Ver. 1 2019

ALYND

A Leading Yonsei Network for Biopharmaceutical R&D

+ Comprehensive Collaboration Program: SALT PLUS
+ Intelligent Mediation Platform: JARVIS

ALYND
Yonsei Biomedical Integration System

YONSEI UNIVERSITY
HEALTH SYSTEM

Yonsei University Health System

Medical Science Research Affairs

Yonsei University Health System (YUHS) was founded in 1885 by the American medical missionary Dr. Horace N. Allen as the first modern medical institution in Korea. It began as a small hospital under the name Kwanghyewon, which changed to Chejungwon and then Severance Hospital. The hospital expanded over the years to include 2 graduate schools (Public Health and Nursing), 3 colleges (Medicine, Dentistry, Nursing) and 4 hospitals (Severance hospital, Gangnam Severance hospital, Yongin Severance hospital and Dental hospital), and was reborn as the Yonsei University Health System with approximately 10,100 employees. (include 2,500 physicians and 7,600 personnel)

The hospitals combined have 3,362 beds and treats over 4 million outpatients and 1.2 million inpatients annually. With more than 130 years of experience in medicine, YUHS strives to be a leader in the industrialization and globalization of medicine and become the medical hub of Northeast Asia.

Yonsei University-Industry Foundation was established in 2001 to enhance the capability of researchers, promote research collaborations, and efficiently manage research projects.
In 2013, Yonsei University transferred all related medical services such as patents, intellectual property rights and technology commercialization to the University-Industry Foundation at YUHS. The patent fair launched in 2012 made YUHS the first medical institution in Korea to build an open research infrastructure and nurture the medical industry centered on the medical field. Since then, we have tried to create a forum for communication in order to expand opportunities for mutual information exchange between industry and academia.

As a result, many of the ideas from the clinical field and the outstanding research achievements have been adopted and are utilized by our industrial partners.
The University-Industry Foundation at YUHS will continue to share research information on industry-academia cooperation both internally and externally in a timely and accurate manner. This will contribute to the promotion of research collaboration between Yonsei University Health System and biopharmaceutical industries.

ALYND
Yonsei Biomedical Integration System

Yonsei University Health System
www.yuhs.or.kr

Division of Medical Science Research Affairs &
University-Industry Foundation at YUHS
www.yuhs.or.kr/research

ALYND (R&D consulting center)
alynd.yuhs.or.kr (opened in January 2019)

CONTENTS

GREETING

We will do our best to operate the program and promote industrial collaboration with an open mind.

Academic medical institutions are playing an increasingly large role in developing new products for the healthcare industry. The biopharmaceutical industry needs clinical knowledge and research experiences from clinicians in order to understand the unmet medical needs and to gain market insights for their new products.

As a pioneer and leader of modern medicine in Korea, Yonsei University Health System (YUHS) is leading this medical research with the passion and creativity. We contribute to the development of industry-academia collaboration by providing solutions for the identified obstacles and inefficiencies inherent in the conventional R&D system.

Partnerships should offer sharing of information for both sides inolved. Working closely with our partners, our researchers are able to understand the commercial R&D process and ultimately obtain useful information for their own research. Efficient research and subsequent successful clinical development can be realized through collective intelligence and collaborative innovation.

We are here to fulfill the unmet needs of our industrial partners with the program and promote research collaboration by your side in business-friendly manners. Come and join us for a true companionship from the start of your long R&D journey.

Best regards,

Eun-Cheol PARK, MD, PhD

President, University-Industry Foundation of
Yonsei University Health System & Director,
Division of Medical Science Research Affairs

Jae Yong SHIM, MD, PhD

Director of ALYND
(R&D Consulting Center of
Yonsei University Health System)

FOREWORD

For Biopharmaceutical Industry & Academic Medical Researchers

Yonsei University Health System (YUHS) has been investing in the R&D infrastructure from high-throughput screening of chemical libraries, next-generation DNA sequencing via preclinical efficacy testing, and early human clinical trials to aid the development of drugs for targets identified in laboratories. The biopharmaceutical industry not only needs access to these facilities but also to considerable intellectual resources for medical practice expertise, clinical trials experiences, and market trends for next generation therapies.

Academic researchers can also learn significantly from their biopharmaceutical counterparts. Sharing experiences in technology, project management and operational excellence would benefit most medical institutions. The exposure of academic researchers to the translation from biomedical science to therapeutic commercialization helps fuel innovation and entrepreneurship. Medical institutions must try to understand the business objectives of their strategic industry partners and not assume that they have unlimited budget and timeline.

Positive human interaction, mutual respect, trust, and accommodating the viewpoint of others are essential for successful collaboration. In addition, transparency in data sharing and confidentiality, professional project coordination and management, and partner specific incentives can further improve these partnerships.
This booklet introduces the specific approach to how YUHS can successfully collaborate with biopharmaceutical companies in the healthcare industry.

