REVIEW ARTICLE

Japanese initiative for education in pharmaceutical medicine and clinical research training

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Abstract: Development of new medicines has become increasingly difficult with less possibility of success in seeds-finding and ever rising operational costs. Failure to comply with ethical standards for human research protection also erodes social trust in clinical development. In order to develop competence of professionals in medicines development such as clinical investigators and drug development scientists, a variety of educational courses and training programs have been developed and executed worldwide. As Japan is no exception and shares the same concerns, significant governmental and non-governmental efforts have been made to invest in the development of academic educational courses and adherence to international standards. This article introduces examples of the adoption of technologies to realize a user-friendly and sustainable learning management as well as an adaptation of syllabuses and core curricula to meet international standards in the era of global medicines development.

Keywords: PharmaTrain; CLIC; CREDITS; JAPhMed; SMD; pharmaceutical medicine; learning management system; continuous education

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1. Introduction

The discovery and development, regulation, and market introduction of medicines have become increasingly complex. Getting a new drug to market currently takes 13–15 years but the annual number of approved New Drug Applications has remained flat at around 20 per year for the past 30 years[1]. In addition, the costs to develop a new drug are increasing between US$ 2–3 billions on average[2]. Consequently, the efficiency of research and development of new drugs in the US halves every nine years and declines as described by "Eroom's law"[3]. A notable change is the industry's recent interest in niche markets such as the development of orphan drugs often priced high, in which conventional development methodology cannot be applicable due to limited numbers of patients available for clinical evaluation of safety and efficacy of the product in question. To address the efficient medicine development under the current situation there is the growing need for professionals to understand the integrated process of development, and manage all aspects of medicine development with knowledge and competency of pharmaceutical medicine which could interface various aspects of the process.

The International Federation of Associations of

Pharmaceutical Physicians and Pharmaceutical Medicine (IFAPP), a non-profit professional organization, has been promoting pharmaceutical medicine and medicines development by creating awareness and fostering education and training[4,5]. IFAPP also extended its partnership to develop PharmaTrain, one of the Innovative Medicines Initiative (IMI) educational projects, jointly undertaken between the European Commission and the European Federation of Pharmaceutical Industries and Associations (EFPIA)[6]. PharmaTrain provides standards and quality through a common syllabus and learning outcomes to form the curriculum with modular structure. Moreover, PharmaTrain has started the global implementation of its Education and Training system from 2014 to utilize the Shared Standards established in the EU for affiliates outside the EU.

As a member country of the International Conference on Harmonization (ICH), Japan has experienced similar difficulties and decided to enhance its educational investment. Since the enforcement of ICH-GCP in 1997, the number of investigational new drug applications has significantly dropped in Japan[7]. The Japanese government, the Ministry of Health, Labor and Welfare (MHLW) and the Ministry of Education, Culture, Sports, Science and Technology (MEXT) started the "Clinical trial activation plan" in 2003, a plan which has been revised three times since its initiation. The latest 5-year plan was published in 2012[8], in which, "human resource development for clinical research" is the key topic. Japan has also taken the step to develop international partnerships in establishing educational programs, such as the e-learning program by the University of Tokyo in addition to educational activities by the Japanese Association of Pharmaceutical Medicine (JAPhMed) which are based on PharmaTrain standards.

2. Human resource development for clinical researchers in the University of Tokyo

2.1 UMIN e-Learning

UMIN e-Learning was developed on the "University Hospital Medical Information Network (UMIN)". The UMIN was established in 1989 as a cooperative organization for national medical schools in Japan, sponsored by the MEXT. It is the largest and most versatile academic network information center for biomedical sciences in the world, and is considered as indispensable information infrastructure for the Japanese medical community[9].

A user with a UMIN account is eligible for e-learning. Because UMIN offers a single sign-on system, a potential user who doesn't have an account can obtain one by simply accessing the web site (https://moodle2.umin.ac.jp/moodle/), and follow the instructions to create a user account.

The major feature of this e-learning is the systematized program. The contents are stratified by professionals and skill-levels. The professionals have 6 categories: "Medical doctor (MD)", "Clinical research coordinator (CRC)", "Institutional Review Board (IRB) member", "Biostatistician (Biostat)", "Medical clerk" and "Data manager (DM)". The skill-levels have two categories: basic and advanced course. There are three types of courses for each level and professional: required (Req), optional (Opt), and not required (-). If a user completes all required courses, a certificate can be downloaded.

