sites which fail to fill out questionnaires or attend a telephone conversation or online meeting will likely also lack the time or motivation to properly screen patients, update the database on a regular basis, or answer queries. Engagement of the site staff and PI is essential to actively recruiting and enrolling participants. If local staff is not motivated and committed to enrolling patients, the risk of failure increases considerably.

— A third concern when conducting site selection is not taking the contracting process into account. Contracting issues are a very common barrier to rapidly starting up sites and can severely impact timelines. Sufficient understanding of the local contracting processes and deadlines is essential. Also, involving early on the site administration staff in charge of contracting and budgeting often ensures an efficient and timely start-up.

— Sometimes a site that appears to be an ideal match for a study can have a less-than-ideal track record that is difficult to trace. To avoid making decisions based on incomplete information, knowledge of potential sites and individual investigators, including their past performance in other trials, will assist in predicting a site's fitness.

— Lastly, it is important to be aware of any other trials that will take place at a site during the same period. Concurrent trials can lead to competition for resources and/or participants, which might eventually impact start-up and recruitment goals.

2. Site selection procedure

— Challenges can also stem from the site selection procedure itself. Lack of a pre-defined, standardised procedure can severely impact site selection's efficiency and quality. Following well thought out procedures, on the other hand, ensures that all key selection criteria are covered and minimises the risk of overlooking important elements or steps.

— Linked to the previous challenge is a lack of document standardisation. The use of uniform templates for site selection documents (e.g., the feasibility questionnaire), allows assessment of specific aspects of the study to take place in an objective manner and according to set quality standards. Without this, comparisons between site evaluations and other key factors for informed decision-making might be arbitrary and unreliable.

— Finally, starting the site selection process without a clear description of the evaluation criteria can be detrimental to the outcome. Well-described selection criteria are imperative for successfully identifying the best sites for a trial and help facilitate an objective comparison between eligible sites.

3. Expertise of the site selection team

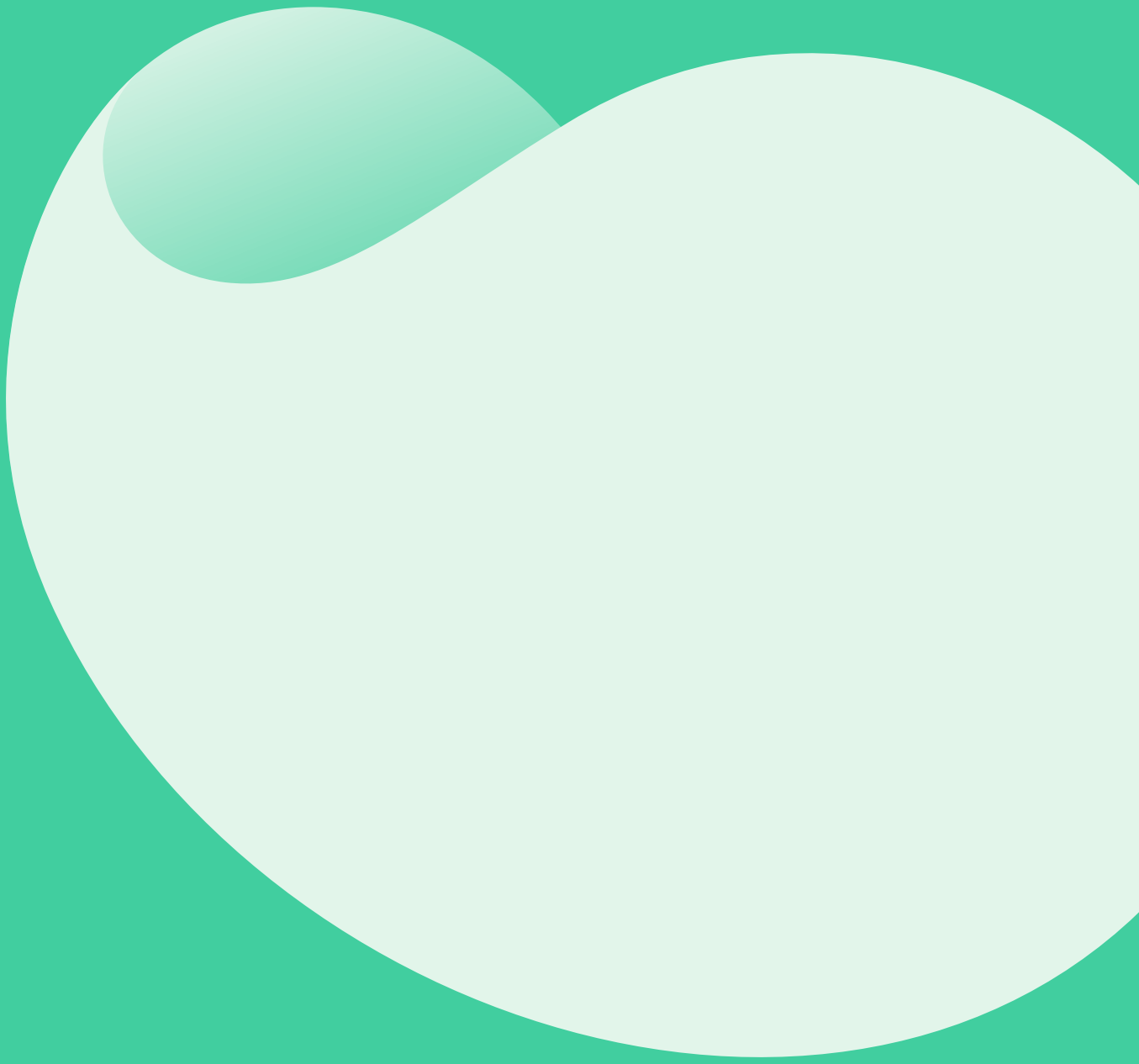
— A team that lacks knowledge of national and local regulations can be less effective in its site selection. Regulatory aspects can cause considerable time delays and even put the success of a trial at risk. Knowing which regulations are relevant for a particular trial, and, subsequently, which countries or regions are best suited for it, can optimise the set-up and outcome of a site selection process.

