RG11

Use of Real-time Application for Portable Interactive Devices (RAPID) for Data Safety and Patient Outcomes. FDA

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ABSTRACT

After the 2009 H1N1 epidemic , FDA staff recognized the need for an integrated electronic system to support real time communication and collaboration between federal and its non-federal stakeholders to coordinate public health decision making for medications and other medical countermeasures (MCM) interventions deployed during public health events .The Data Mining and Informatics Evaluation and Research (DMIER) team in the Office Translational Sciences (OTS) at the Food and Drug Administration (FDA) developed a modular, cloud based, real time data collection and analytics platform system that enables FDA scientists to direct and evaluate MCMs deployed during national health emergencies. The system is needed because MCMs, including drugs, biologic products, antidotes, vaccines, in vitro diagnostic laboratory tests, and other drug products to diagnose, prevent, protect from, or treat conditions associated with chemical, biological, radiological, or nuclear (CBRN) threats, or emerging infectious diseases such as pandemic influenza () need to be monitored and evaluated for safety and efficacy in real time, even in complex public health scenarios. The RAPID system team leveraged cloud based technologies and Ethereum blockchain[1] to provide to FDA and its collaborators a mobile phone based bidirectional communication system to create to enhance FDA’s preparedness to respond CBRN and emerging diseases threats. Additionally, the RAPID system provides support for secure data collaborations between federal and non-federal collaborators and a real time internal FDA analytics and data management system to support regulatory decision making.

I**NTRODUCTION**

The Real-Time Application for Portable Interactive Devices (RAPID) is an Amazon cloud based system designed to receive electronic information, analyze it and respond to the sender of the information within 24 hours. The modular system accepts a variety of data types which may be evaluated by internal federal data analysts in real-time. The bidirectional design permits the transmission of timely emergency information to health care providers or other individuals during public health emergencies.

BACKGROUND)

FDA surveillance and epidemiology staff recognized the need for a flexible and bidirectional communication, data exchange and analysis system to be used for national health emergencies after their experiences performing drug safety and to a lesser extent, patient outcome data collection and analysis during the 2009 H1N1 influenza A pandemic[2]. FDA drug safety analysts were required to monitor and evaluate the safety and efficacy of a previously

unapproved anti-influenza drug, intravenous peramavir. The drug was made available for the treatment of seriously ill hospitalized patients during the pandemic who were intolerant of or poorly responding to standard therapies under the auspices of an Emergency Use Authorization (EUA) and prior to completion of the registration trials normally required for marketing approval. Various challenges encountered in conducting the safety surveillance of peramivir included limited digital computing infrastructure that was not sufficiently flexible to allow quick scalability to accommodate emerging needs, inability to quickly communicate with and provide feedback to health care providers (HCPs) in actual time as events unfolded, and adverse events reporting that tended to be inconvenient and time consuming for HCPs and often included reports of variable quality. Analysts recognized that without an organized data collection system, they were not able to quickly respond to drug regulatory requirements to accurately evaluate real time health data required for real time regulatory decision during public health emergencies.

CDER scientists chose to develop RAPID, a mobile phone based bidirectional communications and analytics system to solve many problems noted above during a national emergency. A smartphone enabled system connected to a cloud service, was felt to be the best option for a reporting system for two reasons. First, based on experiences reported that during the Fukushima Daiichi nuclear emergency[3] and the Hurricane Katrina crisis[4], mobile phone systems could transmit information even though significant infrastructure damage occurred during those emergencies. Second, mobile phones are carried by 79%[5] of the healthcare provider (HCP) and general population to send and receive health information. For those reasons, the RAPID system incorporated linked technologies similar to Internet of things (IoT) strategies[6]. The key IoT elements in the RAPID instance are to be a bidirectional data communication system, have a cloud base system which is flexible, scalable and provides a data lake of information with analytic tools to evaluate real time and streaming information and provide real time situational awareness to leadership enabling collaborative regulatory decision making and communication of key health data back to individuals in the field.

FUNCTIONAL DESCRIPTION OF RAPID

RAPID has three major IT components which support the key reporting, analytic and communication abilities of RAPID. They are a cloud infrastructure, a secure data broker and a data lake platform design.

