e-Protocol

A Translational Research (TR) Protocol Generator and Monitor

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Summary
Conflict resolution of the clinical safety and the clinical efficiency is the first hurdle for the success of TR that is a kind of experimental phase of human based clinical trial. Maximizing both safety and efficiency produces conflicts, and it requires optimization of the TR protocol. Protocol management tool named "e-Protocol" having function of the protocol generation and the protocol monitoring can help optimization of the TR protocol. The protocol generator assists the generation of an optimized TR protocol by modifying the standardized TR protocols with four steps. The protocol monitor keeps watch on the execution status of the generated protocol and records the status of the results. This paper shows a basic concept, prototyping, and its evaluation of a TR protocol generator and monitor.

Key words:
Translational Research, Genome, Clinical, Protocol, Generator, Monitor

1. Introduction

Translational research is the transitional phase of new findings from basic research to clinical practice. This phase needs to verify whether the newly developed clinical procedure is safe and effective on human body. Considering that translational research is a kind of experiment on a human body [1], the first priority in translational research should be securing safety. Securing safety needs proper protocol formation and its careful execution. Then the second priority should be optimizing efficiency. Optimizing efficiency without losing maximized safety is principal in translational research. To keep these priorities, protocol optimization, protocol keeping, and clinical log recording are essential.

Protocol optimization can make translation effectively safe. Clinical activities based on optimized safe protocol make each clinical action reasonable and minimize the risk.

Protocol based activity is essential to proceed translational research properly. Keeping optimized protocols and keeping reasonableness of each clinical action are basic issue to secure safety. But protocol based activity is difficult to keep because protocol has too many rules to keep all in daily activity. Pre-generated optimized protocol and its working-activity-plan can ease burden of keeping protocol.

Through the precise following-up of optimized working activity plan, we can secure the safety and can maximize the efficiency of translational research process. Keeping protocol during the operation of the working activity plan makes the execution of TR reasonable and reliable. The protocol-based activity is highly demanded in TR.

Thus precise recording of the log for TR is principal for both securing safety and optimizing efficiency. The clinical log recording makes process of TR clear. Computerized translational research protocol and electrical log enable easy but complete migration of its protocol and whole process to next clinical trial phase. On the other hand, translational research requires heavy documentation to keep protocol. Precise clinical protocol and its log can be the basis of documentation that is the heaviest work in practical translational research process. Automating documentation based on protocol management tool makes translational research process reliable and eases translational research manager's heaviest task effectively.

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2. Background

As indicated in NIH Roadmap [2], translational research has important role to let new findings to clinical field. Translational research itself is popular in cancer research. Recently genome based translational research starts in response to the accomplishment of the human genome project. Genome-translational research is a clinical experimental research aiming to introduce genomic novel findings to clinical medicine. Its clinical endpoints are to improve QOL (Quality Of Life), clinical safety and clinical efficiency.

As for applying methods of electronic knowledge technology to the medical field, a tool project based on ontology called PROTÉGÉ [3] is under way. Based on PROTÉGÉ, they are developing the EON system [4] for protocol-based care. Recently genomic ontology dictionary is constructed as Genetic Ontology (GO) [5]. But the integration of genome and clinical knowledge has not been tried yet. Liaison on our integrated knowledge architecture that is previously published [6], we designed translational research protocol management tool. We focus on the verbal side of ontology and try to put knowledge based on words based description for translational research.

Basic idea of composing working activity plan comes from factory management planning Tool in engineering field [7,8].

3. Methods

A TR protocol is a set of designated rules of the procedures for the validation and the smooth processing of TR. It includes diagnosis procedure, treatment procedure, and evaluation methods. Protocol management tool has three supporting functions as protocol generation, its execution monitoring, and log recording (Fig. 1). Protocol generation function supports safe and effective protocol composition from the integrated knowledge base. It has function of customizing protocols from the standardized protocols that are stored in the integrated knowledge base. The daily working activity plans are composed based on the generated TR protocol. Working Activity plan monitoring function works as a checker for the processing of the generated working activity plans. On the accidental situation, the irregular events handler wakes up and the working activity plan will be changed according to previously generated emergency protocols, the documentation and data recording are logged in any cases.

