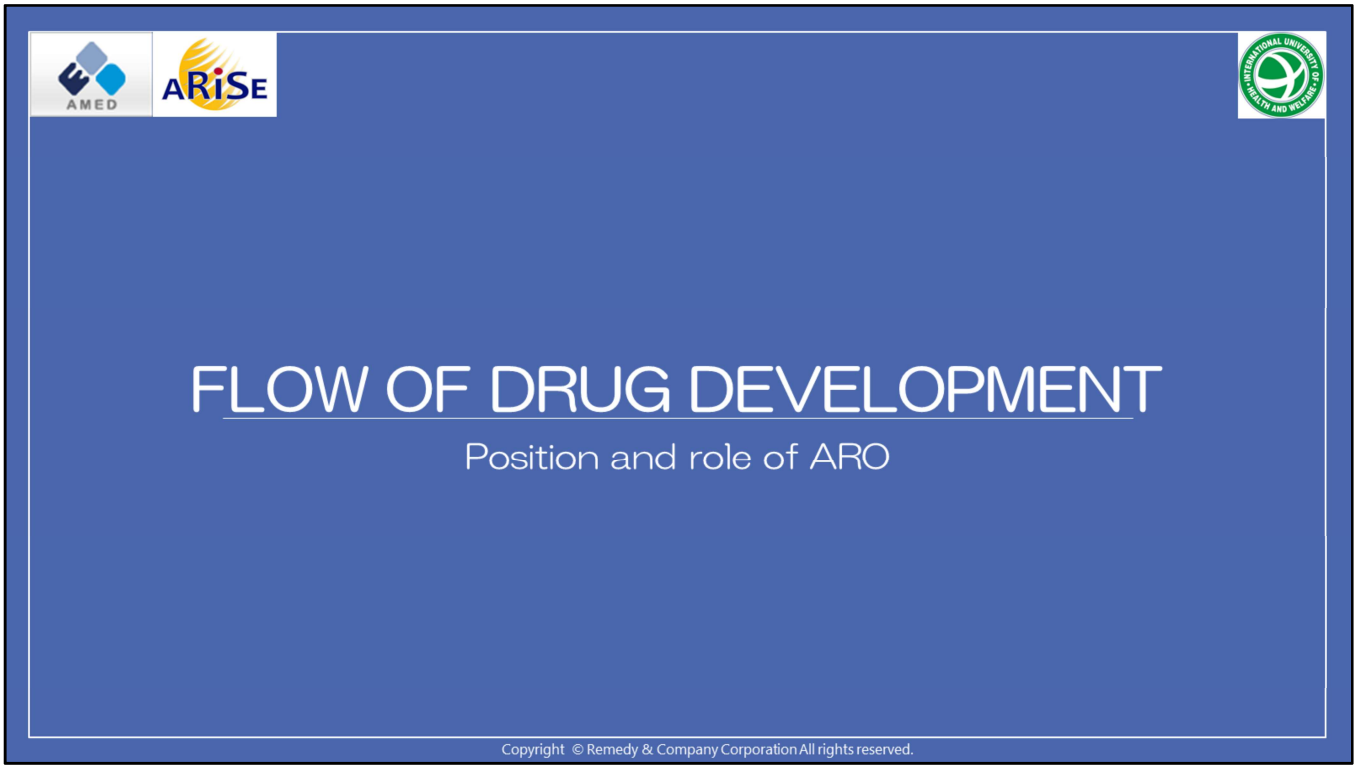

Good day everyone! Today, we will be discussing about “flow of drug development, position and role of ARO.”

Relationship between clinical research, clinical trials, and Drugs or MD clinical trials

Clinical research, clinical trials, and Drugs or MD clinical trials are related as shown in the figure.
A clinical trial is a clinical study that evaluates the results of interventions such as treatment and guidance.
A Drugs or MD clinical trial is a clinical trial that aims to collect objective data so that new drugs and medical devices can be approved by the government and used in general practice.

Clinical research: medical research conducted on human subjects

Clinical trial: Clinical research aimed at evaluating the safety and efficacy of drugs, therapeutic methods, diagnostic methods, preventive methods, etc.
New Drugs or MD Clinical trials: Clinical trials conducted to obtain government approval for the manufacture and sale of new drugs and medical devices

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Today, we would like to take you through the complex and vitally important process of drug development.

This process commences with basic research and spans through clinical trials until finally, we have a drug available for medical use.

Clinical research is the foundation upon which the entire decision-making process regarding new drugs or medical devices is built. It's an investigative science, carried out on human subjects.

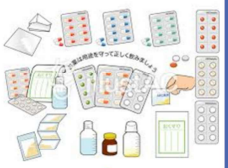
It's the elemental stage in the drug development process and contributes significantly to enhancing medical knowledge and patient care.

Now, let's move on to a subset of clinical research – which is clinical trials. A clinical trial is a rigorous evaluation of the potential benefits and risks associated with a new drug or a therapeutic approach. It is precisely during these clinical trials where the safety and efficacy of drugs, therapeutic methods, diagnostic approaches, and preventive methods are scrutinized. So, in essence, it takes the theoretical promises of clinical research into the practical realms to test hypotheses in a controlled, regulated environment.

Finally, let's discuss drug or medical device clinical trials. Commonly referred to as new drug or MD clinical trials, these are the very specific clinical trials conducted with the purpose of gaining government approval for the manufacture and sale of new drugs and medical devices. It is these trials that ensure the new drug or medical device meets the stringent requirements for safety and efficacy set forth by government regulations before it can be manufactured and sold.

