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A WORKFLOW BASED CLINICAL DECISION SUPPORT SYSTEM THROUGH INTEGRATION OF CLINICAL WORKFLOW AND KNOWLEDGE PROCESSING

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Abstract. *This paper proposes a workflow based clinical decision support system(CDSS) incorporating two main parts of CDSSs: 1) clinical workflow to control diagnostic activities and clinical events, and 2) knowledge processing by rule based inference for decision-making of clinicians. The requirements of a workflow based CDSS were derived by analyzing SAGE (Standards-Based Sharable Active Guideline Environment), which representatively incorporates the workflow concept into clinical guidelines. An open-source based workflow management system (WfMS) was adopted as a framework for integrating a guideline converter, a rule engine, and a CDS service provider. We implemented the proposed system in local clinical institutes using different guidelines: 1) Lab alerting to test the architectural plausibility, 2) Hypertension to verify the coverage for clinical knowledge processing, and 3) Severe Sepsis to validate the functions of event handling and workflow automation.*
Keywords: CDSS, Workflow, BPM, Clinical guideline, SAGE

1. **Introduction.** Clinical Decision Support Systems (CDSSs) have long history of more than 40 years, and have been used for variety of purposes, ranging from quality and safety to efficiency, and across a variety of clinical domains such as screening, diagnosis and therapy [1]. CDSSs provide clinicians with clinical knowledge and patient related information at right time of patient care. With the advance of IT, the architecture of CDSS has been improved from stand-alone systems to service models for decision support [2], and recent CDSSs commonly are based on computer interpretable guidelines (CIGs) and a layered architecture. A CDS engine, which is an essential part of a CDSS, employs various tools such as a graphical guideline editor, guideline repository, a formal encoding language, service coordination mechanism, a simulator, a connection with patient records, and security handlers [3].

To develop a CDS engine, a widely used approach is to develop it based on a particular CIG. This approach is beneficial less misunderstanding of guideline interpretation because the CDS obliged to have dependency on a CIG. By contrast, it is lack of compatibility when to be used for heterogeneous guideline formalisms. The other approach is to adopt commercial S/W products as a CDS engine. This approach may require customization or an additional knowledge translator to enable the engines for general purpose to interpret and execute the particular clinical guidelines, and thus there exist gaps between guideline formalisms and semantics of execution engines. Nevertheless, it has advantages of matured and reliable execution, reusable S/W components, and extensible architecture.

Although the two approaches have pros and cons, we consider latter promising. The background is that recent CDSSs are required of too many functions such as knowledge acquisition, guideline modeling, guideline execution, event handling, and knowledge management. It is not only difficult but also inefficient to develop and maintain those components directly. Moreover, there is not de facto standard language for clinical guidelines yet [3], and thus developing a CIG specified CDS engine may lack extensibility and interoperability. For these reasons, we decided to adopt commercial knowledge management tools to develop a CDSS.

In this study, a workflow management system (WfMS) was used to integrate the CDSS components such as a rule engine, a guideline converter, an event handler, and a CDS service provider. The requirements of this workflow based CDSS were derived by analyzing SAGE (Standards-Based Sharable Active Guideline Environment), which incorporates the workflow concept into clinical guidelines [4]. It is useful in adopting workflow in CDSS: 1) a WfMS can be a framework of integrating the CDSS components and 2) a WfMS can support clinical workflow in terms of workflow pattern and clinical event handling. We implemented three different types of clinical guidelines in order to verify the usefulness: Lab alerting to test the architectural plausibility and performance, Hypertension to verify

the coverage for clinical knowledge processing, and Severe Sepsis to validate the functions of workflow automation and event handling.

The rest of this paper is structured as follows. In Section 2, we investigate the related literature. Section 3 explains the design concept and requirements of the proposed system. Section 4 describes the system architecture and the scenario of CDS execution and Section 5 shows the implementation of three clinical guidelines in practice. Conclusion summarizes the results of the prototyping and discusses the future works in Section 6.

2. **Literature Survey.** The definitions of a CDSS range from precise and narrow definitions that may exclude broad categories of work to all-encompassing definitions. In this paper, we limit the definition as standard based systems and service models suggested by Wright and Sittig (2008) [1]. These models have separated the clinical information system (CIS) and CDSS components of an integrated decision support system, and recombined them by using a standard application programming interface (API).

Although a number of important approaches such as PRODIGY, GUIDE, Gaston, GLARE, HELEN, DeGel, and SEBASTIAN have been tried over the decade [5], SAGE and SEBASTIAN [6] are recognized as one of the improved CDS architectures. The notable literatures on CIG based CDSSs are listed in Table 1. In most cases, the CIG based CDS engines have been developed by the research group which developed the CIG formats. Some literatures tried a hybrid approach to make a generic execution engine for sharing different CIGs [9].

Table 1. Literatures on CIG based CDS engines

Knowledge base	**Engine type**	**Implementation**	**Author**
Protégé	ATHENA DSS	Hypertension	Goldstein et al., 2000 [7]
PROforma	PROforma execution engine	Acute Myeloid Leukemia in children	Bury et al., 2001 [8]
GLIF, PROforma	GESDOR	DTP immunization	Wang et al., 2003 [9]
GLIF3	GLEE	Childhood immunization, Cough	Wang et al., 2004 [10]
GLIF3	GLEE	Diabetic foot care	Peleg et al., 2006 [11]
GLIF3	GLEE	Depression screening and management	Choi et al., 2007 [12]
SAGE	SAGE execution engine	Immunization	Ram et al., 2004 [13]
SAGE	Process + rule engine	Ductal Carcinoma In Situ	Ceccarelli et al., 2009 [14]
Executable Knowledge Modules (EKMs)	SEBASTIAN CDS Web service	Mammogram	Borbolla et al., 2010 [15]

The literatures adopting commercial S/W products into developing a CDS engine are listed in Table 2. Commercial rule engines have been used as a powerful inference engine for clinical knowledge processing by simulating the behavior of a clinical guideline with particular patient data values [16,17]. As to knowledge processing algorithms, we do not deal with alternatives such as Bayesian, heuristic, neural network, genetic algorithms, or case-based [18]; these have been done as experimental trials. The benefits of using a rule engine is standardized if-then rule modeling so that non-programmers domain experts can use them, and good performance through the optimized algorithms [19].