— A lack of knowledge of the prevalence of a specific disease or pathogen across countries and regions can affect the quality of site selection. Knowing which geographical areas are appropriate for the study and where to find sites with access to the right target population will result in a more effective site selection.

Warm base networks: an innovative approach

In order to ensure the success of a trial, professionals within the clinical research field are looking for ways to optimise the efficiency of executing clinical trials. One path towards that goal is the warm base network.

Warm base networks are an innovative approach to the set-up and management of clinical research that also helps avoid many of the challenges and pitfalls of the site selection process. In the next chapters, we explain our vision of the concept of a warm base network and its attributes and offer an example from the field of infectious diseases: Ecraid's CLIN-Net.



The warm base network

The warm base network

Traditional site networks

In its most common form, a site network is a group of sites suited for conducting clinical trials with a focus on a specific research topic (e.g., a specific range of pathogens or diseases) and/or in a specific geographical area. It can consist of different individual sites that are contacted and brought on board separately each time a new study starts. A network can also exist as one organisation that manages or even owns the sites, handling trial negotiations, contracts, and budgets centrally rather than for each site individually (e.g., UK's NHS trusts). Importantly, this traditional model usually involves a research collaboration anchored around a specific study or grant with a limited scope and timeframe.

Warm base networks

We see the warm base network as an advanced approach to organising sites for clinical research. Rather than a temporary collaboration, it is a *permanent* infrastructure in which trial sites with a common focus are engaged in recruiting patients in one or more clinical studies on a continuous basis.
A key capability of the warm base network is rapid adaptation, either through rapidly implementing new trials or through rapidly responding to new infectious disease threats.

Sites in a warm base network are specialised and experienced in clinical research and include a variety of clinical and laboratory settings. Their staff are experts at conducting trials and are able to understand specific patient needs during clinical research. Collaboratively, the network and its sites have the capability to facilitate all aspects of the study from design to regulatory submissions and contracting, to execution and reporting.

While the sites in a warm base network can be completely independent from each other in terms of management or ownership, the network's joint activities are supported by an overarching coordinating body. It ensures that common procedures, processes, and systems are in place to support the research teams. The central body also provides access to data collected from previous and active trials across its sites that can inform site evaluation and selection. Finally, it establishes and maintains professional relationships with trusted local experts and ensures consistency of communications with other internal and external stakeholders. Taken as a whole, this sustainable set-up facilitates quality, efficiency, and long-term continuity.

The defining characteristics of a warm base network are summarised in the "OPERATES" criteria.

Figure 2. The "OPERATES" criteria.