Clinical research to clinical trial

- Substances discovered from chemosynthesis, plants, soil fungi, marine organisms, etc., are predicted to be effective against diseases and safe for human use through test-tube experiments and animal experiments. Those that are tested are selected as “drug candidates”.
- In the final stage of development of this "drug candidate", it is necessary to examine the efficacy and safety in humans with the cooperation of healthy people and patients.
- The results obtained in this way are reviewed by the government, and drugs that are approved as necessary for the treatment of illness and safe to use become "medicine."
- Human trials are generally called "clinical trials", but clinical trials that use "drug candidates" to collect results for government approval are particularly called “New Drugs/MD clinical trials".



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We would like to discuss the process by which medicinal substances derived from various sources become approved for human use.

The journey starts in diverse environments such as underneath the sea, within the forest, or even beneath the earth. From chemosynthesis, plants, soil fungi, marine organisms, and more, scientists work tirelessly to predict potentially beneficial substances for human health. Through rigorous test-tube experiments and animal testing, these substances are thoroughly vetted for potential efficacy against diseases and safety for human use. The compounds that pass these stringent tests are chosen as drug candidates.

However, these drug candidates still have a long way to go before they officially become what we recognize as medicine. The next crucial phase in their development requires human testing. Here, we gratefully collaborate with healthy volunteers and patients to test these drug candidates. This phase, typically known as a “clinical trial”, provides essential insights into the drug’s efficacy and safety when used by humans rather than laboratory animals.

Specifically, clinical trials used to gather results for governmental approval are called “New Drug/MD clinical trials”. The data derived from these trials is extremely important because it forms the backbone of the review process conducted by the government.

Clinical trial

Clinical trials are conducted in hospitals.

Only hospitals that meet the requirements stipulated in the "Ministerial Ordinance on Good Clinical Trial Practices (GCP)" are selected for clinical trials.

What are the requirements

Sufficient medical facilities

Have doctors, nurses, pharmacists, etc. responsible for conducting clinical trials

Be able to use the ethical committee* that reviews the contents of the clinical trial

In case of emergency, the necessary treatment and measures can be taken immediately

* Institutional Review Board (IRB)

We would like to clarify the protocols, procedures, and requirements associated with conducting clinical trials in hospitals.

First and foremost, it's significant to consider that not all hospitals are qualified to conduct clinical trials. Only those that fulfill the prerequisites outlined in the Ministerial Ordinance on Good Clinical Trial Practices, or GCP, can be selected.

Now, you might think, what are these specific requisites? Let me go over them for you. These include the possession of sufficient medical facilities and the employment of certified health professionals - such as doctors, nurses, and pharmacists - who are tasked with the responsibility of carrying out the clinical trials.

Furthermore, the hospitals must have access to an Institutional Review Board, also known as an ethical committee. This board plays the crucial role of reviewing the proposed activities and protocols of the clinical trial to ensure everything is ethically done.

Lastly, the hospitals should have the capacity to promptly respond and provide the necessary treatment and countermeasures in case of any emergencies that may arise during the course of the clinical trial.

These stringent requirements have been put in place to ensure the safety and well-being of the patients, the integrity of the clinical trials, and the accuracy of the data collected during the study.

Clinical trial

There are various rules for conducting clinical trials.

Comply with the GCP and the Pharmaceuticals and Medical Devices Law*

Comply with the clinical trial protocol

MD will comply with the administration of medicines, the timing and methods of examinations, etc.

Subjects (patients who participate in the clinical trial) must follow MD instructions, such as taking the study drug on a regular basis and visiting the hospital on a set day.

MD must obtain written consent * from the subject (almost the same as a surgical consent form)

* Informed consent (IC)

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Being pivotal for bringing new medical interventions to the market, these trials play a crucial role in confirming safety and efficacy. Understanding the rules governing these trials is important for ensuring thoroughness, accuracy, and legal compliance.

Firstly, one must comply with Good Clinical Practice (GCP) and the Pharmaceuticals and Medical Devices Law. GCP is an international ethical and scientific quality standard, enforced by the International Committee of Harmonisation (ICH), which guides the design, conduct, performance, monitoring, and evaluation of clinical trials. The Pharmaceuticals and Medical Devices Law, on the other hand, regulates the standards and process of approval for drugs and medical devices.

Secondly, adherence to the approved clinical trial protocol is paramount. The protocol is the plan that details what will be done in the study, how it will be conducted, and why each part of the study is necessary. It describes the study's objectives, design, methodology, statistical considerations, and organization.

In addition to this, medical doctors (MDs) must strictly adhere to the guidelines regarding the administration of medications, timings, and methodologies of examinations. This ensures data reliability and consistency throughout the trial.

Moreover, trial subjects or patients also have an important role to play in clinical trials. They must comply with MD instructions, such as regular intake of study drugs and visiting the hospital on predetermined days. Their adherence to the trial protocol has a direct impact on the study's success.

Lastly, one of the major ethical considerations is obtaining informed consent from trial subjects. Essentially, informed consent is the process where a healthcare provider educates a patient about the risks, benefits, and alternatives of a given procedure or intervention. It must be signed by all trial subjects, similar to a surgical consent form, ensuring patient's understanding and agreement to the clinical trial procedures.