Nevertheless, using rule engines cannot cover complete for clinical guidelines and the external parts such as control of the guideline flows, invocation of rule execution and

interfaces with local applications have to be supplemented. A WfMS is a powerful solution, which employs various tools to support the entire life cycle of workflow from design to execution and analysis [20]. Since a workflow model can represent diverse flow patterns such as data, resources, logics, and controls, the workflow approach to executing clinical guidelines have been noticed in the related literatures [21-24]. It is also promising in that as the coverage of knowledge bases in CDSSs gets wider, so does the original use of workflow as a business process management which can be utilized in clinical processes.

Table 2. Literatures on use of commercial S/W

Knowledge base	Engine type	Implementation	Author
Java based WizOrder (HTML)	Rule engine	Blood product ordering	Heusinkveld et al., 1999 [25]
VGR scripting language	Rule engine	Deep venous thrombosis pulmonary embolism	Starmer et al., 2000 [26]
EON + Translator	Workflow engine (for Petri-net)	Acute Myeloid Leukemia in children	Dazzi et al., 1997 [27]
Workflow definition language	Workflow engine (ADEPT flex)	None	Greiner et al., 2004 [28]
SPREAD guideline	Workflow engine (Oracle workflow builder)	Patient care process (events)	Panzarasa and Stefanelli 2006 [29]
Not stated	Rule engine (iLog rules)	Lipids, smoking, BMI, Anti plt, ACE, BB, etc.	Goldberg et al. 2006 [30]
Xpath expression language	Workflow engine (ActiveBPEL)	Not stated	Heard et al., 2006 [31]
Xpath expression language	Portable CDS rule engine	Not stated	Huang et al., 2006 [32]
SAGE + Translator	Workflow engine + rule engine (uBrain)	Hypertension, Lab Alerting	Kim et al., 2008, 2009 [33,34] Lee et al., 2010 [35]

It is remarkable that the two approaches have been trying to get closer. Mulyar et al. (2009) compared guideline modeling languages with workflow patterns, and concluded that both are remarkably close and WfMSs are suitable for clinical guideline applications [36]. This movement indicates that the gap between workflow and CIGs is narrow theoretically and use of WfMSs will increase.

3. **Design.**

3.1. **Design concept.**

As a design concept of this study, we set SAGE as a conceptual framework to derive the requirements of a workflow based CDSS. The reason of selecting SAGE is that one of its key approaches is to integrate guideline based decision support with the workflow of care process [4]. In addition, SAGE is recognized as one of the improved CDS architectures with its large coverage of knowledge base [2]. SAGE includes a knowledge authoring tool based on Protégé. The clinical knowledge base can be modeled

as a SAGE guideline, and it can be translated to be executable for the CDS engine by a guideline converter.

Table 3. Matching table between SAGE objects and the integrated engine

SAGE object		Concept	Matched element in a WfMS
Recommendation specification	Activity graph	Guideline-directed processes	Workflow models with time domain and event handling
	Decision map	Recommendations involving decisions at a time point	Decision based workflow models at a time point
Sub guideline		Hierarchical nesting of recommendations	Hierarchy of workflow models mutually connected
Decision model		Representation of decision knowledge required to recommend a choice among alternatives	Workflow control functions for branching and selecting a proper node
Action specification	Actions operate on VMR classes	Operations involves making or retracting conclusions	Workflow activities involve rule based recommendation
	External action	Actions with external systems	Messaging between systems
	Aggregations of actions	Set of actions	Set of related workflow activities
	Deprecated action specifications	Ad hoc actions	Specified activity types for ad hoc actions
Evidence statement		Guideline statement regarding the relationships between clinical conditions and interventions	Not included in this study
Expression language	GELLO	Formal representation of eligibility criteria and decision criteria	Not included in this study
	Basic data types	Basic and HL7's abstract data type specifications	Java classes for specified clinical data types
	Variable	Static data representation	Rules defined as a function
	Function	String-valued expression and a reference to the expression language used	Rules defined as a set of functions
	Queries	Information structure of the external knowledge sources	Queries for retrieving patient data in CISs
	Criteria templates	Structured templates to encode decision criteria in a syntax-independent form-based method	Rules defined as a set of functions consists of variables, functions, and other criterion

In Table 3, principal SAGE objects are mapped to the elements of a WfMS and a rule engine. In SAGE objects, recommendation specification, sub guideline, and decision model represent the structure and metadata of SAGE guidelines. Thus they can match to the workflow control functions of a WfMS. Action specifications are related to the interactions between CDSSs and clinicians, and can be converted into task delivery functions of a WfMS. Evidence statement and expression language can be converted into a set of rules which can be executed by a rule engine.

As a result of the comparative analysis, it is found that a WfMS and a rule engine can cover SAGE objects mostly. Nevertheless, a few remaining engineering issues should be solved; 1) data formats should be shared to keep consistency of patient data and outcomes of CDS executions. 2) The methods and protocols to handle diverse clinical events, a CDS

client and server should employ event handlers and external control ports such as open APIs.

3.2. **Development strategy.** The proposed CDSS consists of a WfMS, a rule engine, a guideline converter, and a CDS service provider. A WfMS and a rule engine were adopted from open source S/W, and the guideline converter and the service provider were additionally developed. The followings development strategies were established.