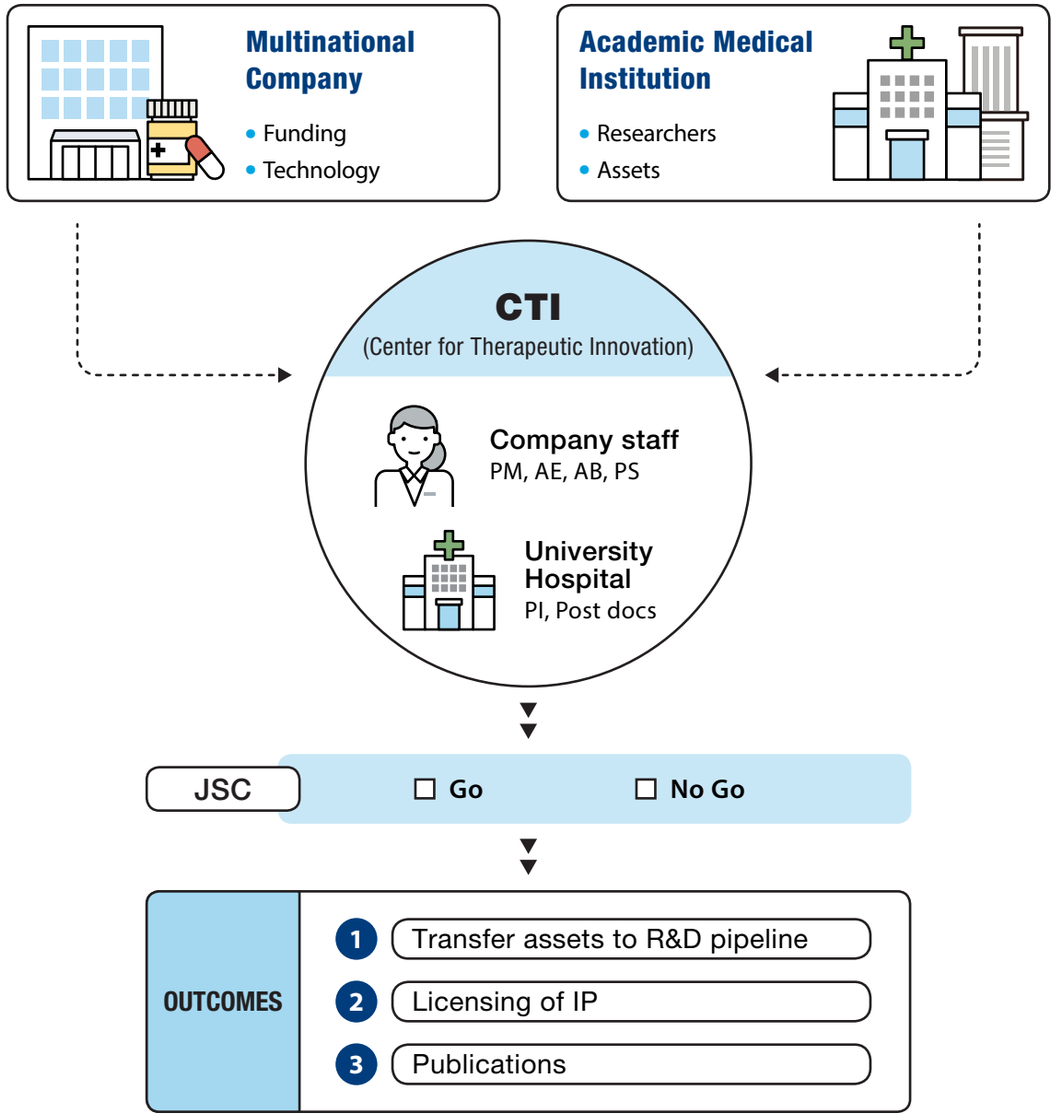
TRENDS

Growing Trends of Open Innovation

Outstanding medical institutions worldwide have already begun the evolution of reshaping organizations to improve the efficiency of attracting industrial R&D businesses. Along with the expansion of their roles and functions, they are also pursuing active and interactive communication in the coordination process to facilitate collaboration with industry partners. DCRI (Duke Clinical Research Institute), the academic research organization (ARO) of Duke University is no longer focused on independent academic clinical studies, but instead actively communicates with the industry for research collaboration. Boston Children's Hospital operates a technology licensing office (TLO) with the TIDO (Technology Innovation Development Office). It has not limited itself to the area of IP protection and licensing business. Through mentorship guidance programs and technology development funds, the hospital is making efforts to acquire industry expertise, by which researchers can advance innovative technologies into actual development stages. These organizations are promoting the commercialization of academic assets through cooperation and collaboration with R&D enterprises.

Global biopharmaceutical companies recognize medical institutions as a key collaborator for the R&D of innovative therapeutics. They are disclosing technology to academic researchers. Merck provides technology infrastructure for new targets or lead compounds owned by academia through the independent, nonprofit Calibr (California Institute of Biomedical Research). Pfizer, through its CTI (Center for Technology Innovation), opens up technology infrastructures for developing biologics to academic medical institutions. To date, CTI has partnered with more than 20 institutions and plans to expand its network with hospitals. Researchers from Pfizer and hospitals work closely together to bridge the gap between therapeutic knowledge and clinical experiences, and to advance new drug candidates to the clinical trial phase.

Open Innovation Case



Modified from the original figure:
Investments and outcomes from the center for therapeutic innovation

Abbreviations

PM Project Manager
AE Antibody Engineer
AB Assay Biologist
PS Protein Scientist
PI Principal Investigator
JSC Joint Steering Committee
IP Intellectual Property