Items to be described in the clinical trial protocol (protocol)

The protocol states:

- Purpose of the study
- Selection criteria/exclusion criteria
- Investigational drug overview
- How to use the investigational drug
- Subject visit schedule
- Test items to be performed (subjective and objective findings, blood sampling, urine sampling, CT, etc.) and implementation timing
- About the collection of safety information
- Data to be collected
- The target number of cases and the grounds for setting the number of cases
- Primary and secondary endpoints, etc.

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The primary objective of our protocol is to outline the purpose of the study. This includes a detailed explanation of what the trial intends to achieve and the medical or scientific reasons for carrying out the trial.

A critical stage in the process is defining our subject selection criteria. This key area secures participants who meet the required health specifications. Moreover, this includes an overview of any exclusion criteria to precisely outline who cannot take part in the trial, making sure that each participant's safety is a priority.

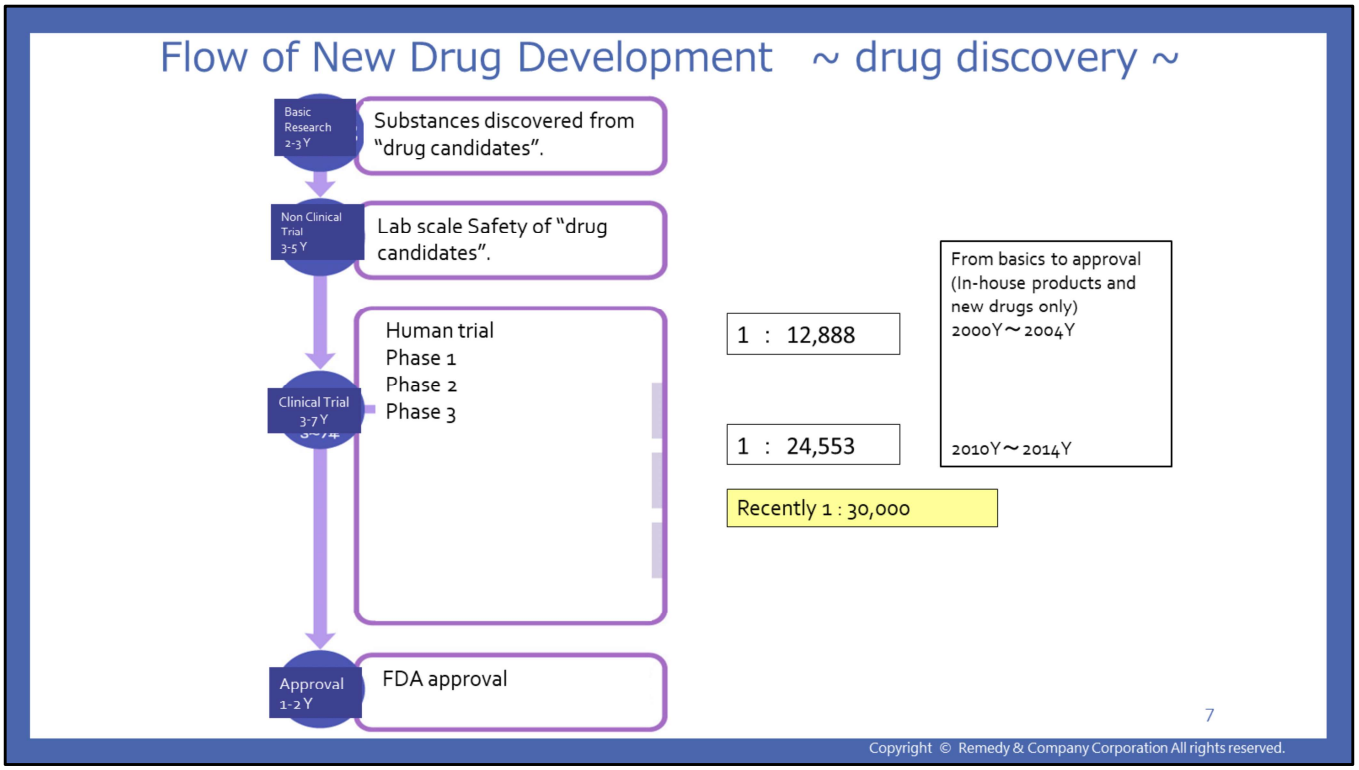
The protocol will provide a comprehensive overview of the investigational drug to be used. We will cover how to correctly administer the drug, ensuring participants and administrators follow a specific, regulated process and make consistent notations in trial records.

In terms of visit schedule, we will conduct regular check-ups with our subjects to monitor their status throughout the study, responding promptly to any potential side effects or complications that may arise.

The protocol also calls for the execution of various test items at specific timings. This could include subjective and objective findings, blood sampling, urine sampling, and CT scans, forming a comprehensive and holistic evaluation of the drug's effects.

One of the protocol's prime factors includes the emphasis on safety information collection. The data collected from this trial will serve as stepping stones for future advancements in the field. It will also provide a benchmark for setting up the target number of cases and establishing why these particular numbers have been chosen.

Lastly, the protocol will specify the primary and secondary endpoints. These benchmarks will act as significant indicators for the trial's success or potential areas for improvement.