Integration of a workflow engine and a rule engine

Clinical guidelines can be effectively separated into the combination of workflow and rule models in terms of knowledge processing. We used a workflow engine as an interpreter of the guideline model, and used a rule engine as an inference engine. The following criteria were considered to select suitable products.

- In order to achieve reliability of execution, the two engines should be easily integrated. The ingredients of integrity are the common programming language, fully object-oriented design, and simple and extensible interfaces.
- The products are required to have sufficient industrial references in order to assure stable performance against physical stress in practical uses.
- The framework of engines should be based on a well-known architecture (J2EE, etc.) so that the components can be easily added or reconfigured.
- Because our project was involved in a national perspective, the proposed system should be non-profitable and open to the public. Open source products also have benefits of better interoperability and encouragement of participation for developers and institutions.

Consequently, two open source products; uEngine and BRAIN were selected. uEngine is a WfMs which has advanced in convenient development of customized workflow activity types so that it can integrate the other modules with ease. BRAIN is a business rule engine based on an object rule model and <if then> rule expression. The two engines were fully developed in the Java language platform and based on object-oriented design patterns. They were already verified in decision supporting module of management information applications. The integrated CDS engine was named uBrain.

Integration of a WfMS into clinical workflow

A clinical workflow involves sequences of diagnosis, clinical events, actions such as alerting and recommendations. A WfMS can control the activity flows and deliver messages from a CDS engine to clinicians. Various types of delivery tools such as email, instant messenger, SMS, or portable devices can be used.

CDS service provider through web services

The recent CDSS architecture aims to a client-server system to provide services for physically distributed clients. uEngine basically acts on a web application server, and we added a CDS service provider using web services. A guideline model which is deployed in uBrain server will be automatically produced as a service with a unique identification. Through the service provider, any CDS client in distributed locations can request a service in remote uBrain server.

A web service based service provider enables to solve the interoperability issues between CDS servers and clients. uBrain uses a sharable XML format for exchanging patient data and CDS execution outcomes. A CDS client can compose a patient data set using this format without dependency of particular applications or systems. In addition, the CDS service provider supports various workflow automation functions such as invoke, control, and finish the services at operation.

4. Development.

4.1. **Knowledge acquisition and translation.** There are two use cases of uBrain; 1) the design phase to make a new clinical guideline, and 2) the operation phase to execute the guideline in the CDSS in the realistic manner. Our research group consists of knowledge engineers who are domain experts with background of clinician or nursing and IT engineers. In design phase, the knowledge engineers encode a SAGE guideline using a

