Enhancing Multi-Center Patient Cohort Studies in the Managing Epilepsy Well (MEW) Network: Integrated Data Integration and Statistical Analysis

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Abstract

Self-management techniques that assist patients with chronic conditions, such as epilepsy, diabetes, and arthritis, play an important role in managing and caring for their conditions. The US Center for Disease Control and Prevention (CDC)-funded Managing Epilepsy Well (MEW) Network consists of 11 study sites across the US that aims to develop and disseminate self-management techniques for epilepsy patients. Epilepsy affects more than 65 million patients worldwide with serious negative impact on their own as well as their family member's quality of life. Taking advantage of advances in biomedical informatics, the MEW Network has created an integrated database (MEW DB) using a common data model and two tiers of study variables. The MEW DB consists of 1680 patient data records covering a wide range of patient population nationwide. Therefore, there is growing interest in the use of the MEW DB for different cohort query analysis. To address the challenges in: (1) selecting appropriate MEW research studies based on inclusion/exclusion criteria; (2) creating a patient cohort for given research hypothesis; and (3) performing appropriate statistical tests; we have developed an integrated data query and statistical analysis informatics tool called Insight. The Insight platform features an intuitive user interface to support the three phases of study selection, patient cohort creation, and statistical testing with the use of an epilepsy domain ontology to support ontology-driven query expansion. We evaluate the Insight platform using two user evaluation methods of "first click testing" and "user satisfaction survey". In addition, we performed a time performance test of the Insight platform using four patient datasets and three statistical test. The results of the user evaluation show that Insight platform is strongly approved by the users and the results of the time performance show that there is marginal difference in performance as the volume of patient data increases in the MEW DB.

Introduction

Epilepsy is a serious neurological disorder and it severely affects the quality of life of both the patients as well their family members (1, 2). Epilepsy affects more than 65 million persons worldwide with more than 2.8 million persons in the United States who experience seizures, which lead to disabilities, decreased ability for daily functioning, and common comorbidities including depression as well as cognitive impairment (1, 3). The cost of care for epilepsy is high with total cost burden estimated to be more than $36 billion per year, which disproportionately affects the elderly and minority populations who are economically vulnerable (1). The challenges in managing patients with epilepsy are significant with a growing population of older persons (estimated to increase to approximately 80 million by 2060) (4), high utilization of healthcare services often due to non-adherence to medication, and stress on patients as well their family members.

Self-management techniques have been successfully developed for many chronic conditions, including heart diseases, asthma, and depression, which enable patients to address disease symptoms, stress, and improve their quality of life (5). Epilepsy self-management techniques aim to address the limitations of existing approaches for providing care, for example difficulty in monitoring of daily medication adherence, and lack of availability of time or clinical resources to common comorbidities of depression or other psychosocial conditions (6). Self-management techniques for epilepsy patients involves improving their medication adherence, memory, and quality of life (7). Therefore, in 2007, the US Center for Disease Control and Prevention (CDC) created a network of multiple institutions to develop "self-management" techniques for epilepsy called Prevention Research Centers' Managing Epilepsy Well (MEW) and disseminate the best practices to patient population (8).

The MEW Network institutions have developed multiple epilepsy self-management programs that use multi-modal communication and dissemination techniques to advance the adoption of self-management techniques in the patient population (7). These programs include the Epilepsy Awareness Support and Education (WebEase) project (9), the

Home Based Self-management and Cognitive Training Changes Lives (HOBSCOTCH) (10), and the Program for Active Consumer Engagement in Epilepsy Self-Management (PACES) (11). Therefore, the data collected as part of these projects in the MEW Network represents a unique resource describing epilepsy self-management techniques and the results from the application of these techniques on a variety of patient population (7).

As part of the MEW Network initiative, we have harmonized the data from different MEW Network sites using a traditional Extract Transform Load (ETL) approach to create the MEW database (MEW DB) consisting of 1680 patients from 11 study sites. The MEW DB is being used to analyze different aspects of epilepsy treatment, including self-management techniques. For example, a study by Friedman et al. examined depressive symptoms and suicidality in epilepsy patients who were enrolled in self-management studies (12). The study found that depression and suicidal thoughts are common in epilepsy patients who were enrolled in self-management studies. Similarly, a study by Begley et al. evaluated the demographic and clinical correlated in epilepsy patients to characterize their self-management skills (13). This study used data from 436 patients involving five MEW Network studies and found that there was significant variation in the self-management competencies of patients. These studies highlight the need for well-defined data integration techniques as well as statistical analysis methods that can be used to both create a national-level patient population resource as well analyze it to derive insightful results for potential interventions.