RAPID GOV CLOUD INFRASTRUCTURE

The RAPID system is placed in the FDA Amazon Gov Cloud for the purposes of providing a flexible and scalable work platform for the performance of surveillance, analytic and clinical outcomes analysis and regulatory research during MCM and non-MCM events. The critical features Gov Cloud offers are its ability to support major research and analytic work with less hardware and support infrastructure, to provide substantial cost savings because expenses are flexible and responsive to need, and its flexible capacity to support small data sources or massive streaming data sources on demand. About the latter point of processing massive data, RAPID has in its Gov Cloud design a data lake feature, explained in more detail below. Data lakes can store numerous diverse data sets in their original format, and support tools which would enable FDA scientists to evaluate data in real time. Further capabilities include supporting applied research on regulatory issues with data in one place, and lastly, provide the opportunity to support analysis of real time and real world data which will be produced in future clinical trials.

RAPID Secure Amazon (AWS) cloud structure (Gov Cloud)

RAPID is designed as a four-tier cloud structure with the Amazon cloud. The four tiers fulfill scientific and communications requirements for CDER to communicate and share information in real time. The first tier of RAPID can ingest a variety of electronic data. The current RAPID version focused in receiving drug safety data and case report elements extracted from electronic health records. The second tier is where the data is stored in its native format in a secure FDA Gov Cloud environment to be evaluated by FDA scientific reviewers. The third tier supports

FDA scientific reviewers by providing work space to analyze incoming RAPID data in an environment where there is room to test ideas (sandbox), make available a variety of evaluation tools to be used on demand and give customizable user interfaces (UI) enhancing the ability of a scientist to ingest large amounts of information in real time. The fourth layer fulfills two functions, presenting summary information to leadership through their own UI and provide them access to the RAPID bidirectional communication design to transmit important multimedia health information or other data to FDA stakeholders within 24 hours.

RAPID SECURE DATA BROKER

. The RAPID team built an external to FDA data broker prototype to prove that cloud based systems may be used to function as an electronic data consolidator to receive, clean and transmit data to FDA in a secure manner and transmit the data between FDA and its stakeholders during MCM events. A secure data broker is a FDA certified site enabled to capture emergency drug safety or possible patient outcome data within days of an MCM event. The secure broker which may be on standby within a contract research organization (CRO) or within the FDA cloud may be turned on when needed. This data capture and reporting system will fill the information reporting gap which occurs between the sudden onset of an MCM event and delay in awarding an emergency contract to engage a CRO to assist with information gathering and reporting to FDA. The data broker model is an electronic data gateway, approved by the FDA security office to receive and transmit clinical or drug safety data, with PHI and PII, in real time. The advantages of the data broker system aside from being activated rapidly, is that it may be used or duplicated by FDA stakeholders to create a rapidly deployable and linkable reporting system which would be responsive to FDA requirements during public health crises. The data broker model being used in RAPID II is currently being used by Center for Medicaid and Medicare (CMS) and Department of Defense (DoD).

In the RAPID II use case, the data broker model will transmit and receive drug safety de-identified EHR data from an EPICs or Cerner electronic health records in real time.

RAPID DATA LAKE

A data lake is a single storage repository for data that facilitates accessibility to analytic system tools and data integration[7]. This type of information structure is adept at using big data infrastructures, to aggregate increasing data volumes which, have multiple formats. The data lake is the best current solution available to FDA to meet its analytic and research needs during MCM events and for future research use by FDA analysts.

DESCRIPTION OF RAPID USE CASE COMPONENTS AND CAPABILITIES

ADVERSE EVENT REPORTING

RAPID's bi-directional adverse event reporting component is designed to collect MCM drug safety information and analyze it in real time, and if necessary, respond to the original reporter within 24 hours. The AE mobile application and its analytic dashboard were designed in collaboration with the OSE's Division of Pharmacovigilance (DPV). The RAPID mobile app, which is based on a design created by the Medicines and Healthcare Products Regulatory Agency (MHRA) for its "Yellow Card" reporting app[8], is designed to enable healthcare providers (HCP) to send to FDA drug safety information within five minutes, in a MedWatch 3500 A or B format.

The RAPID mobile application functions on Android, iPhones and iPads and uses the native speech to text technology in those phones, enabling the reporter to complete structured and unstructured (narrative fields) 3500 A or B forms within five minutes instead of the usual 40 minutes needed to manually complete the forms. The RAPID application is also capable of digitally attaching pictures of the medication or in medication error cases, the national drug code (NDC) or universal product code (UPC) numbers of the drug products and devices for inclusion in safety reports.

The RAPID team evaluates incoming real time data, on a real time analytic dashboard to quickly detect patterns or clusters of information indicating new or changing AE signals or trends[9]. The dashboard provides analytic tools such

as R for statistical analysis and Multi-item gamma Poisson Shrinker (MGPS) for disproportionality testing., In the future, machine learning algorithms, to evaluate the incoming data and contribute to real-time drug safety decisions will be implemented[1].