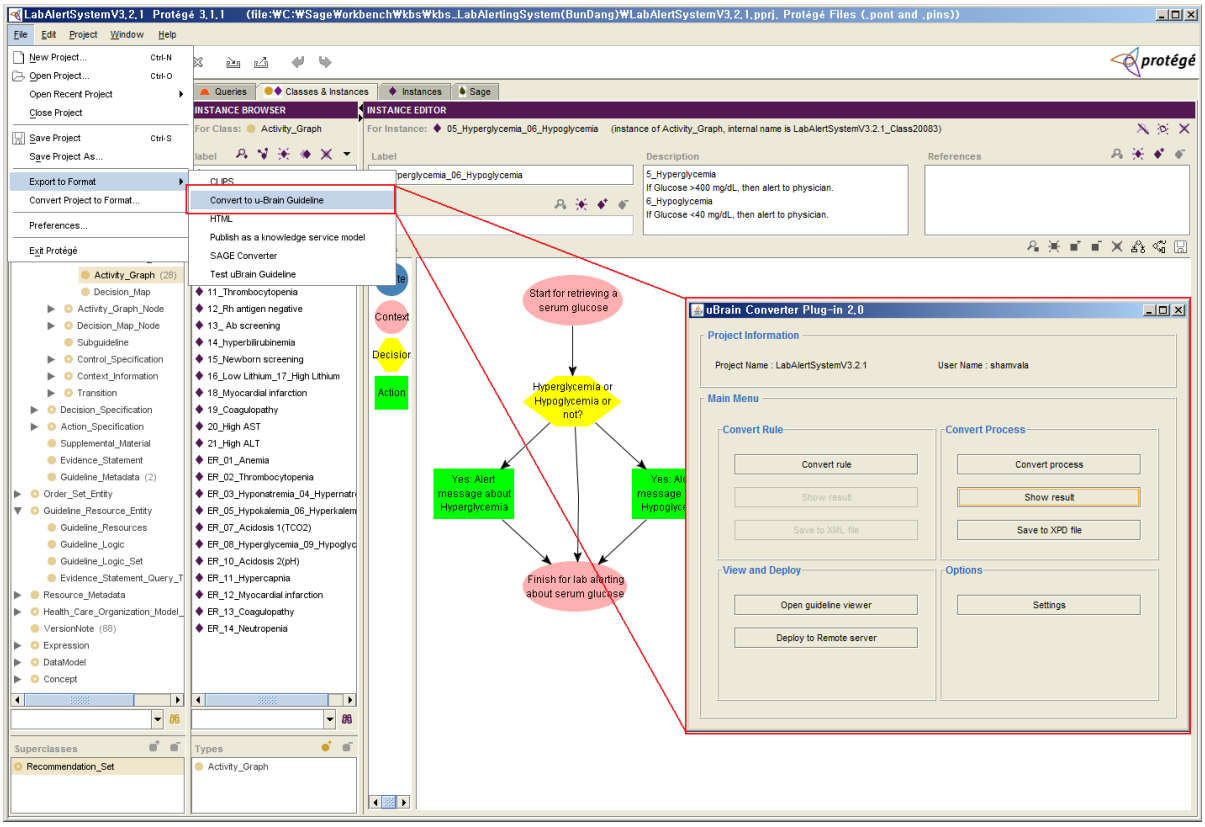


FIGURE 1. Guideline converter embedded in SAGE workbench

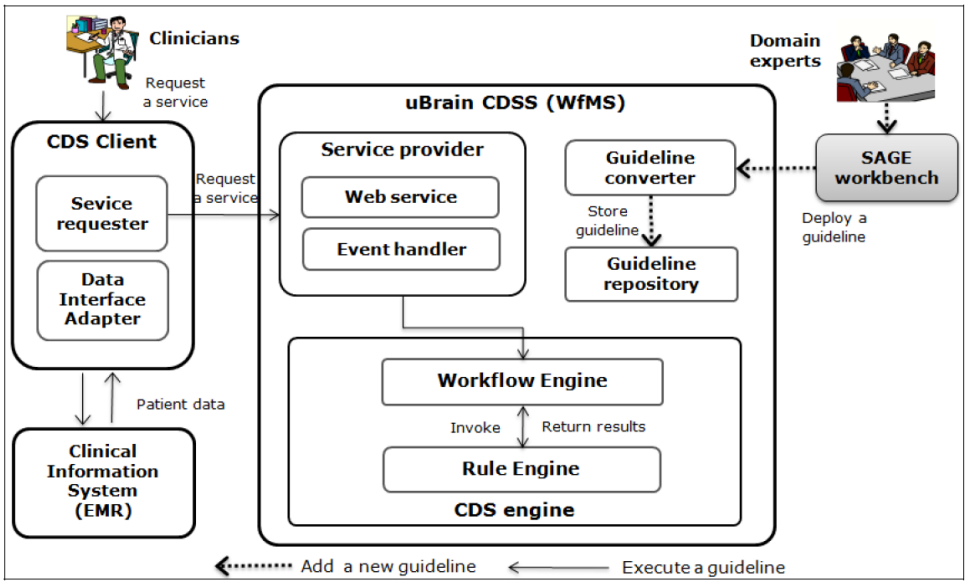
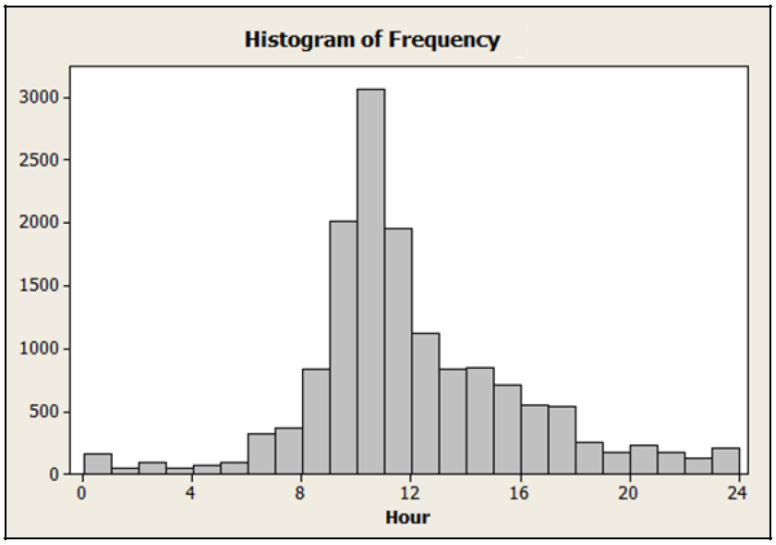
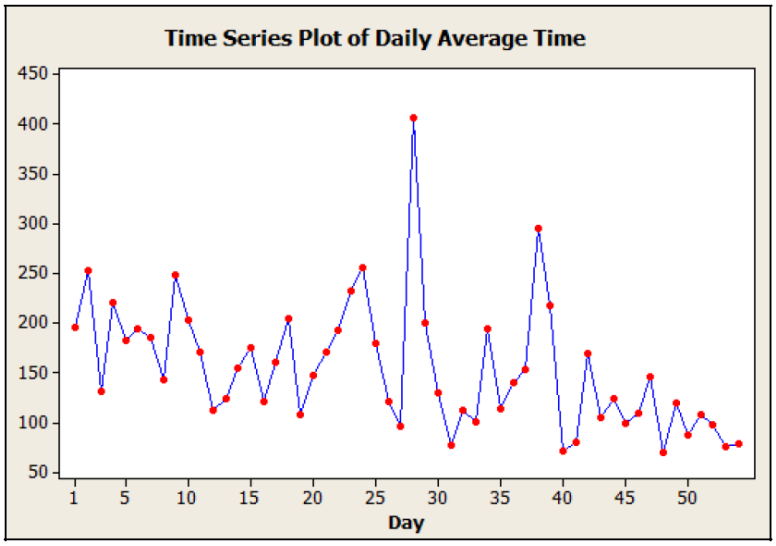


FIGURE 2. Guideline execution flow



(a)



(b)

FIGURE 3. uBrain performance; a) service request frequency, b) response time

SAGE Workbench. The guideline may be converted as an integration model of workflow and rule by a guideline converter. The converter was developed as a plug-in module of the SAGE workbench so that it can directly be converted in the modeling tool as shown in Figure 1.

To be executed, the converted guideline in the workbench should be deployed to a CDS server. Once deployed, the guideline is stored in a repository so that it can be activated by external requests, and the web service registry in CDS service provider may be updated so that potential clients can find the guideline service. This guideline development process is depicted in Figure 2.

4.2. **Guideline execution.** At operation, if a clinician requests a CDS service for a patient at a decision point of diagnosis, a CDS application may retrieve the up-to-date patient data from CISs by using a data interface adapter (DIA). The collected data may be composed as an XML file and be sent to an uBrain server. Then a workflow engine is triggered by the event handler and sequentially invokes the rule engine to generate

appropriate actions. Based on the result, uBrain will immediately send the outcomes to the CDS client to show to the clinician. In this case, the clinician normally has to wait for the response for a while, and so the response time is a critical performance factor of a CDS service.