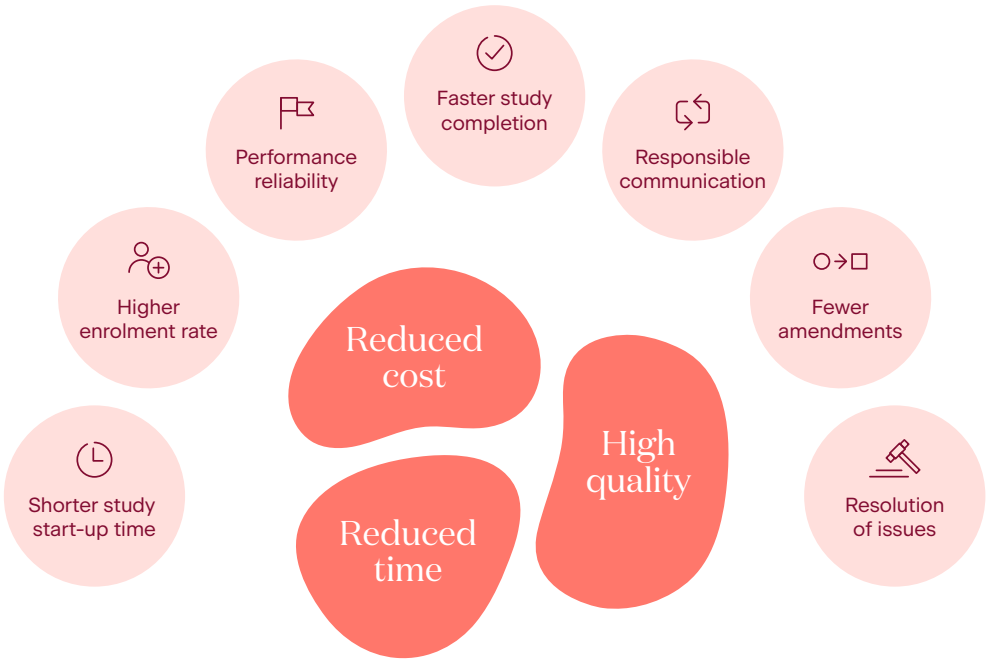
Advantages of a warm base network

Conducting clinical research using a warm base network offers several innate advantages:

1. **Single point of access**: Organisations conducting clinical trial projects can save time and resources by accessing a whole group of sites directly instead of having to approach individual sites.
2. **Operational readiness:** An existing network of suitable sites with a proven track record is available for a new study at any point, increasing efficiency and cost-effectiveness. This is especially valuable in cases when time is of the essence, e.g., during a health emergency such as the COVID-19 pandemic or the MPOX outbreak.
3. **Focused experience:** A warm base network harbours a broad range of expertise on individual diseases and multiple pathogens and is more likely to provide access to the appropriate patient populations across countries or in particular geographical areas.
4. **Uniform quality standards:** Centralised training activities ensure that staff within a warm base network of sites are trained with the same high-quality standards for ICH‘s Good Clinical Practice (GCP). In addition, a warm base network uses standardised templates and processes, which further contributes to uniformity and quality.
5. **In-depth site knowledge:** A warm base network’s coordinating body has access to centralised information collected from previous and active trials across multiple research sites, as well as the current status of disease incidence and prevalence, existing competitive trials, and past trial enrolment information. This information can be used for site evaluation and selection for new studies.

A warm base network benefits all stakeholders participating in clinical research. For the clinical trial sites and investigators it offers: access to various partners, a continuous flow of high-impact clinical trials related to their field of interest (helping to build and maintain their local research infrastructure), access to excellent scientific training opportunities, and best practices shared by fellow sites. For legislators, policy makers and industry, it provides a single point of access to a specialised network of experienced clinical trial sites capable of facilitating all clinical study aspects and delivering rapid, cost-efficient, and high-quality clinical research. In addition, a warm base network provides access to national and local experts with insight into local healthcare infrastructure, legislation, contracting procedures and politics.

Figure 3. Advantages of a warm base network



Setting up a warm base network

Warm base networks offer many benefits over traditional approaches to executing clinical trials. But they also require a substantial initial investment to set up. Creating a fully functioning warm base network takes time, commitment from legislators, partners and sites, and sufficient financial and human resources.

A coordinating body is needed to support all network-related administrative and operational tasks. This includes not only building the network of sites and contacts, but also developing and implementing common procedures and policies, and providing regular trainings to keep sites qualified and engaged. Such an organisation must also ensure continuous availability of trials and maintain effective communication and smooth operations across the network. Furthermore, it is expected to establish and maintain partnerships with local experts, networks, and key opinion leaders, build knowledge on national and local regulations, and develop excellent internal capacity for site selection. Last but not least, a robust IT infrastructure is required to facilitate all aspects of site selection, including maintaining an up-to-date site and investigator database, quantitative and qualitative performance measurements, ongoing trial metrics, etc.