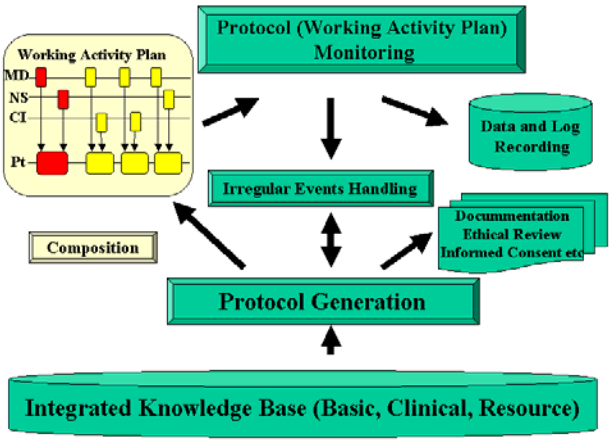

Fig. 1 Outline of Translational Research Protocol management tool

3.1 A. Protocol Generation Process

Fig. 2 shows outline of the protocol generation process. The protocol generation tool is based on knowledge base and its processing. The standard protocol is stored in the integrated knowledge base with the words based ontological technology. As a basis, we classified protocols to four steps as the standard protocol, the modified protocol, the customized protocol, and the working activity plan. Starting from the standard clinical protocols that are stored in the knowledge base, by modifying it with new idea based on genomic findings, we can get the modified protocol as a translational research protocol. Applying the personal information to the modified protocol produces the customized protocol. Then applying hospital resources' conditions and other required conditions to the customized protocol, this application produces the working activity plan of each stuff.

The standard protocol must be the normally accepted and recognized clinical procedure among the domain experts. The examples of the standard protocols are the guidelines, the clinical standards, and the clinical directions released from academic society or committee or consortium. Some of these standard protocols are gathered and are stored in our electronic knowledge base as part of the clinical knowledge.

A modified protocol is a modified result from the standard protocols. Its modification is based on a new idea that comes from the genomic findings or the other basic research. The modified protocol can be the next standard protocol candidate and includes the clinical protocol for the critical clinical situation, the data collection strategy, the statistical analysis strategy, and the decision criteria for the endpoints of the research. In implementation of a new idea to clinical field, the new idea should be transformed to its clinical application through this process. As for

inspiring a new idea with knowledge processing, we can use e-pathfinder that is a kind of intelligent amplifier [9].
The customized protocol is the personalized protocol of the modified protocol. The personalization is achieved with considering the patient's particular set of circumstances like his/her familial or previous history etc.

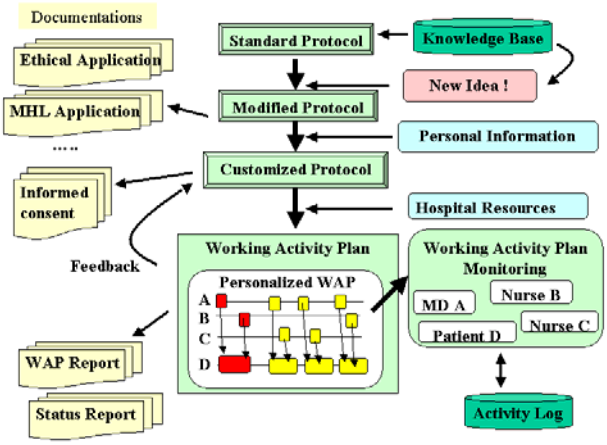

Fig. 2 Outline of Protocol generation process

3.2 Working Activity Plan composition process

The working activity plan is the daily action list that shows an individual action plan of each hospital stuff or of each patient. This is the personalized daily protocol based on the customized protocol with considering the status of the hospital resources, the local rules, and the local protocols. An example of working activity plan for a research nurse in a ward is shown in Fig. 3. Daily activity of a research nurse is listed. The working activities of the nurse are listed up in chronological order. We can also see the list of stuff's activity for each patient at a glance in other window.