REMS REAL TIME EVALUATION

The risk evaluation and mitigation strategy (REMS) component of RAPID is structured as a mobile phone based, bidirectional survey application where scientific evaluators may send to HCPs (physicians and pharmacists) who use REMS restricted drugs having serious safety concerns, surveys to evaluate, in real time, the access and the burden[10] of using medications under REMS restriction. The current application is designed to obtain data from physicians and pharmacists who manage or prescribe REMS restricted drugs with the intent of collating their real-world experiences with the REMS restricted drugs. The structured and unstructured comments and recommendations of health care providers can be analyzed quantitatively and qualitatively on a RAPID REMS analytic dashboard using a regression based algorithm developed by a statistician assigned to the RAPID project.

MEDICATION ERROR REPORTING

The objective of the Medication Error module of RAPID is to capture medication errors as soon as possible. One way to meet this goal is to use the RAPID application to capture pictures of the pill or the medication NDC or UPC number and send the safety report to FDA. Medication errors reported to FAERS, use MedWatch and electronic submission (E2B) forms that are intended to report adverse drug reactions, and thus lack structured fields to capture medication error specific information such as the type of medication error, stage where the medication error occurred, root cause, and the reporter's recommendations to prevent the error. The lack of structured fields, inability to identify the specific products involved in the error, and time required to follow up with reporters to gather additional information has impeded RAPID's ability to perform timely and thorough analyses of the reports in FAERS.

A RAPID mobile app would supplement the current MedWatch and E2B reporting processes, and provide a logical reporting format that aligns with nationally accepted recommendations for how healthcare providers should evaluate medication errors and additional addresses deficiencies.

In addition to aligning with med error reporting requirements, additional technology incorporated into the RAPID mobile app, such the speech to text tools and barcode readers to complete the reporting form may help minimize the number of incomplete or miscoded medication error reports submitted to FAERS. The Division of Medication Errors and Prevention and Analysis (DMEPA) analytic prototype dashboard is designed to find and highlight new and unusual med error reports within 24 hours.

ETHEREUM BLOCKCHAIN TO REPORT CLINICAL DATA FROM ELECTRONIC HEALTH RECORDS (EHR)

After the RAPID team created the bi-directional communication pathway for adverse event reporting, using the open source an Ethereum blockchain platform supported communication line enabling transmission and aggregation of EHR extracted data from multiple clinical sites. A proof of concept to demonstrate the ability to acquire clinical information directly from EHRs was developed with data scientists from the U.S. Critical Injury and Illness group partners at 4 universities. Using synthetic data, 83 clinical data points defining a severe acute respiratory syndrome patient were extracted from Epic or Cerner EHRs transmitted securely to FDA using the Fast Health-Care Interoperability Resource (FHIR) to be evaluated in the FDA secure data broker described above. The intent of the Ethereum blockchain connection is to enable members of the RAPID clinical consortium to provide in real time with FDA public health decision-making.

Summary

The RAPID system is a flexible, modular system initially designed capture multiple streams of electronic during public health emergencies. RAPID supplies a 360-degree view of the incidence, prevalence, location and clinical outcomes of MCMs used during CBRN and normal surveillance situations. The flexibility of the RAPID platform will also serve as a test bed for future regulatory needs as real world data is used for health decision making.

REFERENCE FIELD

[1] https://www.ethereum.org/

[2] Sorbello, A., Jones, S. C., Carter, W., Struble, K., Boucher, R., Truffa, M., . . . Dal Pan, G. (2012). Emergency use authorization for intravenous peramivir: evaluation of safety in the treatment of hospitalized patients infected with 2009 H1N1 influenza A virus. *Clin Infect Dis, 55*(1), 1-7. doi:10.1093/cid/cis351

[3] https://www.ncbi.nlm.nih.gov/books/NBK253923/

[4] https://georgewbush-whitehouse.archives.gov/reports/katrina-lessons-learned/chapter5.html

[5] https://www.statista.com/statistics/416951/smartphone-use-for-professional-purposes-among-us-physicians/

[6] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4981575/

[7] A **data lake** is a cloud storage repository that holds a vast amount of raw **data** in its native format until it is needed. This configuration circumvents the need for rigid data models which tend to form silos of difficult to connect information. http://www.pwc.com/us/en/technology-forecast/2014/cloud-computing/features/data-lakes.html.

[8] https://yellowcard.mhra.gov.uk/

[9] Raghupathi and Raghupathi: Big Data Analytics in Healthcare; promise and potential. Health Information Science and Systems 2014:2-3

[10] Access is ease of obtaining and using REMS restricted medication. Burden being issues which prevent the use of or cause HCPs to avoid using a REMS restricted drug.

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