ALYND

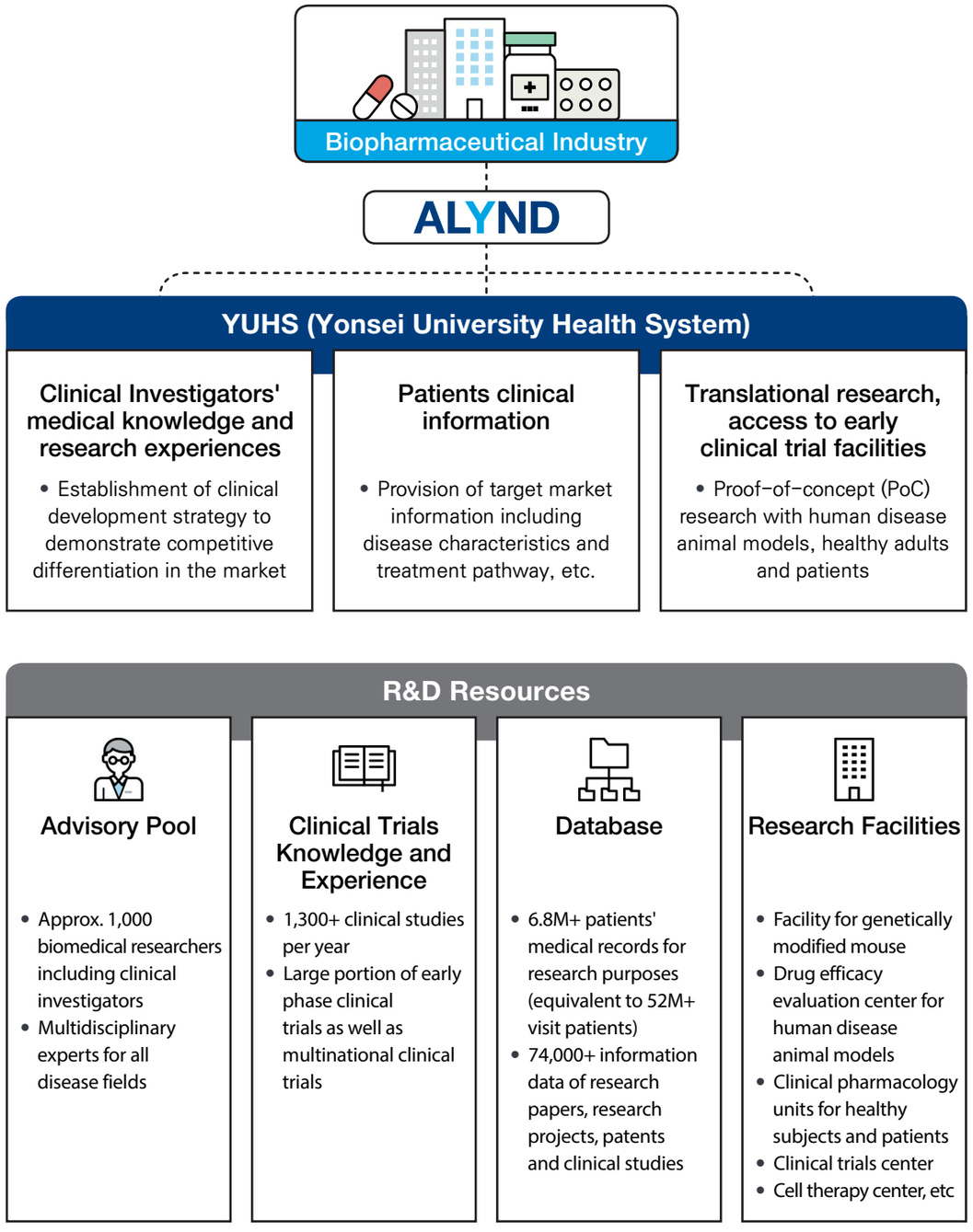
A Leading Yonsei Network for Biopharmaceutical R&D

Yonsei University Health System (YUHS), a leading academic medical institution in Korea, has various R&D resources such as knowledge and experiences of biomedical researchers, electronic medical records of patients care activities, core facilities for translational and clinical studies, etc. Some of these resources have been accumulated and stored as a retrievable database format. However, it is difficult for the biopharmaceutical industry to be aware of such resources because it is mainly used for intramural researchers. Therefore, matching the industrial needs with these R&D resources is the key initiation step of connecting biomedical researchers and subsequently coordinating for the collaborative partnership with the biopharmaceutical industry.

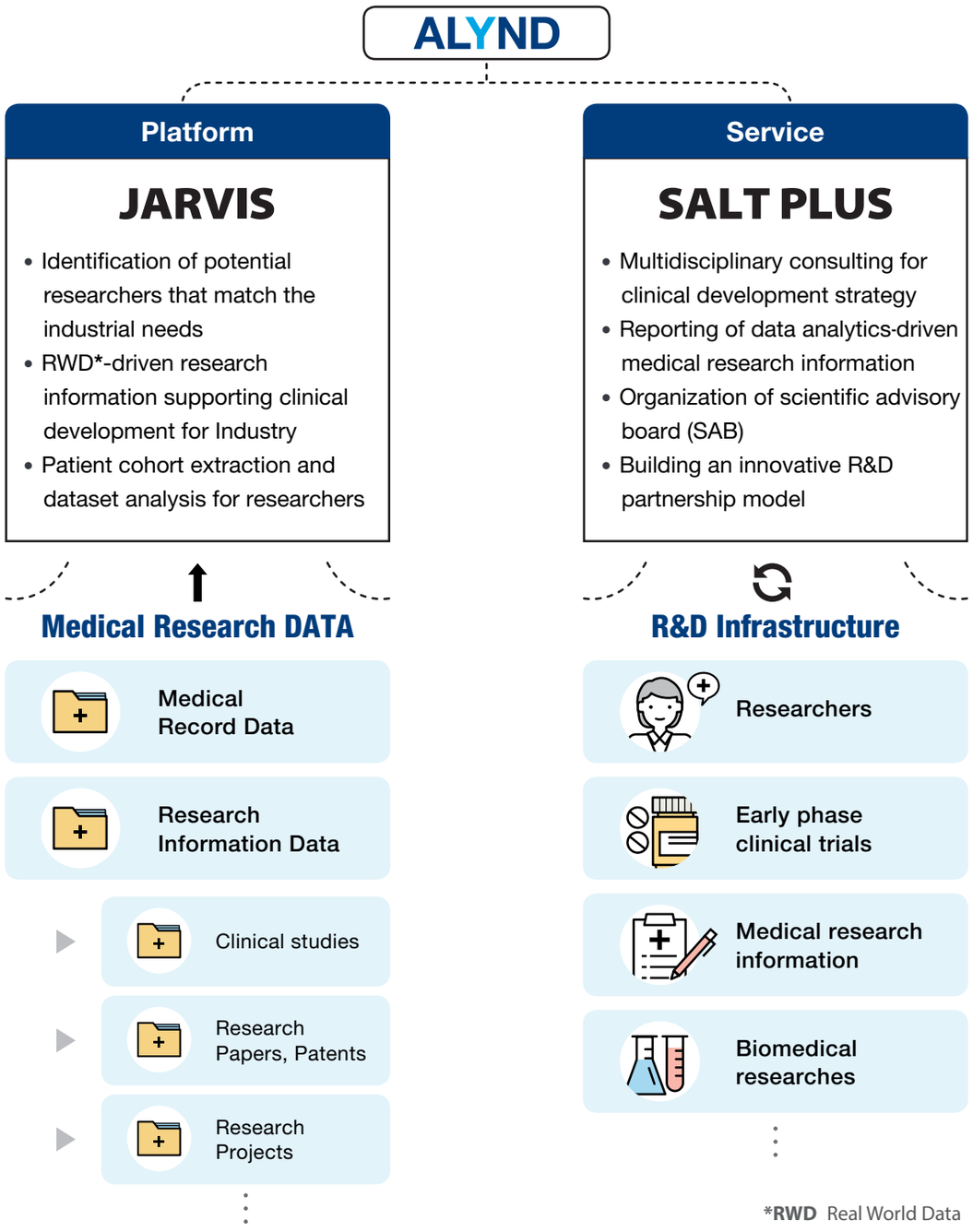
There is a new wave of closer and stronger relationship formations between academia and industry. For this reason, the R&D consulting center (hereinafter, referred to as "ALYND") was recently launched under University-Industry Foundation at YUHS. ALYND is a dedicated center that supports the biopharmaceutical industry to promote industrial research collaboration. It allows industrial partners to seek disease experts to discover unmet medical needs and to consult for clinical development strategy. The close collaboration will open up the opportunity for researchers to advance and accelerate their academic research to commercialization.