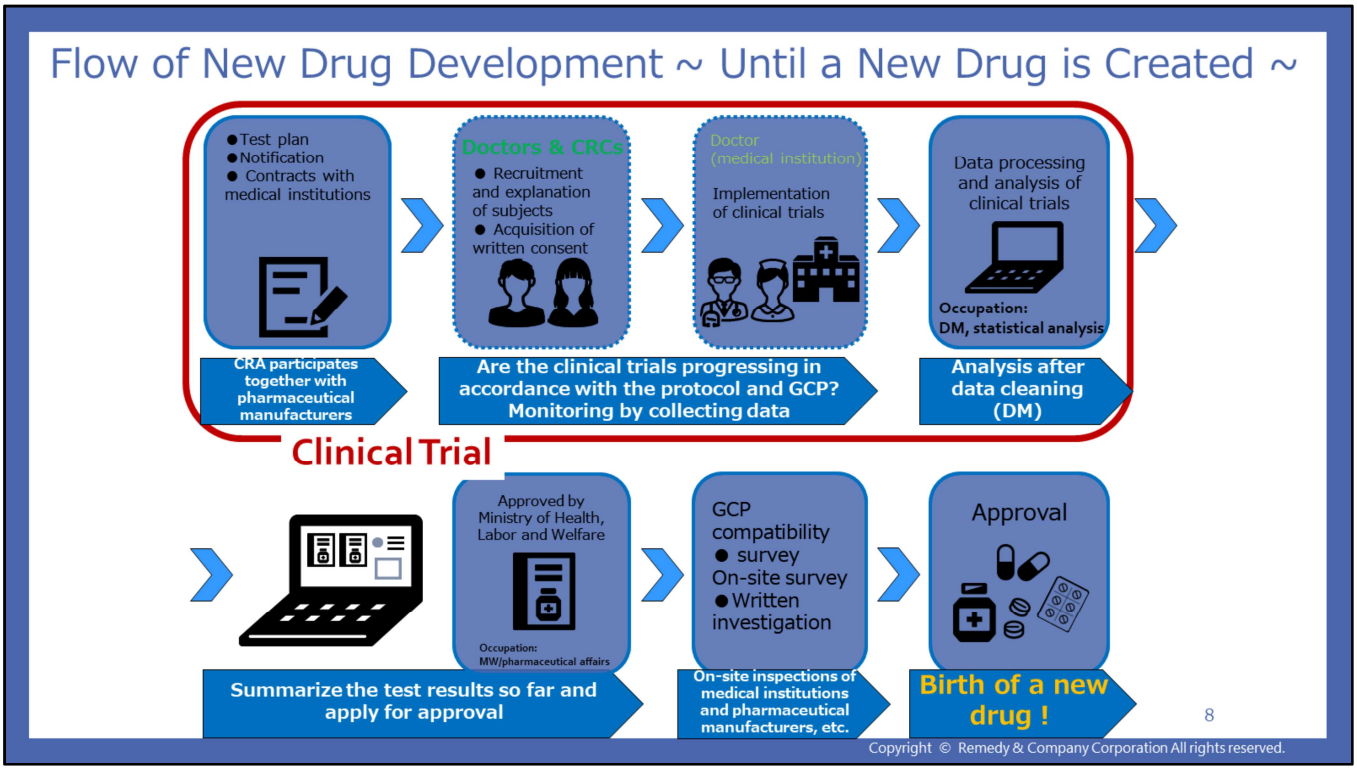
Firstly, it's essential to understand that our ultimate goal is to make scientific breakthroughs that have the potential to become new, effective therapeutic drugs. Our research journey begins with the identification and investigation of substances drawn from our drug candidates.

We commit extensive research to explore these substances, diving deep into their molecular and cellular activity, exploring their potential benefits and side-effects, and position them as our drug candidates.

However, identification is just the beginning. A massive part of our journey is ensuring the safety of these potentials. After the initial discovery, these drug candidates undergo rigorous lab-scale safety tests. These tests work to highlight any potential risks or side effects that could arise when using these drugs thus assuring they are safe and effective.

Once we are assured that our drug candidates are safe, we then move into the human trial phase including Phase 1, Phase 2, and Phase 3 clinical trials. However, the ratio of success from this point is typically 1 to 12,888. This is a stark reminder of the harsh realities accompanying drug discovery and development.

Nonetheless, these rigorous processes and the tough odds embody our commitment to ensuring that only the safest and most effective drugs make it to the market. From the year 2000 to 2004, we were successful in receiving approval for our in-house products and new drugs, testament to the adequacy of our process.