Table 1 lists the basic courses which consist of 4 sections and 32 items. Table 2 shows 13 items for the advanced course, most of which are in Japanese although some are in English considering globalization and standardization measures. Some contents are for advanced focus on Clinical Data Interchange Standard Consortium (CDISC)[10]. As of October 2016, the Japanese Pharmaceuticals and Medical Devices Agency (PMDA)[11] has started to accept new drug applications in the form of the CDISC standards, thereby urgently necessitating CDISC standards learning.

The learning management system (LMS) is "Moodle", a free and open-source software[12]. Due to UMIN security policy, no customization has been applied for Moodle. Any customization would require continuous updates, which in turn would make it difficult to apply security patches distributed by the software's producer. In addition, customization would be expensive. Consequently, the user interface of this e-learning system is easy to maintain, and, as shown in Figure 1, quite simple. On the other hand, a user interface is important to attract additional users.

2.2 Developing Syllabus for clinical education and new learning management system adjusted for new ethic guidelines

Conducting clinical research requires expertise in safety, knowledge of data management and statistics, in addition to ethical considerations. The Ethical Guidelines for Medical and Health Research Involving Human Subjects enacted in April 2015[13] put more

Table 1. Systematized program (Basic course part 1)

Sec	Contents	MD	CRC	IRB	Biostat	Clerk	DM
Ⅰ	Overview of clinical research	Opt	Req	Opt	Req	Opt	Req
	Basics of new drug development	Opt	Req	Opt	Req	Opt	Req
	Clinical research ethics	Req	Req	Opt	Req	Opt	Opt
	Legal requirements and guidelines	Req	Req	Req	Req	Req	Req
	Laws to protect personal information	Req	Req	Req	Req	Req	Req
	Compensation of clinical trials	Req	Req	Req	Opt	Req	Req
	Basic medical knowledge	–	Opt	–	Opt	–	–
	Diagnosis and treatment	–	Opt	–	Opt	–	–
	Clinical pharmacology	–	Req	Opt	Opt	–	–
	Diseases and medicine	–	Opt	–	Opt	–	–
	Biostatistics	Req	Req	Opt	Req		Req
	Life style-related diseases	–	Opt	–	Opt	–	–
Ⅱ	Elements necessary for clinical trial	Req	Req	Opt	Req	Req	Opt
	From the launch of trial to the application	Opt	Req	Opt	Opt	Opt	Opt
	Regulatory agency	Req	Req	Req	Opt	Req	Req
	Pharmaceutical industry	–	Req	Opt	Opt	–	–
	Medical institution	Req	Req	Req	Opt	Req	–
	CRO & SMO	Opt	Req	Opt	Opt	Req	–
	Roles & functions of medical institutions	–	Opt	–	Opt	–	–
Ⅲ	Understanding protocols	Req	Req	Req	Req	Req	–
	How to read medical records	–	Opt	–	Opt	–	–
	How to read laboratory results	–	Req	–	Req	–	Req
	Data management	Opt	Req	–	Req	–	Req
	QC & QA	Opt	Req	–	Req	Req	Req

MD: Medical doctor, CRC: Clinical research coordinator, IRB: Institutional Review Board member, Biostat: Biostatistician, Clerk: Medical clerk, DM: Data manager. Req: Requirement, Opt: Optional, –: Unnecessary to learn.

Table 2. Systematized program (Advanced course)

Contents	MD	CRC	IRB	Biostat	Clerk	DM
Global study	Opt	Opt	Opt	Opt	Opt	Opt
1) Recent experience with ROCKET AF						
2) Registry study						
3) Database studies						
4) Biostatistics: Step up						
5) Strategy for clinical research						
Early & exploratory clinical development	Req	Req	Opt	Req	Req	Req
Development of medical device	Req	Req	Req	Opt	Opt	Opt
Consultation by PMDA	Req	Opt	Req	Req	Opt	Opt
Medical writing	Req	Opt	Opt	Opt	Req	Opt
Efficient research by IT	Opt	Req	Opt	Req	Opt	Req
CDISC						
1) Introduction						
2) SDTM						
3) ADaM						
4) Overview						

MD: Medical doctor, CRC: Clinical research coordinator, IRB: Institutional Review Board member, Biostat: Biostatistician, Clerk: Medical clerk, DM: Data manager. Req: Requirement, Opt: Optional.