ALYND plays interactive roles in the bio healthcare sector. As a mediator for matching intramural R&D resources customized to industrial needs, it helps connect potential biomedical researchers. ALYND is also a facilitator of industry sponsored research and identifies biomedical researchers of common interests. Finally, it is a supporter for organizing strategic advisory leadership team with the biopharmaceutical company for the R&D collaboration. As a result, ALYND provides industry-academia partnership whereby industry partners funds for preclinical and clinical development programs, and researchers provide their ideas, knowledge, and biomedical research experiences.

Utilization of R&D Resources for Industry Collaboration



ALYND: Mediation Platform and Service Functions



***RWD** Real World Data

PLATFORM

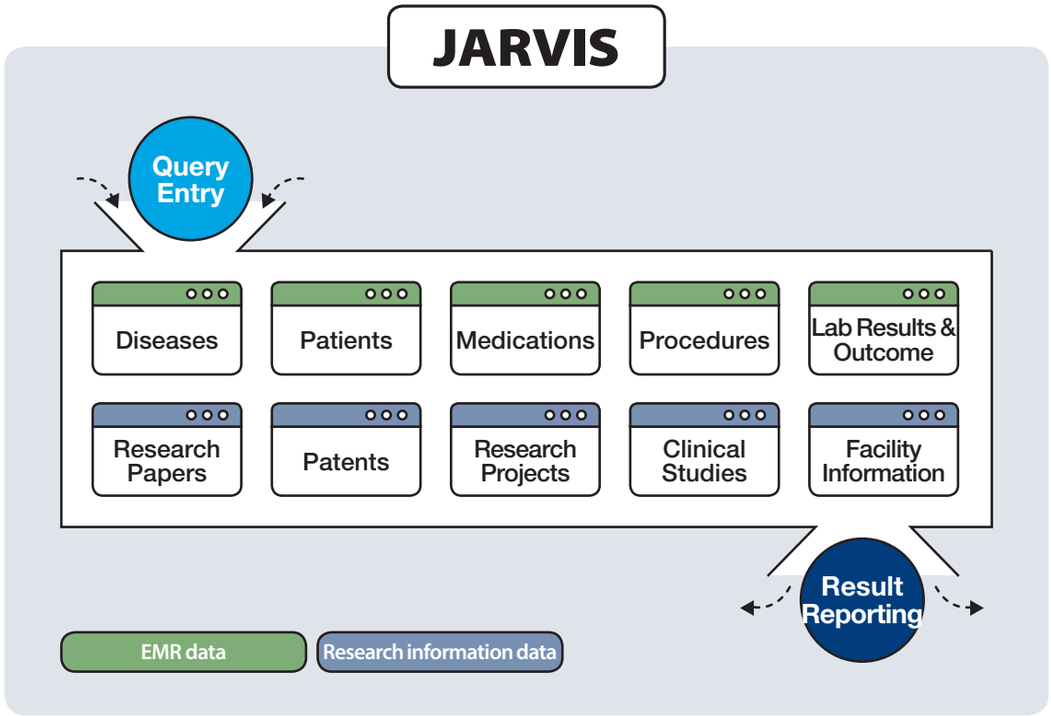
JARVIS

***J**ust **A**ugmented **R**esearch Na**vi**gation **S**ystem*

In order to facilitate R&D collaboration with industrial partners, ALYND operates the intelligent mediation platform: JARVIS. The system manages the clinical research data warehouse composed of two integrated datasets including patient care activities and biomedical research information. The datasets provide useful information to attract translational and clinical researches from the biopharmaceutical industry. The stored medical record data are derived from more than 6.8 million de-identified in- and out-patients care activities such as diagnosis, demographics, treatments, and outcomes including clinical lab results. The accumulated number can be converted to 52 million visiting patients. JARVIS also includes more than 74,000 information data of biomedical researches related to research publication, patents, research projects and clinical studies. More than 1,300 clinical studies are conducted annually and added to the system.