A professionally maintained warm base network can strengthen clinical research in any field. In the next chapter, we showcase an example of a warm base network in infectious diseases: Ecraid's CLIN-Net.

CLIN-Net

CLIN-Net

CLIN-Net is a pan-European warm base network specialised in infectious diseases. Developed under the EU-funded COMBACTE and PREPARE projects, today it is managed by Ecraid – a non-profit foundation that advances clinical research in the field of infectious diseases in Europe. CLIN-Net spans over 1,250 clinical sites across 42 European countries[1] and is linked to LAB-Net – a network of 900 laboratories. Relying on more than 4,000 contacts, it delivers rapid, cost-efficient, high-quality clinical research services to public and private partners. From regular hospital wards to emergency rooms (ER) to intensive care units (ICUs), CLIN-Net offers access to a unique clinical research infrastructure that has enrolled over 52,000 patients in 48 studies.

52,000

patients have been enrolled

1 This number includes Israel and Turkey, in line with the Innovative Medicines Initiative's definition of Europe.

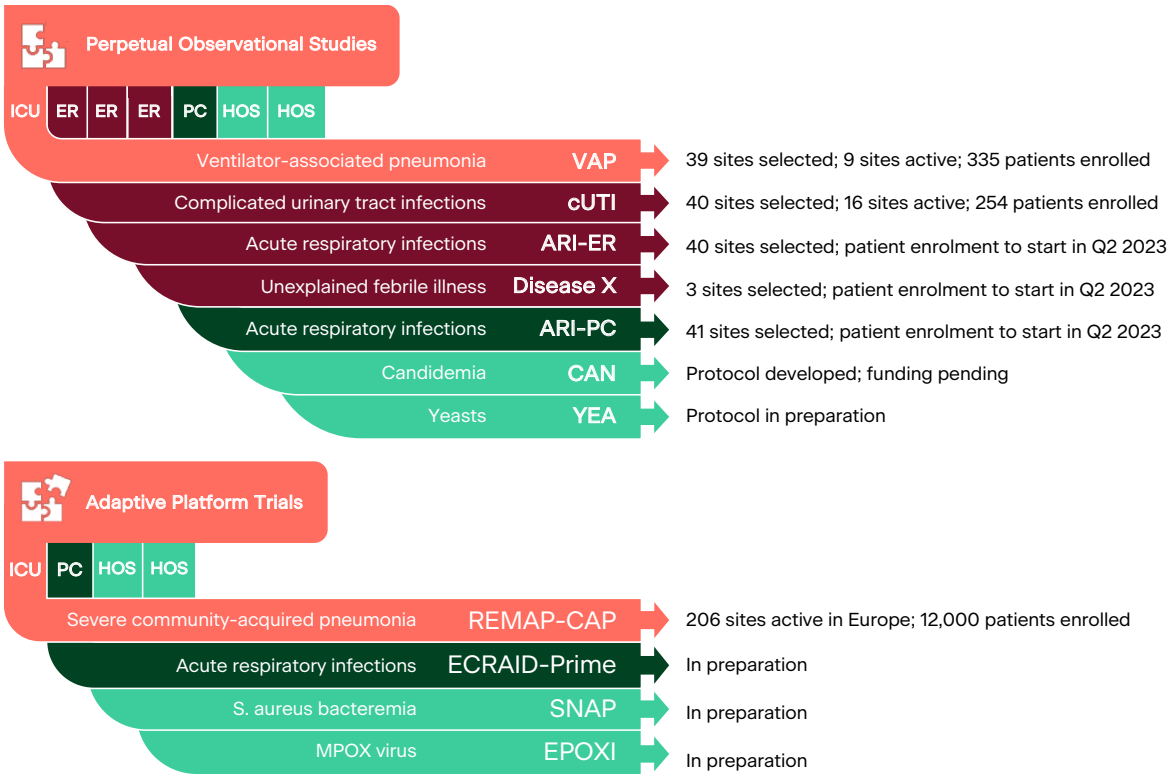
Building the network

The CLIN-Net network was created with the ambition to participate in research at the highest level by engaging investigators and hospitals with extensive experience in clinical trials in infectious diseases. Starting in 2013, the team has spent a decade forging personal contacts amongst motivated clinicians and highly reputed investigators across Europe. It serves as a single point of contact for any site or organisation seeking access to the network.