Figure 1. Screen shot of UMIN e-learning

emphasis than ever on education and training for clinical researchers and others who will be involved in clinical research. According to the above guideline, "Investigators and other professionals shall receive education and training on the ethics of research and on knowledge and skills necessary to carry out the research prior to its implementation. They shall also receive education and training during the research period on a regular basis as necessary."

However, due to the increased stringency and complexity of regulations, clinical researchers are required to increase not only their knowledge of ethics, but also expertise on how to properly conduct research which includes methodological, regulatory, and organizational expertise. Occasionally this also includes project management skills. It is common knowledge that those who work as physicians in hospital settings are already very busy, and have long – as well as irregular – working hours which in turn could result in excessive workloads. Lack of appropriate skills could result in research misconduct, whereas those who are subject to compulsory education may suffer from an overwhelm- ing workload. To ensure the quality and reliability of the clinical research process, there is an urgent need for continuous and systematic education of clinical research professionals once they have started to work in clinical settings.

To adjust to the new requirements for clinical researchers, the University of Tokyo Hospital needed to reconsider and restructure compulsory education provided for its employees. Furthermore, it is necessary for some users to obtain a globally recognized certification.

Until 2015, the compulsory workload consisted of: 1) Face-to-face compulsory ethics seminars on how to teach research ethics; 2) Compulsory within-hospital e-Learning on conflicts of interest and research integrity; and 3) Face-to-face guidance for clinical researchers on protocol writing and informed consent writing.

Our investigation concluded that points 2 and 3 need to be kept given that 2 specifically explains rules at the University of Tokyo Hospital, and 3 was case-specific for each investigator, and subsequently could not be substituted by other alternatives.

To develop a new educational system meeting global standards, we have considered education syllabuses from all over the world aimed specifically at clinical investigators, and further investigated how we, as providers with scarce human resources, can best implement the developed syllabus for researchers with limited time.

Through an extensive literature search[14-16], we have found that PharmaTrain (an IMI programme on training in medicines development), and the European Clinical Research Infrastructures Network (ECRIN) joined force in 2011 to establish a European investi-

gator training syllabus called CLIC (Clinical Investigator Certification)[17,18]. CLIC is well structured and consists of 3 different levels of training related to distinct responsibilities in the performance of clinical trials, confirming that clinical investigators and investigative team members reach a similar level of competency: Level 1: Site staff/sub-investigator, Level 2: Principal investigator/Site manager, and Level 3: Sponsor investigator.

In order to follow the latest ethical guidelines and comply with requirements relevant for Japan, we have made some alterations to the CLIC syllabus. First, we have moved some ethics topics provided in Level 2 into Level 1. Second, we have checked if we could cover compulsory content from the Collaborative Institutional Training Initiative Japan Program[19]. Third, we have added and amended parts of the syllabus in order to cover the introduction of medical devices as well as regenerative medicine. These changes resulted in an increase from 10 to 12 chapters (Table 3). With regards to compulsory education, the University of Tokyo Hospital requires, as of July 2016, that principal investigators, sub-investigators and CRCs take all 12 chapters, while research group members with other responsibilities are required to take between 1–3 chapters.

2.3 CREDITS

To include all the necessary requirements and needs stipulated by researchers, we have developed a continuous systematic education & training curriculum for clinical researchers and specialists entitled "CREDITS", Clinical Research EDucation and Interactive Training System (https://www.uhcta.com/uth/member/index.cfm).

Table 3. Modified CLIC based syllabus for Japanese clinical researchers

Chapter	Title
1	History of clinical research and the subject's right
2	Ethics and code of conduct of clinical research
3	Ethics required to conduct clinical research
4	Overview of development of medicine/ medical devices
5	Introduction to clinical research methodology
6	Legislative framework and guidance for clinical research
7	Planning and preparation of a clinical study
8	Site organization and management
9	Subject recruitment, enrolment and retention
10	Overview of in study procedures
11	Introduction to safety
12	Quality management system

This is a life-long learning and training curriculum, aimed at nurturing clinical researchers and specialists, thereby ensuring continued development of researchers' collective capabilities based on available and up-to-date global standards.

CREDITS is a multiple learning system where users can, among other options, take ICT programs (e-learning and web seminars), and submit applications for participation in face-to-face seminars.

Each user's training log is recorded on the system, allowing the participants to keep track of their attendance record. Reminders are sent prior to the expiration of each user's validity period, thereby enabling them to continue with their learning. Moreover, the system encompasses knowledge of clinical research based on global standards which is useful when conducting global clinical trials.