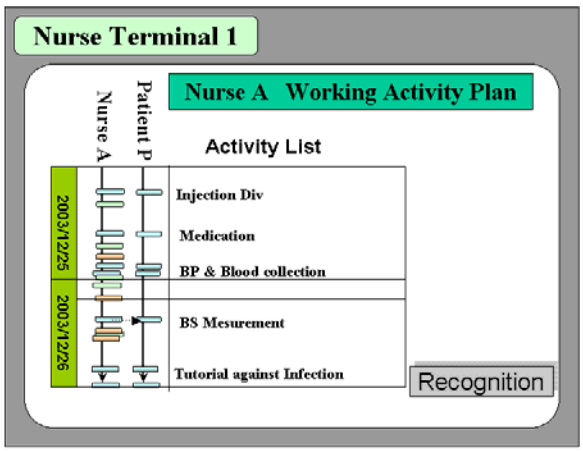

Fig. 3 An example of working activity plan

3.3 Working activity monitor

Fig. 4 shows outline of the working activity monitoring. Through this monitoring, each stuff can work on planed activity designated by working activity plan. Each stuff can see and can check the planed activity list through the terminals. When each stuff has done the planed activity, the stuff can report his/her finished activity and its resulted status through the terminal only by checking the finishing-mark. Reported information is stored electronically as the clinical record and is checked its correctness and violation as compared to the working activity plan. The working activity monitor evaluates the clinical status and the protocol keeping. In case of the irregular events detection, this monitor proposes the sub protocols that are prepared for the irregular events at proper timing, and the monitor generates new working activity plans based on the sub protocols.

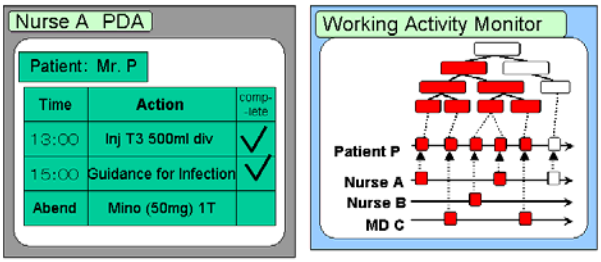

Fig. 4 An example of Working Activity Monitor

3.4 Handling irregular events

Fig. 5 shows a system response to an irregular event. When an irregular event occurs, the working activity monitor alerts the situation and proposes that the protocol for patients should be changed to irregular events protocol. Irregular events protocols are sub-protocols of customized protocol. Receiving the alerts and proposes from this system, MD as human should make all decision and answer to system alerts. The new working activity plan is produced based on new changed protocol. After calming irregular events, the protocol monitor re-alerts that irregular events may be settled. If responsible MD accepts settlement of irregular events and chooses to return to normal protocol, system proposes normal protocol again and reproduce new working activity plan.
These protocol changes are reported to all related stuffs immediately through protocol monitor. Each stuff can know the changes and what they should do immediately.