Ecraid Clinical Liaisons play an essential role within the CLIN-Net network. They are local experts and members of established local cooperative networks of experienced centres specialised in infectious diseases and intensive care studies. Their knowledge and experience are highly valuable for the optimisation of the network and the smooth execution of local site selections and clinical trials.

To consolidate the network, CLIN-Net continuously involves its existing sites in new clinical studies. The team is also always looking for opportunities for growth. It works closely with less experienced sites, helping them to develop their potential for clinical research. In this way, the number of experienced sites expands, augmenting the capabilities of the network to conduct more parallel studies. The current portfolio of clinical trials executed in this warm base network is depicted in Figure 1.

Figure 4. Ongoing and upcoming clinical trials that make use of CLIN-Net's services.
Accurate as of March 2023.



Network quality

To maintain and develop the network's capabilities, Ecraid provides participating physicians and site staff with regular training opportunities. Many of these initiatives are focused on GCP, with more than 1,100 researchers having completed Ecraid's GCP training so far. Sites' qualifications for performing clinical and/or laboratory research activities are further strengthened through post-graduate courses, educational programs, on-site trainings, a virtual learning platform, as well as the upcoming Ecraid Academy – a series of training opportunities for young scientists. CLIN-Net also supports potential new sites by inviting them to participate in less rigorous (non-interventional) studies, as a training for future participation in randomized studies.

To keep the network updated, a newsletter highlighting recent developments is sent out to all sites on a regular basis. The team strives to meet face-to-face with PIs, site staff and Ecraid Clinical Liaisons as often as possible in order to further maintain relationships. These site and country visits provide an opportunity to meet local contacts and investigators in person, learn about the challenges and opportunities they encounter, and gain deeper understanding of the local healthcare infrastructure.

Efficient and effective site selection

CLIN-Net uses a highly standardised process to streamline site selection and optimise the start-up of new trials. Its close collaboration with Ecraid's laboratory network, LAB-net, allows for simultaneous selection of clinical sites and laboratories. A tailored online network management system (NMS) is used to collect, archive, and store contacts, communications and feasibility questionnaires from sites, investigators, and studies.

NMS's Feasibility Questionnaire module allows the CLIN-Net team to easily configure, format, and send out feasibility questionnaires from the system directly to contacts. Over 9,000 feasibility questionnaires have been distributed to the network so far. The system then tracks all sent invitations and questionnaire completion statuses and can generate a comprehensive overview when needed. The outcomes of the site selection and study start-up process are recorded as well, ensuring that NMS can keep track of the entire site selection process.

9,000

feasibility questionnaires have been distributed to the network so far.

Input from the Ecraid Clinical Liaisons is crucial for selecting the most suitable sites for ongoing and future studies. The liaisons provide advice on a country's feasibility for any given study, share knowledge on country-specific regulations and potential hurdles, and propose suitable sites and help engage them.

To ensure a solid and sustainable infrastructure and to consolidate the network, CLIN-Net also focuses on performance measurement. The team actively analyses (the development of) the network and identifies excelling clinical sites by checking site capabilities and previous study performance. This process is continuous. Information about countries, sites, and contacts is gathered through a series of quantitative and qualitative data collection. As more trials are completed and new ones commence, the data that is collected and analysed enables CLIN-Net to differentiate between the capabilities of different study sites. This level of knowledge of each individual site allows the team to quickly and transparently pair sites and investigators with several clinical trials simultaneously.

Conclusion

Conclusion

A warm base network has the potential to markedly improve site selection for clinical trials. This novel approach offers a number of benefits over conventional site selection methods: it provides a single point of access for sponsors, maintains operational readiness by offering continuous participation in trials, harnesses expertise in a specific range of pathogens and diseases and provides access to specific geographical areas, encourages cross-site uniformity/quality standards, and uses various types of data from previous and active trials to inform site selection. Together, these substantial improvements result in less delays and added costs, and enhance the quality and efficiency of clinical trials.

About Ecraid

Ecraid – the European Clinical Research Alliance on Infectious Diseases – is a not-for-profit foundation that advances clinical research in the field of infectious diseases by establishing a long-term, financially self-sustainable, clinical research network in Europe. Headquartered in Utrecht, the Netherlands, Ecraid is the first network of its kind in Europe to offer a single point of access to a pan-European clinical research network for infectious diseases and spans over 1,250 clinical sites and 900 laboratories across 42 countries.

For more information, please visit ecraid.eu
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