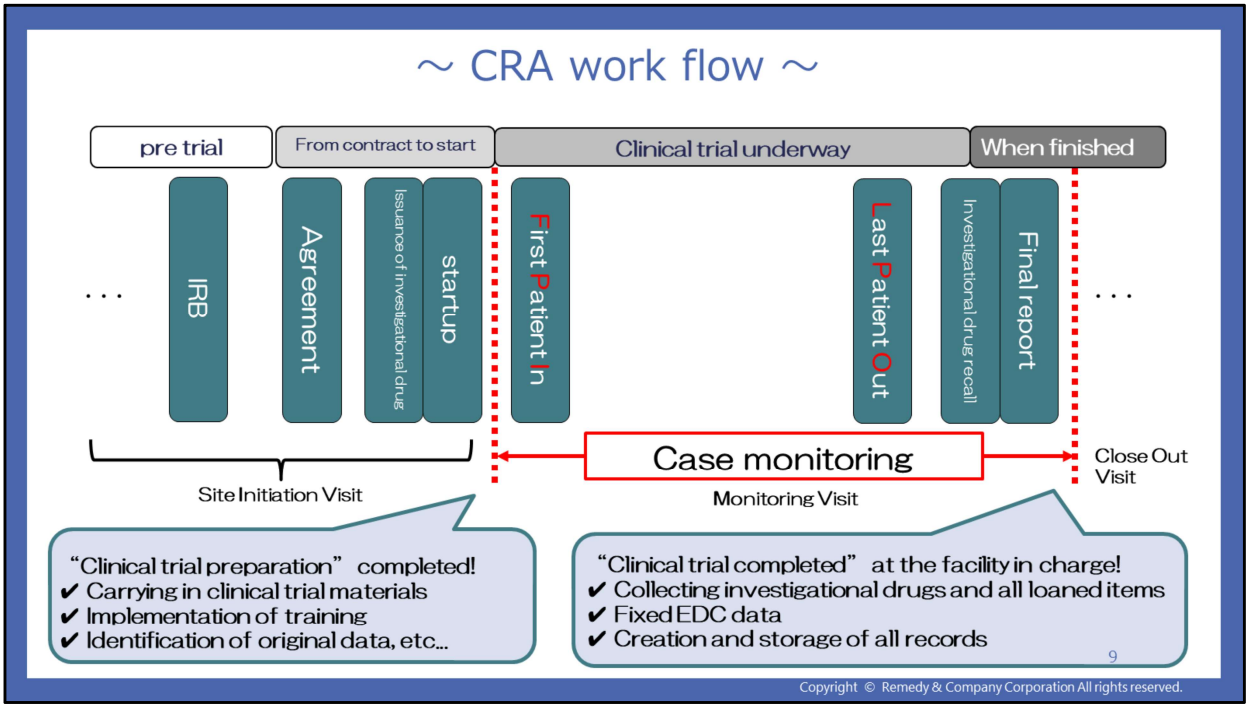


The initial stage of the clinical trial involves the formulation of a test plan, the notification of contracts with medical institutions, and the recruitment and briefing of subjects. This phase's success is underpinned by receiving express written consent from all participants involved.

Once the early arrangements are in place, we move to our next step, which involves the actual implementation of the clinical trials. At this juncture, ensuring that the trials follow the predefined protocol and the regulations set out by the GCP is paramount. This adherence is ascertained through the efficient monitoring and collection of data.

Subsequent to the experiential phase, data processing and statistical analyses come into play. In this phase, we work to decipher the gathered data, which helps steer us closer to our main objective of reducing and, if possible, eliminating ailments with new drugs. Trained Data Managers (DMs) play a crucial role in this effort.

The final stage consists of submitting the compiled results to the Ministry of Health, Labor, and Welfare for approval. This comprehensive report should consist of all the results obtained during the clinical trials.



Clinical Research Associates play a crucial role in the conduction of clinical trials, which are indispensable in the development of new treatments, therapies, and drugs. They are tasked with ensuring these trials adhere to the regulations set out by governing bodies, thus guaranteeing the safety and rights of participants.

CRA Responsibilities

The responsibilities of a CRA are diverse and can vary depending on the stage of the clinical trial. They include designing and writing trial protocols, presenting trial protocols to a steering committee, managing regulatory authority applications and approvals, locating and assessing the suitability of facilities at a study site, liaising with doctors and consultants, and much more.

Pre-Study Visits

The CRA conducts pre-study visits to potential study sites to assess its appropriateness for the given study. They gauge whether the site possesses the necessary facilities, resources, and capable staff to conduct the trial. Any protocol-related questions, expectations, and regulatory requirements are clarified during these visits.

Initiation Visits

After selecting the site, the CRA makes an initiation visit, where the team is trained regarding the study protocol, procedures, and regulatory compliance. The CRA also explains the investigational product and how it should be stored, dispensed, and accounted for at the site.