Cooperation between researchers and other professionals (such as CRC, biostatisticians, data managers, monitors, auditors and ethic committee members) is vital to ensure the reliability of clinical research. It is thus essential to build a baseline training curriculum for all professionals involved in research, irrespective of background and current position.

2.4 Collaboration with other universities

Based on the background above, The Clinical Research Support Center of the University of Tokyo has been collaborating with two relevant working groups: 1) The National University Hospital Clinical Research Initiative (NUH-CRPI), founded in October 2012 to promote clinical studies and clinical research at national university hospitals by supporting preparation of systems for conducting high-quality clinical research and clinical studies safely and efficiently through information sharing and coordination, and 2) The University Hospital Clinical Trial (UHCT) Alliance, a volunteer group consisting of 8 universities in the Kanto area established in Feb 2006 in collaboration with industry associations, and funded by MEXT.

Together with NUH-CRPI, the aforementioned syllabus is the product of the University of Tokyo's position as a central workforce of a topic group on setting the learning objectives for education and training and creating a syllabus for clinical researchers in Japan.

As for the implementation of the new syllabus, together with the UHCT Alliance learning management system, we developed CREDITS to maximize the ability of each national university hospital (Figure 2).

Figure 2. Screen shot and main function of CREDITS

So far, we are providing mandatory learning courses on ethics and on the topic of how to conduct clinical research both prior to the approval of research plans as well as during ongoing research projects.

CREDITS is a program which has just been recently introduced (October, 2016) with a gradual increase in e-learning content and the number of face-to-face seminars. We have thus not yet been able to assess the effectiveness of CREDITS. Potential evaluation indicators will be based not only on the number of completed certification programs but on more substantial measures such as the amount of clinical research conducted in the user universities, and fewer reports of research misconduct or an increased number of clinical research articles which abide by current research guidelines.

3. Educational activities in pharmaceutical medicine by JAPhMed

JAPhMed was established in 1969 as a professional organization by physicians working in pharmaceutical industry, and it joined IFAPP in 1975 as its national member association in Japan. Under its vision and mission to promote pharmaceutical medicine, JAPhMed has actively committed to facilitate educational opportunities.

As a local implementation of the global quality standards by PharmaTrain on Education and Training (E&T) of pharmaceutical medicine, JAPhMed took the first initiative by establishing the nation's first pharmaceutical medicine course in collaboration with Osaka University, and recently started a second initiative by implementing the pilot project of Specialist in Medicine Development (SMD) program which is the competency- and workplace-based education and certification in collaboration with ACRP-Japan and EFPIA-Japan.

3.1 Pharmaceutical medicine educational course in Japan

Utilizing governmental efforts to revitalize development of pharmaceutical medicine in Japan from 1990s, Osaka University developed the Clinical Research Professional (CRP) training course program targeting postgraduate students and industry employees to teach fundamentals of the development of drugs and medical devices. This program is accredited as part of the curricula of the Graduate School of Osaka University.

Taking advantage of this prior establishment at Osaka University, JAPhMed has started to collaborate

with Osaka University and undertaken to expand this program along with the PharmaTrain syllabus and curriculum to meet PharmaTrain quality standards. In 2013, Osaka University started a two-years course in pharmaceutical medicine which is fully aligned with the PharmaTrain program.

In particular, by selecting a number of suitable modules from the CRP training course, the new course was amended to meet PharmaTrain standards. Accordingly, some additional modules were added in 2013 to form a one-year "Base Course" comprised of the 6 PharmaTrain Base Course Modules. In 2014, this was followed by 4 Extension and 4 Elective Modules aligned with the "Extension Master" curriculum conditions of PharmaTrain. The Module composition of the Pharmaceutical medicine educational course in 2014 is shown in Figure 3.

This course is offered to the students at two sites, one is in the course organizer's facilities in Osaka and the other is at Osaka University's remote office in Tokyo, allowing the participation of students in Tokyo via videoconferencing attended by a local facilitator. Although this course is the first integrated educational program in pharmaceutical medicine in Japan, it is not possible to achieve a master's degree from Osaka University due to governmental regulations. Instead, the university is certifying successful completion of the respective modules within this overall program by issuing the CRP Certificate. On the other hand, JAPhMed is issuing a "Year 1-Certificate in Pharmaceutical Medicine" and a "Year 2-Certificate in Pharmaceutical Medicine".