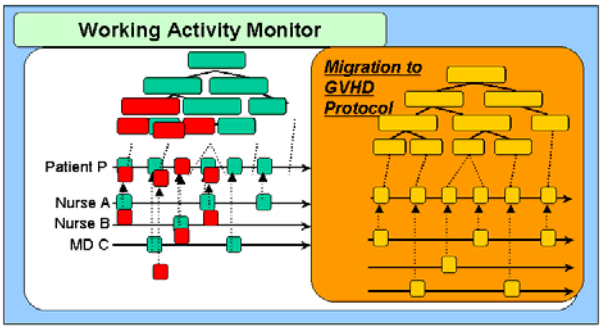

Fig. 5 System response to handle irregular events

3.5 Documentation, data recording, and its analysis

Clinical record is the integrated log of all clinical activities by all stuffs for each patient. Clinical activities from Stuff's terminals and data from monitoring system are integrated to build clinical record. Clinical record should be the summation of the history for a patient.
Based on generated protocol and working activity plan, documentation is done automatically and appropriately. This documentation is customized for each personnel. Through authentification, system recognizes personnel and supplies appropriate documents for each personnel. Digital signature is introduced for the signed documents for security protection. Its security functions are access restriction by authority level and tamper-proof packaging.

4. Results

We developed scenario checking tool as a prototype and checked our initial concept from user side of view. This tool enables checking transition of screen image from the view of user's scope. By setting user's clinical story through screen image transition, this tool shows transition of screen image. In the clinical theme of umbilical cord blood stem cell transplantation, we set the story and checked the screen images. Evaluation was done through this focused area at first. This tool can show transition among plural terminals, and it enables testing of connection among each system element of protocol management system. This tool can reveal difficulty and its level clear before developing costly prototype for protocol composition itself. This tool is also useful to explain usage of this system to the users.
Fig. 6 shows an example of scenario checker. This scenario stands on the point from the research nurse side. Transition of screens on nurse's terminal can be shown like picture card show. This scenario is about umbilical cord blood stem cell transplantation and screen is written in Japanese.

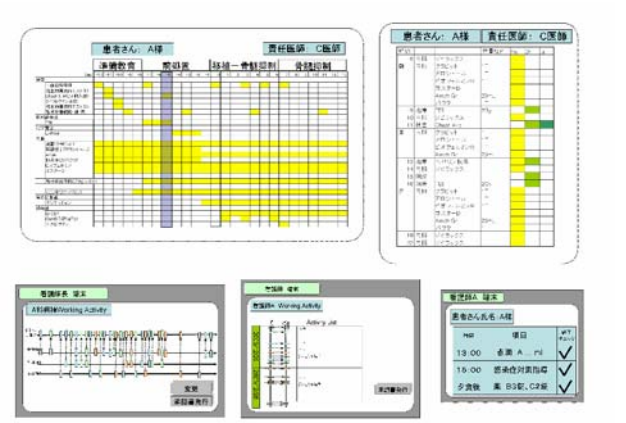

Fig. 6 An example of scenario checker

5. Discussion

In translational research, protocol plays an important role to protect safety or to guarantee reliability. But too many rules to secure safety make translational research protocol generation complex and difficult. Rule based composition tool that can generate translational research protocol easily is practical demand of translational researchers.
Keeping protocol is a backbone of securing safety in translational research. Optimized and secured protocol based activity can minimize human failure and clinical accidents. Because of its novelty, translational research protocol is always unusual protocol and has unknown procedures. Planed activity and its understanding can eliminate stuff's anxiety and hesitation. This leads to secure safety and to enhance effectivity.

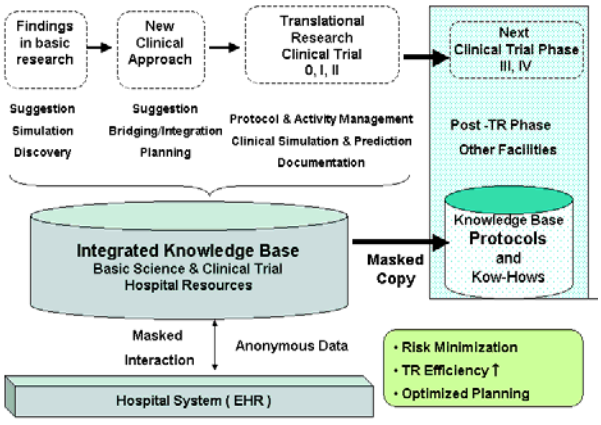

Fig. 7 Knowledge Based Translational Research Support Concept

On the other hand, translational research requires heavy documentation to keep its protocol. Pre-designed protocol make timely documentation possible and ease burden of principal investigator's work. Eliminating burden of stuffs leads to secure safety and to enhance effectivity.