JARVIS has a query-enabled web-browser application that provides visualized analytics-driven information using medical record and research information data. It also has a variety of algorithms specifically designed for biopharmaceutical R&D. The two major functions are: cohort designer and researcher finder. The cohort designer operates by assembling query boxes sequentially. Each query box contains conditions such as disease diagnosis, patient demographics, treatments (medication, procedure/operation), clinical labs, etc. Based on clinical practice and biomedical research information, this system can also assist in identifying either potential clinical investigators for industry-sponsored study or clinicians for medical consulting.

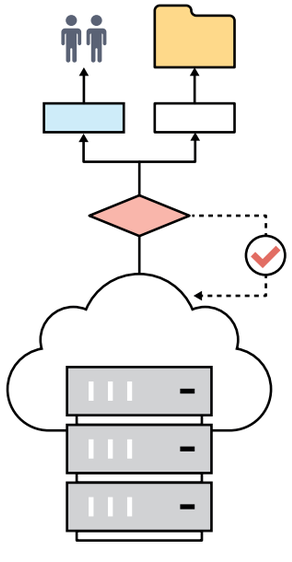
Therefore, JARVIS serves as a research navigator based on the clinical research database and is expected to play an important role in industry-academia R&D collaboration.



Enabling JARVIS to Support R&D collaboration

JARVIS is able to lead R&D collaboration for both partner sides. Companies can request for medical research analysis information and academic researchers can extract the desired specific patient cohort to gain research ideas through data analysis.
The information provided to the company is required to have the researcher's interpretation. This allows the company to connect the received information to the appropriate researcher. In addition, researchers can collaborate with the industry by linking their ideas with companies of interest.

Operational Algorithms of ***JARVIS***



BioPharma Industry-Researcher Matching

Identify potential researchers customized to industry's needs (e.g., translational/clinical studies and medical consulting)

Clinical Development Plan

Create profiles of patient journey, patient subpopulation and treatment pathway. Analyze therapeutic response data (clinical effectiveness)

Clinical Trial Design

Optimize protocol designs with real-world settings (e.g., patient pool estimation by eligible criteria, dosage information of control drug, patient visit information, etc.)

Study Feasibility Assessment

Estimate availability of eligible patients in specific departments and identify potential researchers based on clinical and medical research information

Retrospective Evaluation

Provide label expansion support for drugs by retrospective analysis of patient cohorts extracted for specific clinical conditions

SERVICE

SALT PLUS

Comprehensive Collaboration Program

ALYND utilizes its R&D resources to provide multiple services through the SALT PLUS program : ▲ Multidisciplinary consulting for clinical development strategies ▲ Reporting of medical research information through big data-driven analysis ▲ Organizing scientific advisory board (SAB) ▲ Building diverse R&D partnerships ▲ Holding academic events such as symposiums on academia-industry collaboration ▲ Developing new businesses by utilizing other resources to fulfill additional industry needs.

The resources comprise of both soft- and hard-infrastructure. Soft infrastructure resources are information and knowledge based and include biomedical research activities such as research papers, patents, clinical study experiences, etc., de-identified clinical research data warehouse, clinical researchers and patients, human tissue and blood samples. The hard infrastructure resources are physical assets including research facilities such as the efficacy evaluation center with human disease animal models, disease-specific research centers and clinical trials centers.

Once a request is received from the industry partner, ALYND connects its internal resources to provide optimized solutions suited for the request. This solution can include consulting of unmet medical needs and strategies for translational research and clinical development, reporting medical research analysis information on target disease profile and prescribed drug characteristics and providing in-depth feasibility studies for attracting contracted researches.

Program Overview

Consulting	Multidisciplinary consulting for clinical development strategy
Medical Research Analysis Information	Reports of data-driven analysis information for supporting R&D decision-making
Scientific Advisory Board (SAB)	Supports for organizing SAB between a company and researchers
Partnership	Attracting industry-initiated, funded researches or joint researches
Academic Events	Academic events such as symposium on cooperation between industry and medical institution
New Business	New business plan of utilizing R&D resources available in the academic medical Institution

1. Consulting

SALT PLUS offers multidisciplinary consulting services by biomedical scientists and clinical experts working at YUHS. Biopharmaceutical companies can gain insights on unmet medical needs of the target disease as well as clinical development strategy support from clinical researchers based on their practice, medical knowledge and research experience. This service provides not only experts' opinions but also big data analytics-driven information. The balance between data-driven information and advice based on the knowledge and experience of researchers brings new medical insights into the service; a unique offering not available in the conventional consulting market.

SALT PLUS consulting comprises of three main domains: TMP (target market profile), CDP (clinical development plan) and CTD (clinical trial design). TMP provides a detailed profile of the target disease characteristics and current medical treatment. CDP identifies differentiation and competitiveness points of an investigational product compared to conventional therapies and provides a guide to demonstrate those points in non-clinical study and early phase clinical trial. Finally, CTD optimizes the trial protocol designs and minimize protocol changes by applying the current medical practice of the target disease: for example, patient visit information, treatment pathway, eligible patient population, dosing regimen, etc. This consulting service will be extended to support protocol synopsis development for FIH & Clinical PoC study and medical evaluation of licensed product for clinical development.