In April 2015, following an audit by PharmaTrain, this course was the first in Asia to be awarded a Centre of Excellence (CoE) recognition.

3.2 Specialist in Medicine Development (SMD) program in Japan

Under the changing and complex status of medicines development, academically qualified people in the workplace further pursue to obtain higher degrees and acquire a certain array of competencies across multiple domains through their on-the-job training and university training courses. There is, however, currently no qualification/degree/title available which certifies such achievement.

A Specialist in Medicine Development (SMD) title for pharmaceutical physicians and scientists based on the concept of competency-based and vocational training is developed to fill the above-mentioned gap[20]. In particular, a working group of representatives from PharmaTrain, academic institutions, IFAPP executive

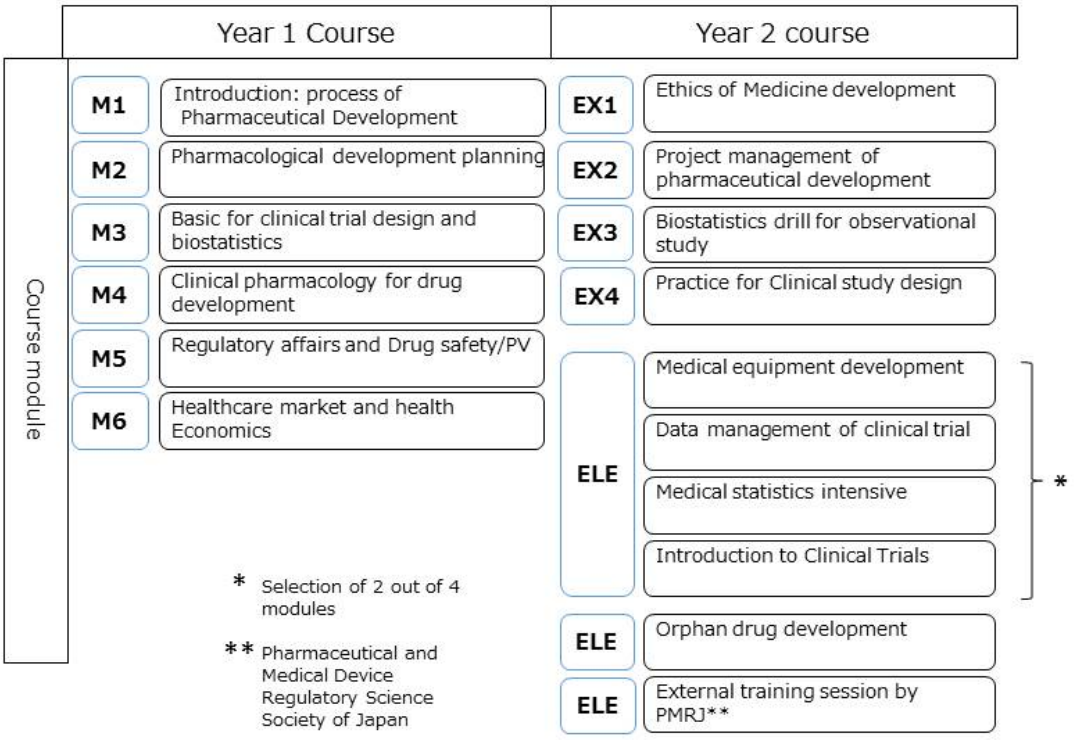

Figure 3. The module composition of the pharmaceutical medicine educational course in 2014

office and national member associations is formed and expected to define core competencies for the SMD E&T system[21]. The core competencies for pharmaceutical physicians and drug development scientists were developed to align with the Learning Outcome of the PharmaTrain Base course. Thus, 7 domains and 57 core competencies were identified and aligned accordingly. Each competency is evaluated by perspectives of acquired knowledge, skills and attitudes/behaviors. The structure of these domains and competencies is shown in Figure 4 (modified from Appendix 13.4 of the PharmaTrain Manual).

A minimum of 2 of the 6 operational domains relevant to the professional work in medicines development, and one general domain for communication, management and leadership must be completed in the workplace to be awarded the SMD title. The frameworks of the SMD program such as organization, management, administration and governance are defined under the auspices of PharmaTrain[1,6].