Using event handlers for recommendation services enables uBrain to be used as an event-based real time advising system. For example, a guideline can be modeled as a closed-loop process which iterates based on a specified event; e.g.) an update of a patient status data. Suppose there is an in-patient who should be checked every hour. Every time he/she is checked and the data is updated, a CDS client can also update the patient data to uBrain server in automated manner. If uBrain finds any serious symptom in the new data, the CDSS will remind the related clinical staffs, otherwise the CDSS will not do any action.

5. **Implementation.** In order to verify the availability of the proposed system, three different types of clinical guidelines were implemented in local institutes. The guidelines were commonly encoded in SAGE by domain expert groups and executed in the realistic manner with the empirical patient data and test cases.

5.1. **Lab alerting.** Lab alerting is based on laboratory tests that are medical procedures that involve testing samples of blood, urine, or other tissues or substances in body of patients. The lab alerting guidelines encoded in SAGE include one or two rules, decisions and actions as Table 4. Each guideline implies the types of laboratory tests. The purpose of implementation is to verify the stability and performance of the CDSS in a local hospital.

Table 4. Property of lab alerting guidelines

Guideline name	Guideline type	No. of SAGE objects used		
		Rule	Decision	Action
1_Hyponatremia_2_Hypernatremia	Main	2	1	2
3_Hypokalemia_4_Hyperkalemia	Main	2	1	2
5_Hyperglycemia_6_Hypoglycemia	Main	2	1	2
7_Falling Hct	Main	1	1	1
8_Rh antigen negative	Main	1	1	1
9_CBC blast (leukemia screen1)	Main	1	1	1
10_Elevated WBC (leukemia screen2)	Main	1	1	1
11_Neutropenia	Main	1	1	1
12_Thrombocytopenia	Main	1	1	1
13_Hyperbilirubinemia	Main	1	1	1
14_NST	Main	1	1	1
15_Ab screening	Main	1	1	1
Total		15	12	15

After implementation, we collected empirical data of 14,795 executions during two months. Figure 3(a) shows a histogram for hourly frequency of the service requests. It represents that most of the requests are concentrated around noon (9 am to 12 am). Figure 3(b) shows a time series plot of average response time for a service. The statistics of response time is mean of 154.2 msec, median of 78 msec, and standard deviation of 725.5 msec. The chart indicates that; 1) there is a trend of weekly seasonal fluctuation, and 2) the average response time decreases as the system gets stabilized.

5.2. **Hypertension.** A hypertension guideline was implemented to verify the knowledge coverage of uBrain for complicated clinical guidelines. The guideline was encoded based on JNC 7 [37], which is used a standardized guideline for healthcare professionals. The encoded guideline consists of three recommendation sets; a main guideline which branches to sub guidelines according to existence of diabetes mellitus (DM), and two sub guidelines which make actions based on rules and decisions as listed in Table 5.

TABLE 5. Property of hypertension guidelines

Guideline name	Guideline type	No. of SAGE objects used		
		Rule	Decision	Action
Hypertension_evaluation_main	Main	1	1	2
Hypertension_evaluation_with_DM	Sub	9	4	10
Hypertension_evaluation_without_DM	Sub	9	4	10
Total		19	9	22

The hypertension guideline was implemented as an open service in a web site as shown in Figure 4. The purpose of this implementation is to verify the correctness of CDSS recommendation under a complicated guideline, and to feedback the usability of CDSS as a web application. Clinicians can access to the web site and test the system using patient data. Three clinicians in a hospital evaluated the system, and the outcomes of CDS executions and the usability of the CDSS were verified.

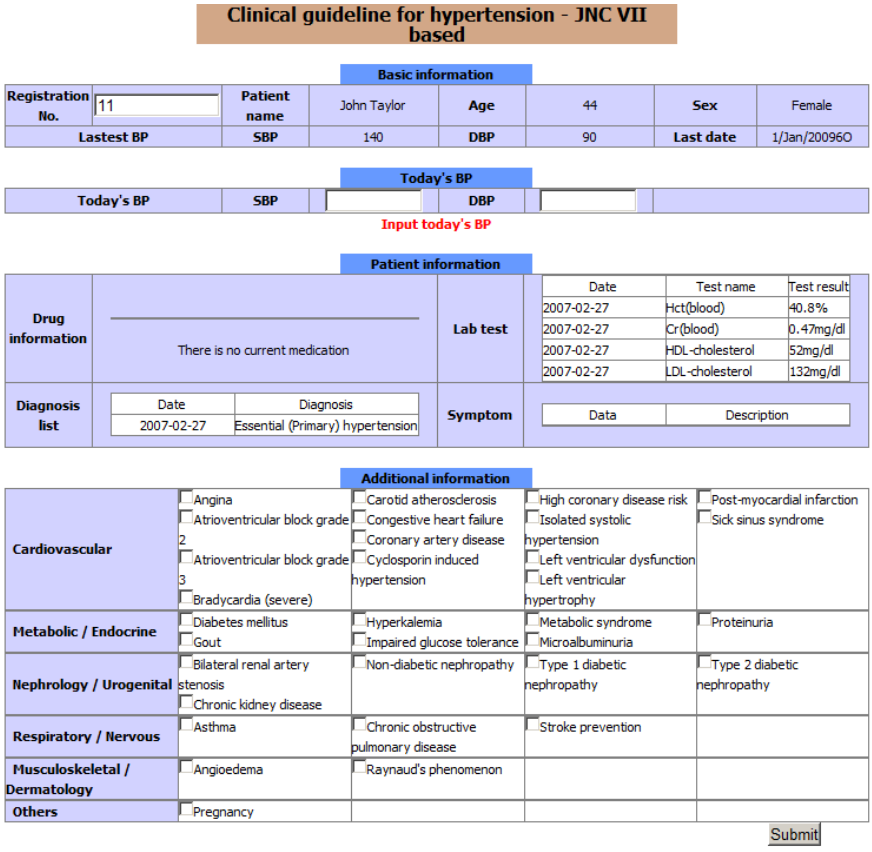
5.3. **Severe sepsis.** Severe Sepsis is a serious medical condition of a patient body involving infection and generalized inflammation. The Severe Sepsis guideline consists of three main guidelines as Table 6; Severe sepsis monitoring to monitor a patient status continuously, SIRS screening to determine a patient status every 3 hours, and Septic shock_CVP to get recommendation when a patient is at shock by CVP (central venous pressure). Septic shock_CVP includes two sub guidelines to generate recommendations.