Considering that translational research is an early phase of clinical trial, the outcome of translational research should migrate properly to next clinical trial phase like IIb or III. Computerized translational research protocol can make migration easy and reliable through copying its process, protocol and log. This can make next phase clinical trial safe and appropriate (Fig. 7).

This protocol management tool can prepare documentations required in translational research automatically and in proper timing. But this kind of responsible documentation still needs confirmation of translational research manager. Considering responsibility of each action done in clinical field, the same issue rises at each planed clinical action. Who takes responsibility of every action is the fundamental issue. This system cannot take responsibility of any clinical action. The role of this system is to ease burden of everyone concerned to translational research through supporting or assisting his/her jobs. The stuffs as real human still must have responsibility to his or her decision and action.

Generated protocol should have maximized safety and should be efficient. But safety and efficiency are conflicted objects. Generally safety needs additional process or extra cost, and improving efficiency eliminates superfluous process. Optimized protocol based on standard protocol can maximize safety within the realm of standard protocol and our knowledge. Efficiency should find its meeting point after setting maximized safety in translational research.

Users of protocol generator will be Principal Investigator, Clinical Investigator, stuffs, and responsible protocol designer, and this system supports generation of safe and effective protocol for these personals.

Users of protocol monitor will be all stuffs related to translational research project. Each user can see necessary information as authority level through monitor. Respective information is cut out from unified knowledge that is integration of translational research protocol and clinical practice. Users can see multi-faceted information as his or her authority level, but the source of information is the only one knowledge stored in our knowledge processing system.

Through proper following-up of working activity plan, we can secure safety and effectivity of translational research process. Keeping protocol during operation of working activity plan make translational research execution reasonable. Precise information transduction is the basis of keeping protocol. Information transduction through centralized execution monitor can show planed accuracy.

Storing log as clinical record and its tamper-proof make security of record safe and reliable. Properly stored clinical record can be used as the raw data for research analysis and official document.

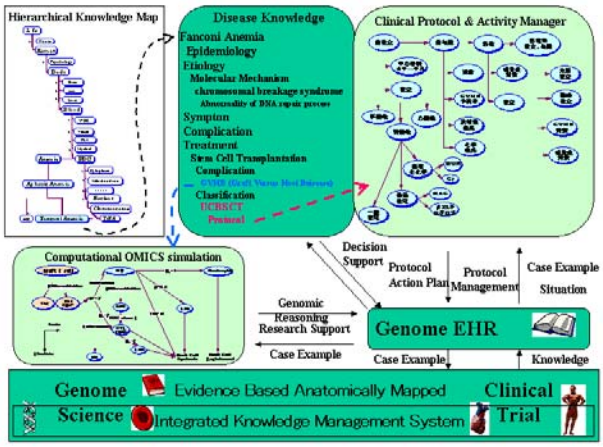

Fig. 8 Relation with HIS, EHR, KMS

To establish daily work protocol management system, we should consider more practical prototype (in progress) and reasonable connection with electronic health record (EHR), knowledge management system (KMS), and systems biology (Fig. 8). As for inputting data through terminal, introducing ubiquitous computing for automatic input and checking tasks is more desirable.

6. Conclusion

Translational research protocol management tool is highly demanded to secure safety and is practically useful to help the translational research managers and the stuffs. Automating documentation based on protocol management tool can make translational research process reliable and help translational research manager effectively. Computerized translational research protocol makes perfect migration of its protocol to next clinical trial phase possible. Through copying translational research protocol and its log, all experience in previous phase can be migrated to next phase. This precise data can make restaging translational research precisely possible. Recording log of translational research automatically make translational research easy and reliable. Basic concept was confirmed by prototyped scenario checker of translational research protocol management tool.

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