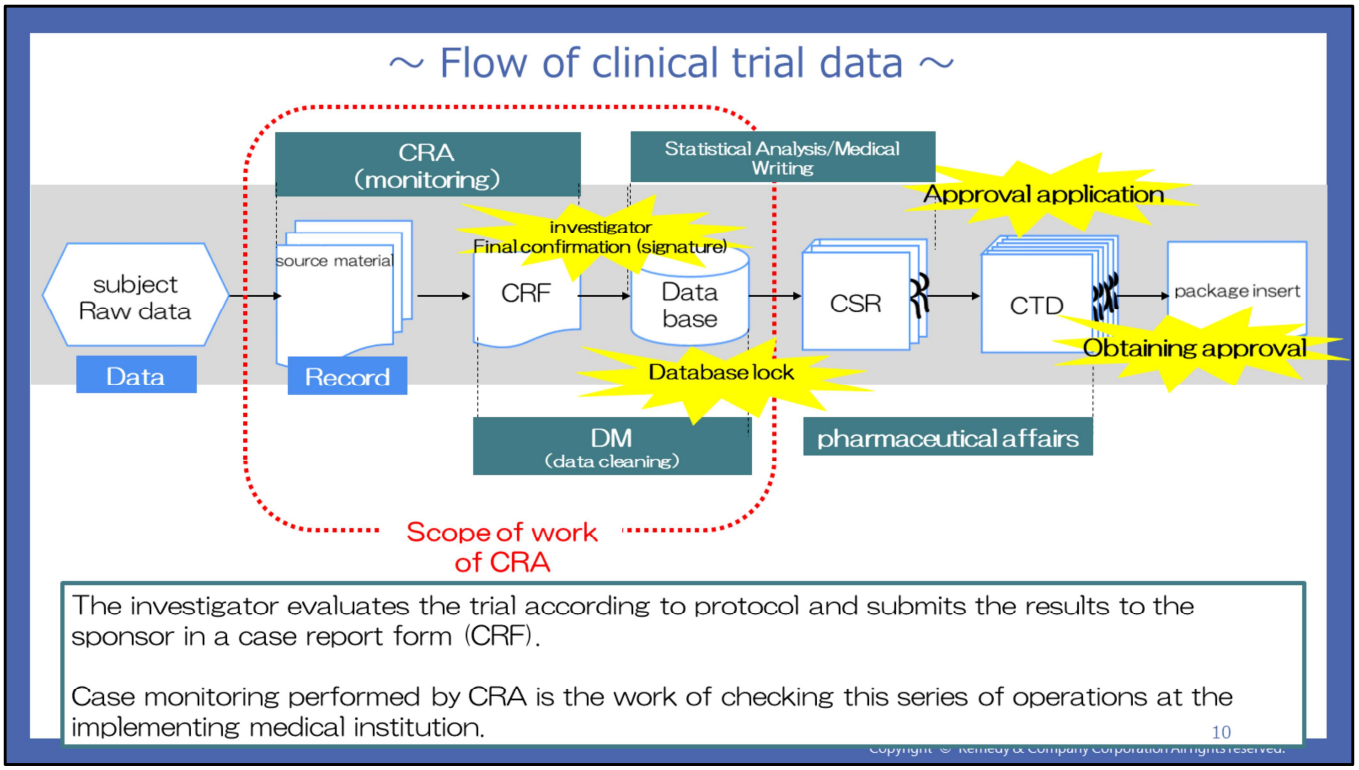
Monitoring Visits

Considered as the backbone of a CRA's workload, monitoring visits are conducted regularly throughout the trial. These visits ensure that clinical trials are conducted, recorded, and reported in accordance with the protocol, regulations and ethical considerations.

Close-Out Visits

After the completion of the trial, the CRA conducts a close-out visit. They ensure that all

necessary documentation is ready for final audit, all investigational product has been accounted for and returned, and the investigators have fulfilled all their responsibilities.



Clinical trials involve numerous subjects, and these subjects generate a significant amount of raw data. This data is then processed and packaged into a more manageable format for further review. This task is performed primarily by Clinical Research Associates (CRA).

The CRA is responsible for monitoring this raw data. They act as the crucial link in the chain, ensuring the integrity and accuracy of the data obtained from the clinical trial.

The investigator at the helm of the trial evaluates the procedure according to the clinical trial protocol and then submits the results to the pharmaceutical sponsor in a case report form, commonly known as a CRF.

The CRA carries out case monitoring. Their work involves checking this sequence of operations at the medical institution implementing the trial. Therefore, CRA plays a significant role in validating the whole clinical trial process and ensuring that all processes are carried out according to the protocol.

Moreover, the case report form, or CRF, containing collected data is further transformed into a clinical study report, CSR, helping in creating a comprehensive analysis of the trial.

The Database is locked after the data has been reviewed and cleaned by data management. Locked, in this context, means that all missing data or discrepancies have been resolved, ensuring that no more changes can take place.

Finally, the clean and locked database is sent off to pharmaceutical affairs for the final steps in the trial process.

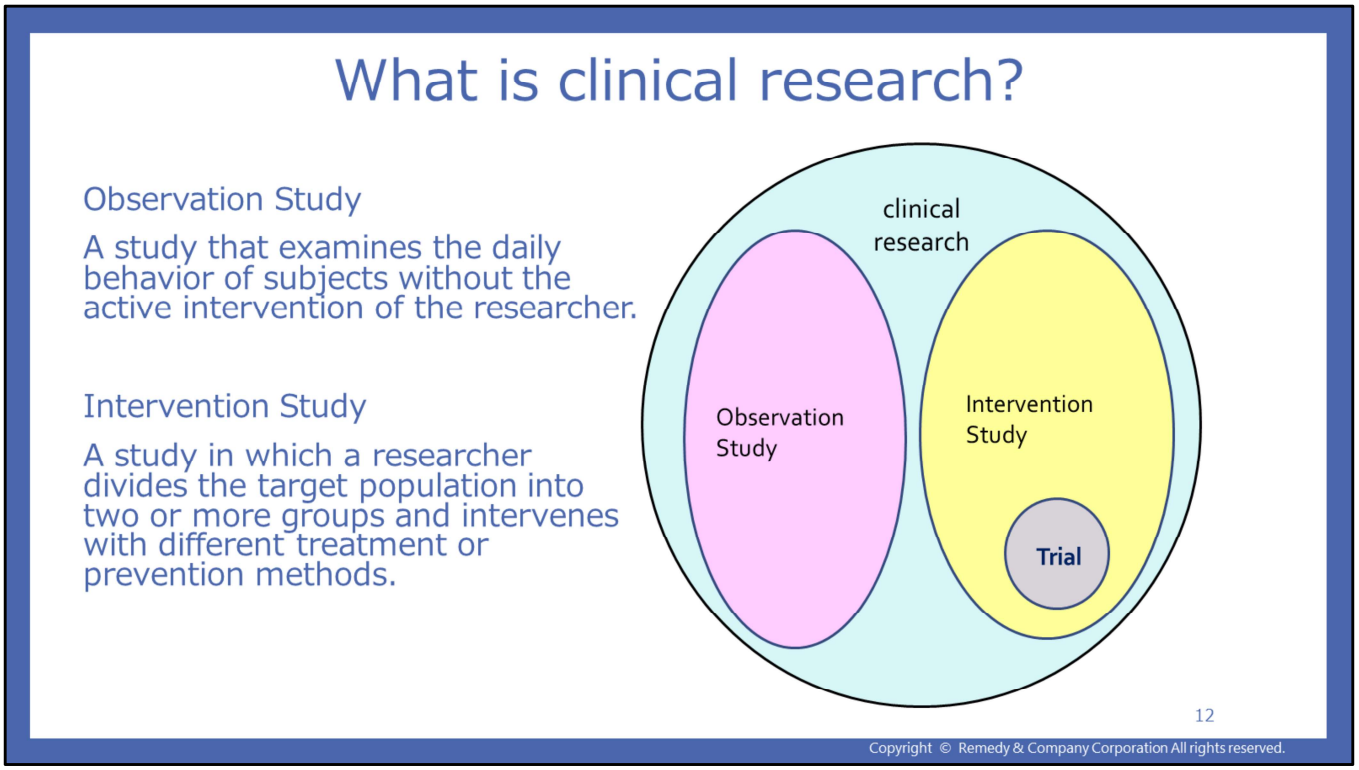
In conclusion, the role of a CRA is vital in the clinical trial data flow. They support and assure the function of the clinical trial process right from the commencement to its final phases, carrying out tasks such as monitoring, data cleaning, and the proper execution of the clinical trial per the predefined protocol.