TABLE 6. Properties of the severe sepsis guidelines

Guideline name	Guideline type	No. of SAGE objects used		
		Rule	Decision	Action
Severe sepsis monitoring	Main	9	5	4
SIRS screening within 3 hrs at ER	Main	40	9	16
Septic shock_CVP	Main	26	8	6
Septic shock subguideline_MAP	Sub	12	3	4
Septic shock subguideline_ScvO2	Sub	14	3	4
Total		101	28	34

Figure 5 shows the workflow of Severe Sepsis monitoring. This guideline is executed based on interaction between a CDS client and a CDSS. When a patient was required to be monitored for his/her status, a clinician starts the monitoring service of uBrain. Then the CDSS repeatedly updates the patient data based on closed-loop monitoring workflow, sends an alarm to the CDS client when a problem is discovered, and finishes when the patient status is improved and needs not to be monitored any more.

6. **Discussion and Conclusion.** In this study, a workflow based CDSS was proposed and the two important aspects of CDSSs were verified; clinical workflow support and rule based knowledge processing. Our research is theoretically based on the approach of developing a generic CDS engine using commercial S/W. Because the definition and coverage



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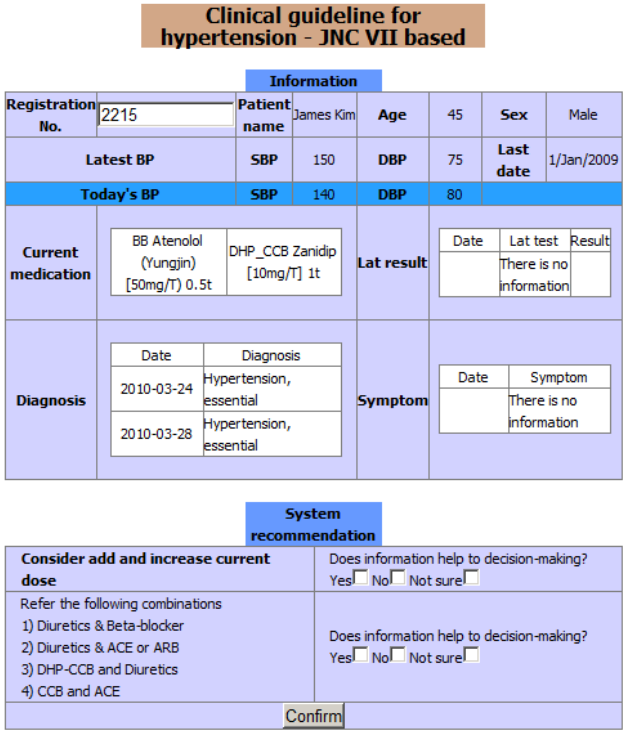

(b)

FIGURE 4. Web based recommendation service; (a) input of patient data, (b) CDSS recommendation