Disease areas available for consultation are as follows: ulcerative colitis, new oral anticoagulants, multidrug-resistant tuberculosis, acute myeloid leukemia, peripheral T-cell lymphoma, myocardial infarction, diabetes mellitus, nonalcoholic steatohepatitis, eosinophilic esophagitis, hypercholesterolemia, asthma, chronic obstructive pulmonary disease, constipation, atopic dermatitis, anti-emetics, oncolyitc virus, autoimmune disease, wet age-related macular degeneration, allergic rhinitis, diabetic neuropathy, post-herpetic neuralgia, growth hormone deficiency, immunoglobulin, H. pylori disinfectants, peripheral arterial disease, graft-versus-host disease, senile gastritis, and anti-cancer novel compounds.

Key Consulting Areas

Clinical indication
diagnosis criteria, target patient pool size, current therapy

Disease characteristics
distribution of comorbidity and complication, disease staging

Patient journey
dynamic flow information for outpatients and inpatients (drug, procedure, operation)

Treatment period
minimal treatment period for evaluating efficacy or effectiveness

Clinical laboratory test
blood chemistry urinalysis, function tests, pathologic examinations, biomarker, etc.

Prescribed medication
medication classifications and drug response

Drug positioning
medication orders (1st, 2nd , and 3rd), drug combination

Route of administration
RoA candidates based on consideration of target disease characteristics.

Dosage
initial dose, dose escalation, administration period, optimal FDC strength

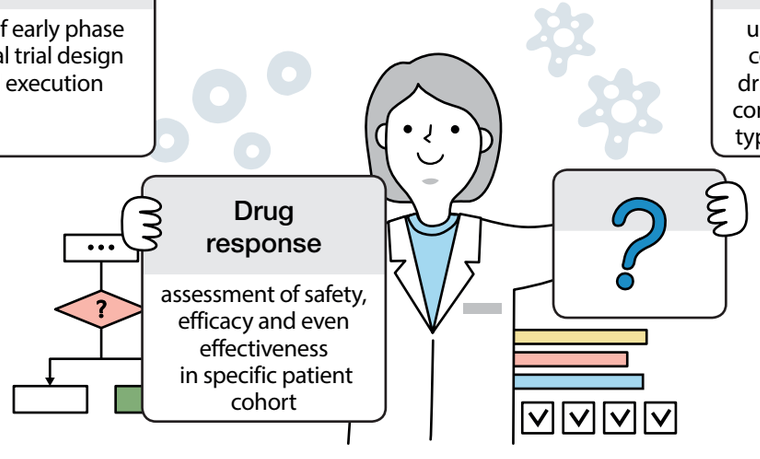
Human disease animal model
research collaboration with specific disease animal model

Study subjects
eligible patients for clinical trial design (based on inclusion and exclusion criteria)

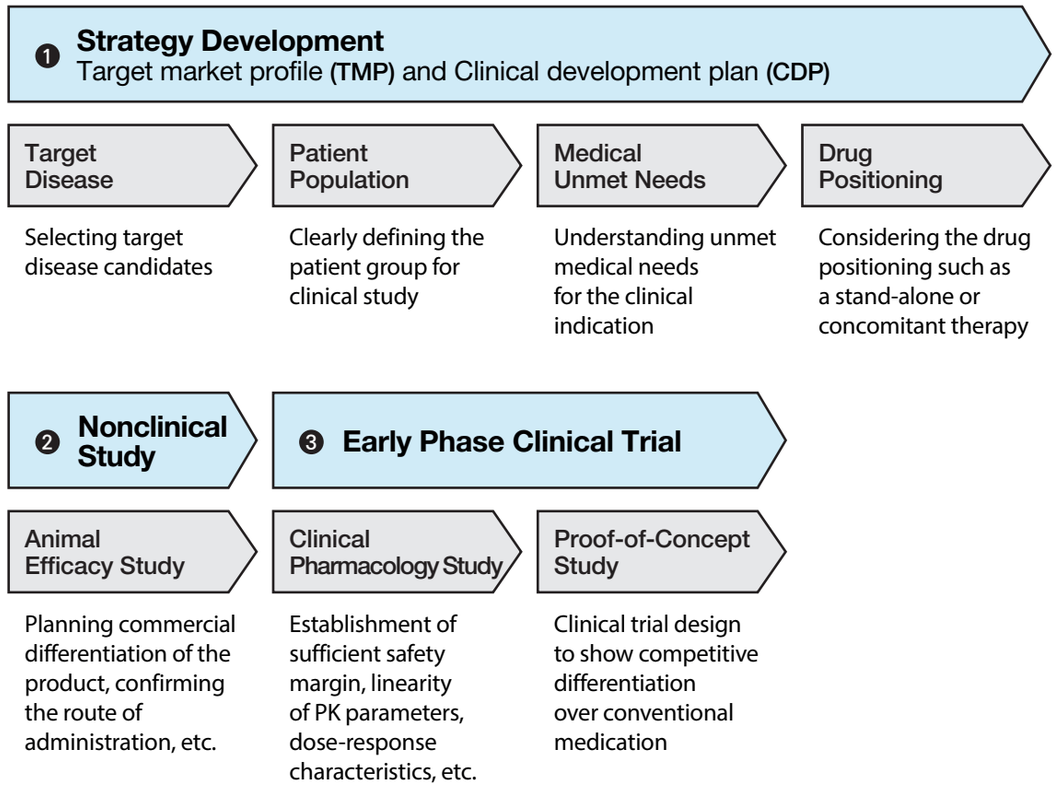
Market trends of investigational product
unsatisfying medical elements of existing therapeutic agents

Cost of clinical trials
cost of early phase clinical trial design and execution

Patient-centric perspective
users' experience, convenience, etc. drug compliance in comparison to other types of medication