What is clinical research (medical research involving humans)?

According to the Ethical Guidelines for Medical Research Involving Human Subjects, it is necessary to understand the causes of injuries and illnesses (including the frequency and distribution of various health-related events and the factors that affect them) and the pathology of injuries and illnesses. It is conducted for the purpose of obtaining knowledge that contributes to the maintenance and promotion of public health, recovery from injuries and illnesses of patients, and improvement of quality of life through improvement or verification of preventive methods, diagnostic methods and treatment methods in medical care activities.

Medical research includes medical science, clinical medicine, public health, preventive medicine, dentistry, pharmacy, nursing, rehabilitation, laboratory science, medical engineering, nursing care and welfare, food hygiene and nutrition, and environmental hygiene. This includes epidemiological research and qualitative research using information on individual health in the fields of occupational health and safety, etc.

Some research in the humanity and sociology fields, such as medical law and social welfare studies, is not included in "medical research", even if it is related to medical care, nursing care, welfare, etc.



Let's talk about an integral part of the Clinical Research.

Clinical research plays a unique and indispensable role in improving healthcare by finding new ways to treat, prevent and diagnose diseases. It's through this systematic investigation that ground-breaking medications and innovative methods of treatment are discovered. It's designed for a better future, for better health outcomes for all of us.

Now, let's discuss the two main types of clinical research: observational studies and intervention studies.

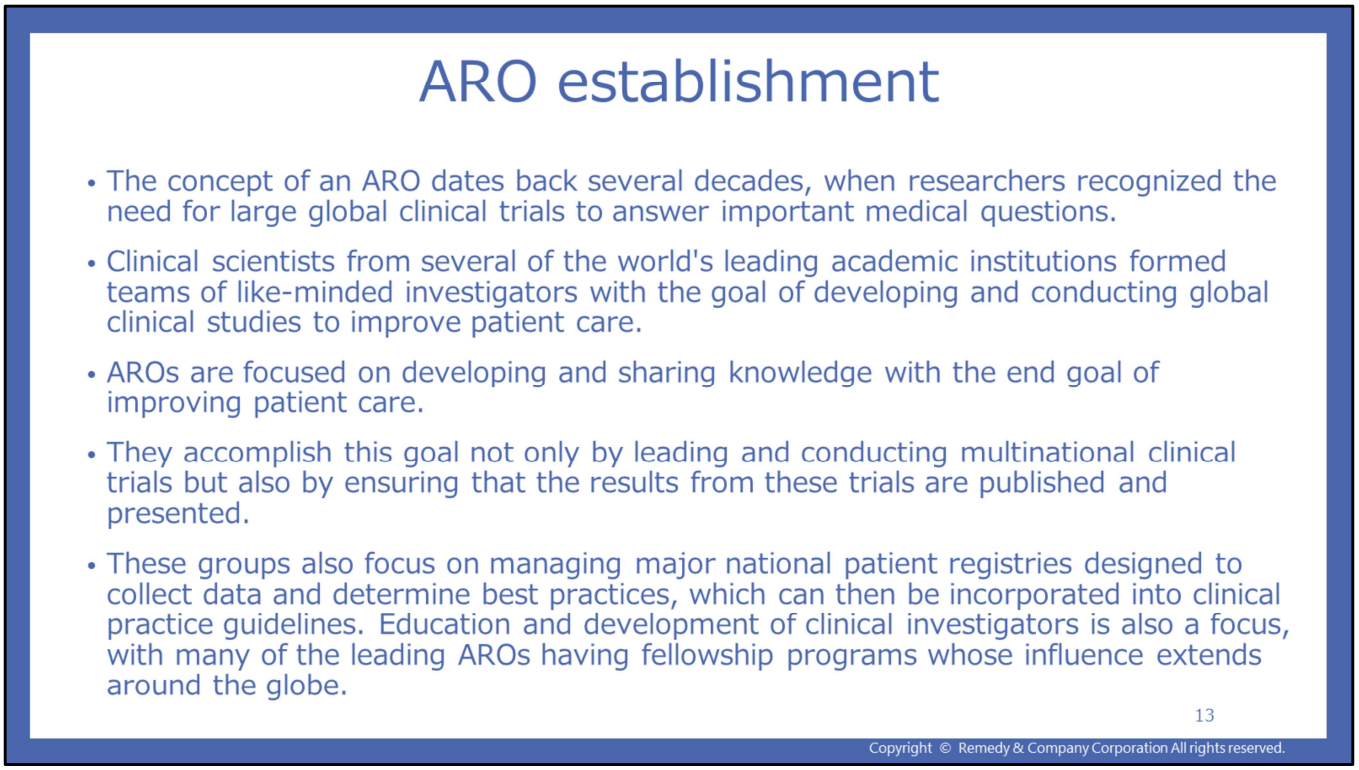
Observational studies involve observing individuals in their natural settings or observing the events that happen without intervention. Say, for example, observing the daily behaviors of a group of individuals, noting their habits, lifestyle, and health outcomes without intervening. These passive kinds of studies are extremely helpful in establishing links or associations between different health-related phenomena. Or the other example to observe the process of disease in living object.