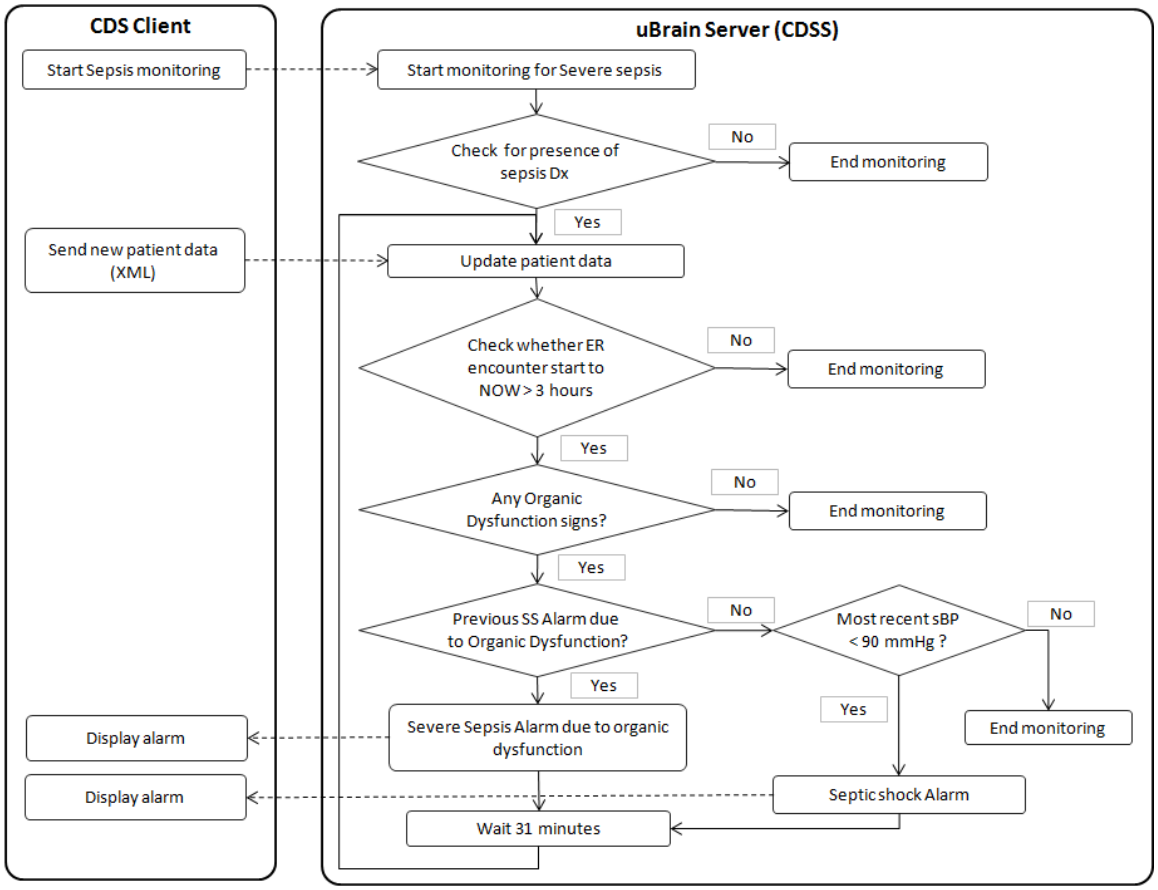

FIGURE 5. Workflow of severe sepsis monitoring in uBrain

of a CDSS can vary in a myriad way, we established SAGE as a conceptual framework and the various components were adopted, customized, and additionally developed for the new CDSS.

The contribution of this paper is to verify the workflow based CDSS by integrating a rule engine, a knowledge translator, and web services. We also verified the plausibility of using open-source S/W products as an integrated CDSS. We used GPL licensed open-source so that the reproduced outcomes can be utilized by other research groups or clinicians without any restriction. This policy is based on the feature of our project as a national perspective.

The WfMS we adopted successfully supports clinical workflow and event handling. This implies that managing clinical workflow can be done effectively in a way of business process management (BPM). The powerful methods and tools of BPM such as process discovery, modeling, execution, and analysis are promising to be used to automate and improve clinical workflow.

We consider our research as a practical approach than a theoretical way. The gap between the semantics of SAGE and the coverage of the proposed CDSS still remains and has to be overcome. The role of a rule engine is still arguable. Rule engines have been used to process complicated medical concepts such as evidence statements or composite criterion. Despite these benefits, rule-based inference for clinical knowledge processing has not been semantically investigated yet and occasionally rule-based inference is lack of knowledge coverage than other alternative methods mentioned in Section 2. We are currently implementing our CDSS into a u-health project with various use cases, and try to overcome the limitations.

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REFERENCES

[1] A. Wright and D. F. Sittig, A four-phase model of the evolution of clinical decision support architectures, *International Journal of Medical Informatics*, vol.77, no.10, pp.641-649, 2008.

[2] A. Wright and D. F. Sittig, A framework and model for evaluating clinical decision support architectures, *Journal of Biomedical Informatics*, vol.41, no.6, pp.982-990, 2008.

[3] D. Isern and A. Moreno, Computer-based execution of clinical guidelines: A review, *International Journal of Medical Informatics*, vol.77, no.12, pp.787-808, 2008.

[4] S. W. Tu and J. Glasgow, *SAGE Guideline Model Specification 1.65*, http://sage.wherever.org, 2006.

[5] *OpenClinical*, http://www.openclinical.org.

[6] K. Kawamoto and D. F. Lobach, Design, implementation, use, and preliminary evaluation of SEBASTIAN, a standards-based Web service for clinical decision support, *AMIA Annual Symposium Proceeding*, pp.380-384, 2005.

[7] M. K. Goldstein, B. B. Hoffman, R. W. Coleman, M. A. Musen, S. W. Tu, A. Advani, R. Shankar and M. O'Connor, Implementing clinical practice guidelines while taking account of changing evidence: ATHENA DSS, an easily modifiable decision-support system for managing hypertension in primary care, *AMIA Annual Symposium Proceeding*, vol.6, no.262, pp.300-304, 2000.

[8] J. P. Bury, V. Saha and J. Fox, Supporting 'scenarios' in the PROforma guideline modelling format, *AMIA Annual Symposium Proceeding*, pp.870, 2001.

[9] D. Wang, M. Peleg, D. Bu, M. Cantor, G. Landesberg, E. Lunenfeld, S. W. Tu, G. E. Kaiser, G. Hripcsak, V. L. Patel and E. H. Shortliffe, GESDOR – A generic execution model for sharing of computer-interpretable clinical practice guidelines, *AMIA Annual Symposium Proceeding*, pp.694-698, 2003.

[10] D. Wang, M. Peleg, S. W. Tu, A. A. Boxwala, O. Ogunyemi, Q. Zeng, R. A. Greenes, V. L. Patel and E. H. Shortliffe, Design and implementation of the GLIF3 guideline execution engine, *Journal of Biomedical Informatics*, vol.37, no.5, pp.305-318, 2004.

[11] M. Peleg, D. Wang, A. Fodor, S. Keren and E. Karnieli, Adaptation of practice guidelines for clinical decision support: A case study of diabetic foot care, *Workshop on AI Techniques in Healthcare: Evidence Based Guidelines and Protocols in Conjunction with ECAI*, Italy, 2006.

[12] J. Choi, L. M. Currie, D. Wang and S. Bakken, Encoding a clinical practice guideline using guideline interchange format: A case study of a depression screening and management guideline, *International Journal of Medical Informatics*, no.2, pp.302-307, 2007.

[13] P. Ram, D. Berg, S. Tu, G. Mansfield, Q. Ye, R. Abarbanel and N. Beard, Executing clinical practice guidelines using the SAGE execution engine, *Studies in Health Technology Informatics*, vol.107, no.Pt 1, pp.251-255, 2004.