Market Value-driven Drug Development



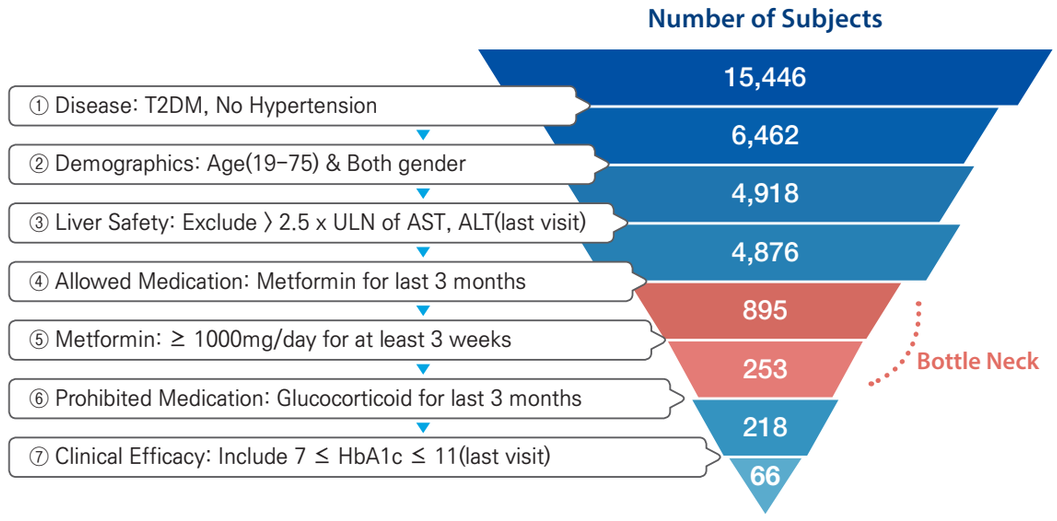
2. Medical Research Analysis Information

This service provides visualized reports with data analysis on the characteristics of target disease, its patient subpopulation, treatment pathway and the therapeutic response in the particular cohort. With this specific patient cohort extracted from real world data, JARVIS creates a patient cohort similar to the control arm for the clinical trial design. It selects patients diagnosed with specific diseases based on key inclusion criteria such as demographics, treatment regimen, and clinical laboratory results. At the same time, it excludes specific comorbidity, complication of the disease under the selected cohort, clinical interventions such as prohibited medications and other clinical variables. Temporal functions can also be

applied for the selected cohort by applying a specific time frame at an individual patient level. For example, the subpopulation of type 2 diabetes mellitus (T2DM) patients can be further defined by certain treatment duration from the beginning of their medication prescription with a certain dosage. The sequential pattern of prescribed medications and the clinical endpoints observations after the diagnosis can also be provided within the selected patient subpopulation. Clinical laboratory results are observed and measured during visits from the selected group.

In addition, the service provides in-depth feasibility study information for clinical trials: identification of potential clinical investigators based on their relevant research activities (clinical trials experiences, research papers, research projects, etc.), estimation of eligible patient pool size for the specific design, and patient recruitment history of similar clinical trials in the past. Moreover, extrapolation approaches combined with claim data make it possible to have a nationwide pool size of target patients. Thus, this information is able to provide medical insights to optimize protocol design, reduce protocol changes, and accelerate recruitment of eligible patients.

Patient Eligibility Determination for Clinical Trial Design

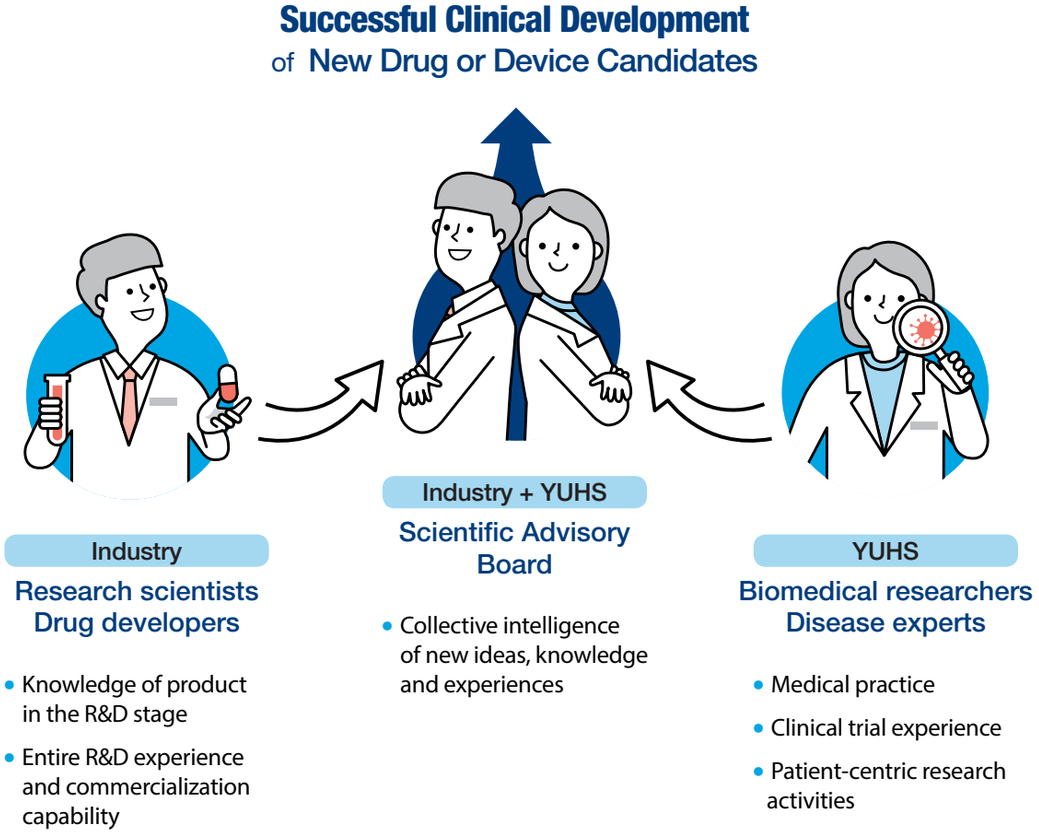


***Note** The number shown in this figure is not the actual number of patients, which is intentionally modified for an illustration purpose

3. Scientific Advisory Board (SAB) Supports

A scientific advisory board (SAB) usually comprises of scientists, drug developer and clinicians from industry and academia in the biopharmaceutical industry. The SAB enables sharing of expertise to fill the gap between academic and commercial knowledge, and provides strategic advice on the critical assessment of R&D projects. For example, given the huge cost of product development, the advice to modify R&D direction or even go/no-go decision at an early stage of R&D process is invaluable.