In accordance with the timing when we obtained the first graduates of the pharmaceutical medicine course at Osaka University, JAPhMED has developed the next and advanced E&T program. The concept of SMD advocated by PharmaTrain, and the qualifications assessed by outcomes through competency-based and vocational training are well received by the academic graduates and also meet the needs of medicines developing scientists initially educated in Japanese pharmaceutical companies. JAPhMed is currently cooperating with ACRP-Japan and EFPIA-JAPAN and is, as of June 2016, undertaking the pilot program of SMD.

Entry criteria for SMD candidates in the Japanese program are following the instructions by PharmaTrain: A) Have completed a formal education (BSc, MSc, MD, PharmD, RN, DV, PhD or equivalent) in life science or healthcare e.g. medical doctors, pharmacists, biologists, chemists, biometricians, certified nurses). B) Hold a function in Pharmaceutical Medicine/ Medicines Development Science, or intend to hold such a function for the practical competency-based, workplace-centred training towards the SMD Award. C) Have a named and qualified mentor in the workplace (such as a line-manager), responsible for overseeing and facilitating their training. So far 10 candidates from pharmaceutical companies and academic clinical institutions are enrolled and preparing for the pilot implementation of the SMD program in Japan.

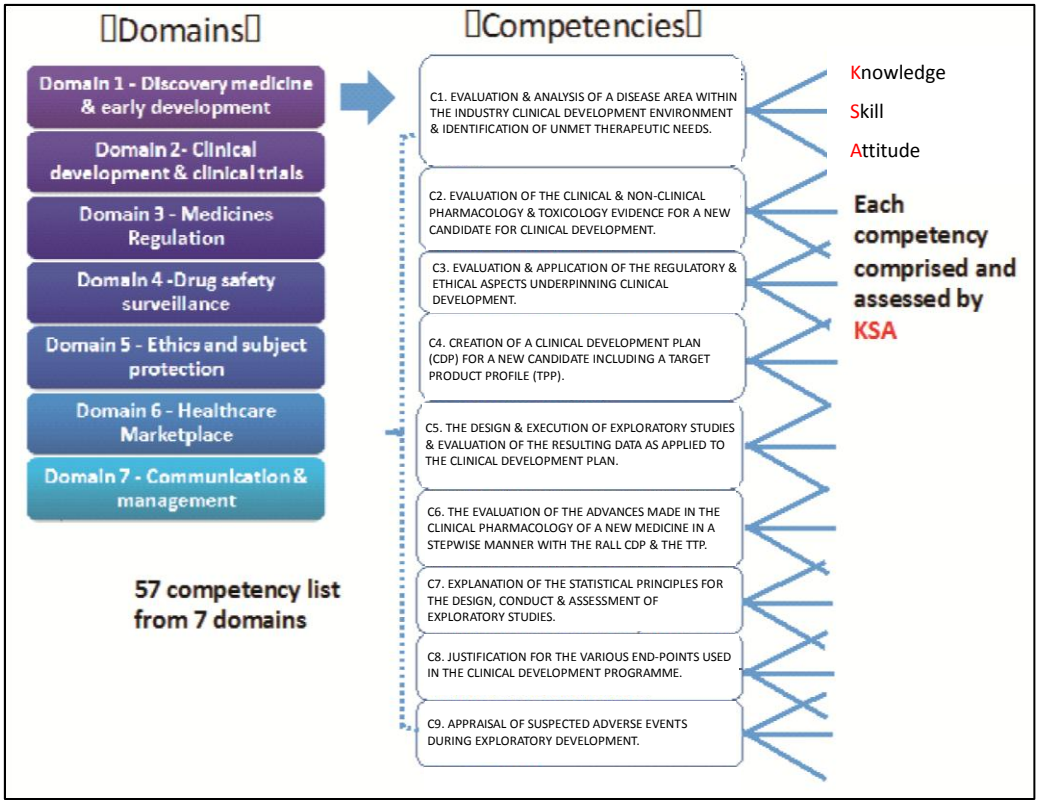

Figure 4. Structures of SMD domains and competencies

4. Conclusion

In the evermore competitive global environment of medicines development, many issues can be shared internationally but solutions are unique to target groups, regions, and nations to meet different social cultures and infrastructures.

Japan has established "today's status" among the many nations strong in medicines development, based on its intense national investment in academic education in science and technology as well as vocational training in the workplace. Despite the rapidly changing environment and diversity in medicines development involving medical devices and regenerative medicine, fundamental strength continues to come from the development of excellent human resource. Professional education and training meeting international standards, and the needs of different learning styles will be required to survive the next generation.

Conflict of Interest and Funding

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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