[14] M. Ceccarelli, A. Donatiello and D. Vitale, KON3: A clinical decision support system, in oncology environment, based on knowledge management, *The 20th IEEE International Conference on Tools with Artificial Intelligence*, Dayton, Ohio, pp.206-210, 2008.

[15] D. Borbolla, C. Otero, D. F. Lobach, K. Kawamoto, S. A. M. Gomez, G. Staccia, G. Lopez, S. Figar, D. Luna and F. G. Q. Bernaldo, Implementation of a clinical decision support system using a service model: Results of a feasibility study, *Studies in Health Technology Informatics*, vol.160, no.Pt 2, pp.816-820, 2010.

[16] H. S. Goldberg, M. Vashevko, A. Postilnik, K. Smith, N. Plaks and B. M. Blumenfeld, Evaluation of a commercial rule engine as a basis for a clinical decision support service, *AMIA Annual Symposium Proceeding*, pp.294, 2006.

[17] J. Heusinkveld, A. Geissbuhler, D. Sheshelidze and R. Miller, A programmable rules engine to provide clinical decision support using HTML forms, *AMIA Annual Symposium Proceeding*, pp.800-803, 1999.

[18] J. B. Yang, D. L. Xu and G. Kong, Clinical decision support systems: A review of knowledge representation and inference under uncertainties, *International Journal of Computational Intelligence Systems*, no.2, pp.159-167, 2008.

[19] J. M. Starmer, D. A. Talbert and R. A. Miller, Experience using a programmable rules engine to implement a complex medical protocol during order entry, *AMIA Annual Symposium Proceeding*, pp.829-833, 1999.

[20] W. M. P. Van Der Aalst, A. H. M. t. Hofstede and M. Weske, Business process management: A survey, *Lecture Notes in Computer Science*, no.2678, pp.1-12, 2003.
[21] M. Sedlmayr, T. Rose, R. Röhring and M. Meister, A workflow approach towards GLIF execution, *The 17th European Conference on Artificial Intelligence*, pp.3, 2006.
[22] R. Shiffman, Toward effective implementation of a pediatric asthma guideline: Integration of decision support and clinical workflow, *Proc. of the 18th Annual Symposium on Computer Applications of Medical Care*, Washington D.C., USA, pp.797-801, 1994.
[23] K. M. Heard, C. Huang, L. A. Noirot, R. M. Reichley and T. C. Bailey, Using BPEL to define an executable CDS rule process, *AMIA Annual Symposium Proceedings*, pp.947, 2006.
[24] K. M. Lyng, T. Hildebrandt and R. R. Mukkamala, From paper based clinical practice guidelines to declarative workflow management, *Lecture Notes in Business Information Processing*, vol.17, no.5, pp.336-347, 2009.
[25] J. Heusinkveld, A. Geissbuhler, D. Sheshelidze and R. Miller, A programmable rules engine to provide clinical decision support using HTML forms, *Proc. of AMIA Symposium*, pp.800-803, 1999.
[26] J. M. Starmer, D. A. Talbert and R. A. Miller, Experience using a programmable rules engine to implement a complex medical protocol during order entry, *AMIA Annual Symposium Proceeding*, pp.829-832, 2000.
[27] L. Dazzi, C. Fassino, R. Saracco, S. Quaglini and M. Stefanelli, A patient workflow management system built on guidelines, *Proc. of AMIA Annual Symposium*, pp.146-150, 1997.
[28] U. Greiner, J. Ramsch, B. Heller, M. Löffler, R. Müller and E. Rahm, Adaptive guideline-based treatment workflows with AdaptFlow, *Studies in Health Technology Informatics*, no.101, pp.113-117, 2004.
[29] S. Panzarasa and M. Stefanelli, Workflow management systems for guideline implementation, *Neurological Science*, vol.27, pp.245-249, 2006.
[30] H. S. Goldberg, M. Vashevko, A. Pastilnik, K. Smith, N. Plaks and B. M. Blumenfeld, Evaluation of a commercial rule engine as a basis for a clinical decision support service, *AMIA Annual Symposium Proceeding*, pp.294-298, 2006.
[31] K. M. Heard, C. Huang, L. A. Noirot, R. M. Reichley and T. C. Bailey, Using BPEL to define an executable CDS rule process, *AMIA Annual Symposium Proceeding*, pp.947, 2006.
[32] C. Huang, L. A. Noirot, K. M. Heard, R. M. Reichley, W. C. Dunagan and T. C. Bailey, Implementation of virtual medical record object model for a standards-based clinical decision support rule engine, *AMIA Annual Symposium Proceeding*, pp.958, 2006.
[33] J. A. Kim, I. S. Cho and Y. Kim, Knowledge translation of SAGE-based guidelines for executing with knowledge engine, *AMIA Annual Symposium Proceedings*, pp.1008, 2007.
[34] J. A. Kim, B. G. Shim, S. T. Kim, J. H. Lee, I. S. Cho and Y. Kim, Translation Protégé knowledge for executing clinical guidelines, *The 11th International Protégé Conference*, Amsterdam, Netherlands, 2009.
[35] J. H. Lee, J. A. Kim, I. S. Cho and Y. Kim, Integration of workflow and rule engines for clinical decision support services, *Studies in Health Technology Informatics*, vol.160, no.Pt 2, pp.811-815, 2010.
[36] N. Mulyar, W. M. P. Van Der Aalst and M. Peleg, A pattern-based analysis of clinical computer-interpretable guideline modeling languages, *Journal of the American Medical Informatics Association*, vol.14, no.6, pp.781-787, 2007.
[37] NHBPEP Coordinating Committee, *JNC 7 Express: The 7th Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure*, US Department of Health and Human Services; NIH publication 03-5233, http://www.nhlbi.nih.gov/guidelines/hypertension/express.pdf, 2003.