ALYND is making efforts to support the formation of SAB by engaging distinguished researchers in the industry's therapeutic field to create collective intelligence for new ideas, innovative knowledge, and unmet medical needs. The involvement of clinical researchers expands



the connection to intramural and extramural investigator networks. This introduces more opportunities to connect with globally prestigious researchers for preclinical efficacy evaluation study or early phase clinical trials.

In addition, many elite clinicians have high-level contacts with major biopharmaceutical companies and other potential strategic partners. The connections could create promising opportunities such as licensing and further develop open innovation. This interactive communication will lead to successful drug development.

4. Partnership

Partnering with medical institutions is important to overcome the current deficit in biopharmaceutical innovation and bring novel discoveries to the patient-oriented clinical development. Industry-academia partnerships can be classified into the following arrangements :

- **Contract Research**

For contract research, medical institutions conduct industry-funded research in their area of expertise. A contract research team will comprise of project-specific research and technical staff working under academic supervision. The industry generally wishes to own all the results of the project and the exclusive commercial usage rights.

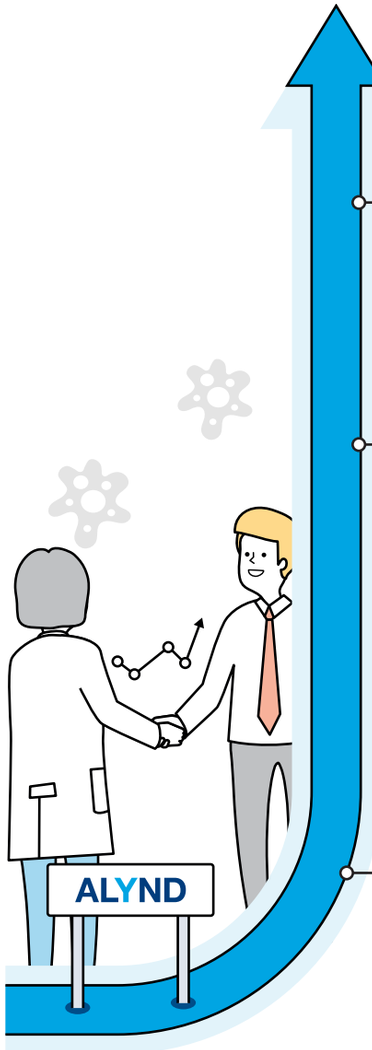
- **Sponsored Research**

For sponsored research, researchers put together proposals, which are reviewed by the industry for funding consideration. The industrial partner does not necessarily provide creative ideas for research, but will contribute by funding the project. The university and the industrial partner negotiate details relating to publication and access rights to the research results to meet the requirements of both partners.

● **Collaborative Research**

Collaborative research is a partnership where the research goals are defined by the partners and all partners actively contribute to the research activity. The project partners contribute to the research costs either in cash or in kind.

Full-cycle R&D Coordination



❸ **Commercialization Support**

R&D Cooperation Accelerator

Avison BioMedical Research Center (ABMRC)
(Support research team consisting of enterprise, basic scientists and clinical researchers)

❷ **Conduct of Translational Research–Clinical Study**

Translational Research

Cardiovascular products evaluation center, Human gene and biobank, Center for mouse models of human disease, Pharmacogenomics center, etc.

Clinical Development

Clinical trials center, Cell therapy center, Severance integrative research institute for cerebral & cardiovascular disease, Cardiovascular and metabolic disease etiology research center, etc.

❶ **Consulting Service**

Medical Consulting

Multidisciplinary consulting with analytics-driven information based on clinical practices and biomedical research experiences

5. Others

ALYND organizes symposiums to share the best practices for R&D collaboration with the biopharmaceutical industry. Workshops are held to discuss programs that can lead to company-led R&D in connection with medical institutions. This enables researchers to identify issues arising from the R&D cooperation process and discuss their solutions.

ALYND is also involved in new business development utilizing R&D resources such as patient samples. The industry is able to conduct target validation, customize the patient treatments, and evaluate the efficacy of an investigational drug with the xenograft animal model.

Evaluation support for R&D pipeline of venture capital funded entities is also available. We provide perspectives from clinicians who understand the medical unmet needs and therapeutic advance in the market.

Service Delivery Process

Understanding Operational Procedures

To request for SALT PLUS services, please fill in the two page application form and send it to saltplus@yuhs.ac. Once your application is submitted, an ALYND staff will be in touch with you within a couple of business days. A preliminary meeting is then set up via video-conference or face-to-face meeting to precisely identify your needs.

Preliminary service estimates are provided with the expected timeline and costs, then a mutual agreement is reached regarding the service initiation. Once the CDA (Confidential Disclosure Agreement) is signed off, specific request and confidential document packages are shared for the consulting service.

For other services, we can proceed with the next step as appropriate based on the type or content of the request. During the duration of the service, the parties can arrange for meetings to conduct further discussions or check the progress. The service is complete after the provided result report is reviewed and confirmed by the requester.