Then we have Intervention Studies. Here, researchers are proactively involved. Inside the intervention study we have clinical trial that specified to fulfill clinical report of efficacy with the intention of submission to get approval by regulatory authority. They divide the target population into different groups. Each group is given a different treatment or a distinct prevention method and the effects are examined and compared. These studies are more direct in establishing cause and effect relationships.

Imagine this - we have 100 people and divide them into 2 groups. Group 1 is given a new drug to manage diabetes, while group 2 is given the standard treatment. Researchers then monitor the patients' health outcomes. From this, we can draw scientifically valid conclusions about the effectiveness of the new drug compared to the standard treatment. That's intervention studies for you.

Well, to wrap up, clinical research provides the basis for the application of ideas to clinical practice. This journey from a concept to a life-saving drug can only be smoothly navigated

through to the end, by thorough and systematic clinical research.



We would like to take you back in time when the concept of Academic Research Organizations, or AROs, was gaining momentum. This conceptual breakthrough was several decades ago, when experts in the field of medicine identified an increasing need for expansive global clinical studies to effectively answer imperative medical questions.

With the noble aim of improving the care that patients receive while fostering scientific innovation and discovery, clinical scientists from many of the world's leading academic institutions proudly became pioneers of this initiative. They unified and formed robust, high-achieving teams of like-minded investigators, all sharing a laser-focused objective of developing and managing global clinical studies of unprecedented scale.

The heart of their work lies in the advancement and sharing of knowledge, all with one ultimate goal in mind - the betterment of patient care. They strive tirelessly towards this aim not only through spearheading and conducting multi-national clinical trials, but also by ensuring that these trials' results are shared far and wide, via published work and presentations.

Moreover, these ground-breaking organizations channel their resources and expertise towards handling large-scale national patient registries. These registries are meticulously designed to collect data and identify the most effective practices available. Once these are ascertained, AROs work diligently to incorporate them into clinical practice guidelines, thereby imparting a direct positive impact on the quality of patient care.

In addition to their trailblazing research work, AROs also play a crucial role in cultivating the next generation of clinical investigators. Many renowned AROs around the globe offer prestigious fellowship programs, providing invaluable learning experiences and opportunities, thus ensuring that their influence extends far beyond the present, moulding the leaders of tomorrow's medical research landscape.

Today, we will introduce to you a comprehensive range of ARO Services commonly we found in Japan that materialize ARO commitment towards bringing innovation, professionalism, and efficacy in clinical research.

Following a systematic approach, we start with ARO **Project Management** service. Effective project management drives the rest of ARO services, ensuring time-bound and efficient execution of projects. We understand that every project is unique and hence, needs ensure the tailor-made strategy that we provide in managing it. In other words, we help you align all your efforts, resources, and schedules towards a common objective.

Next is ARO **Trial Consultation** service. We assist you in making informed decisions about clinical trials. ARO team of experts provides you with insights regarding trial feasibility, expectations, and potential hurdles.

Among ARO core competences is **Protocol Development**, which I believe is the strength of ARO. We help design a robust and rigorous protocol to ensure that the trial results are accurate, reproducible, and free from bias.

Whenever you work in a regulated industry like ours, **Regulatory Affairs** is a critical feature of ARO services. Thus, we provide guidance in ensuring the compliance of procedures, protocols, and practices with the existing rules and regulations.

Moving on to ARO **Study Management office**, we are proud to present a team of Medical Experts with proven experience in their respective fields. They coordinate and execute the study protocols, ensuring the conduct of high-quality trials.

Moreover, we bring you a high level of competence and rigor in managing and analyzing clinical trial data. ARO **Data Center** and Trial Conduct capability ensure that the data collected is accurate, confidential, and compliant with regulatory requirements.

One of the most exciting services we offer is **eClinical Solutions** designed to make the process more manageable, accurate, and efficient. Along with this, ARO Patient Recruitment

Strategies are comprehensive and targeted, ensuring the timely enrollment of ideal trial participants.

We also offer **Monitoring** services to assess the conduct of trials and ensure adherence to protocols. Furthermore, ARO Statistics Department is proficient in analyzing trial data and generating meaningful insights.

Unveiling ARO **Genomics** service, an advanced technology designed to contribute significantly towards personalized medicine. We offer advances in genomics leading to better understanding of diseases and drug response.

Lastly, we provide **Education** services to provide ARO partners with the knowledge and tools essential for conducting effective and successful clinical trials.

To summarize, ARO services are designed with the ultimate goal of making clinical trials more efficient, reliable, and comprehensive, catering to the needs of ARO partners at every step of the clinical trial process. We believe that ARO services are not just about doing ARO jobs but helping you do your job better.

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