There has been significant amount of work in the informatics community related to data integration for patient cohort query using ontology-driven techniques (14-16). However, to the best of our knowledge, many of these existing data integration platforms have limited or no support for the statistical analysis methods that need to be performed on a patient cohort data after it has been extracted from the integrated database. Users often have to download and perform tedious data transformation as well as curation steps over the patient cohort data before it can be analyzed using appropriate statistical methods such as t-test, Chi-Square, Mann-Whitney U test, ANOVA test, Fisher's exact text and Kruskal-Wallsis test. In addition, users often have to rely on external, third-party tools that support these statistical methods for analysis. The lack of support for statistical data analysis in informatics tools for patient cohort query becomes a significant rate limiting step as the number of research studies using the data rapidly increase, for example the governing body for the MEW DB receives multiple requests for new research studies using this unique resource. In addition, the lack of integrated statistical data analysis tools in a data integration platform makes it difficult for users to perform exploratory data analysis by modifying study parameters based on results of statistical analysis.

In our previous work, we developed an epilepsy-focused, ontology-driven data integration and patient cohort query platform called Insight (17). The Insight tool uses the Epilepsy and Seizure Ontology (EpSO) to support data processing, integration, and query to allow users to create research study cohorts via an intuitive visual interface. The results of the cohort queries can be exported as comma separated value (CSV) files for subsequent processing and analysis using statistical tools. In this paper, we describe the development and application of a dedicated statistical analysis component in the Insight platform that can support a variety of statistical methods. This integrated statistical analysis feature of Insight significantly reduces the challenges for patient cohort analysis in the MEW network and we believe it can be easily extended to other domains given the widespread use of statistical data analysis tools in the biomedical research domain. To validate the integrated statistical feature of the Insight platform, we replicate three research studies using MEW-DB data.

Materials and Method

Setting

The goal of the MEW Network is to develop self-management intervention techniques that can be adopted by persons with epilepsy in their home and work environments using a community-based approach (7). At present, the MEW Network consists of centers at eight institutions across the US, including the University of Arizona, Morehouse School of Medicine, New York University, the University of Washington, the University of Minnesota, the University of Illinois at Chicago, and Case Western Reserve University. The MEW Network as developed and tested a wide range of intervention techniques for self-management techniques with a special focus on underserved and minority populations (10, 18-21). The MEW Network works closely with national organizations focused on epilepsy, including the American Epilepsy Society and the Epilepsy Foundation to disseminate evidence-based self-management interventions. This paper integrates and analyzes data in the MEW-DB from 11 studies with a total of 1680 patients and this study was approved by the University Hospital Cleveland Medical Center Institutional Review Board (IRB).

Data Collection

The data in the MEW-DB were obtained as part of the 11 research studies and included a variety of details that based on a set of common data elements (CDE) that are approved by the MEW DB steering committee for inclusion in the integrated dataset. The current set of MEW CDEs are categorized into Tier-1 and Tier-2 variables with Tier-1 variables consisting of 16 CDEs and Tier-2 variables consisting of 15 CDEs. These variables include description of patient demography and clinical outcomes (more details about the variables is presented in our earlier work (17). Table 1 describes the details of the patient data in the MEW DB with a higher percent of female patients (45%) as compared to male patients (28%). The patient data table shows that the MEW DB studies focus on low income group (18% earn less than $25,000 per year)

Table 1: Details of the MEW-DB Patient Population

Variable	**Total sample N=1680**
Age - Mean(SD)	39.96 (13.99)
Gender-N (%)	
Female-N (%)	763 (45.42%)
Male-N (%)	486 (28.93%)
Race-N (%)	
White	832 (49.52%)
Black/African American	176 (10.48%)
Other	100 (5.95%)
Ethnicity — N (%)	
Not Hispanic	711 (42.32%)
Hispanic	107 (6.37%)
Education — N (%)	
High school or less	323 (19.23%)
At least some college	760 (45.24%)
Income — N (%)	
<$25K	305 (18.15%)
$25–50K	83 (4.94%)
>$50K	166 (9.88%)
Marital status — N (%)	
Married or partnered	328 (19.52%)
Other	507 (30.18%)
30-day seizure frequency — Mean (SD)	5.26 (20.34)
QOLIE-10 — Mean (SD)	2.89 (0.81)
PHQ-9 — Mean (SD)	9.35 (6.62)

Reference Studies

The three reference studies used in this paper were conducted using the MEW-DB data. We briefly describe these three studies. The first study (*Study 1*) used the integrated data to evaluate the mood symptoms in 770 patients who are enrolled in self-management interventions using the 9-item Patient Health Questionnaire (PHQ-9) scores (12). The study found that 43.4% of the patients in the study has moderate to severe depression and about 20.1% of the patients had suicidal ideation. The study used multiple statistical methods to evaluate the correlation between demography variables and PHQ-9 total scores, for example Spearman's correlation was used to characterize the relation between age and PHQ-9 scores. Similarly, multiple logistic regression was used to characterize the independent association between demographic and clinical variables to PHQ-9 total scores. This study showed that depression and suicidal ideation are common in the patients enrolled in the various self-management studies.

The second study (*Study 2*) analyzed data from 459 patients that were collected across four research centers to identify correlates of quality of life (QOL) (7). In particular, the study used various demography data, such as age, gender, race, education and employment, together with quality of life QOLIE-10 scale and PHQ-9 scale for depression. The study found that association between the severity of depression and lower QOL scores. The study used Krusksal-Wallis nonparametric methods for analysis of the data. Finally, the third study (*Study 3*) assessed the outcome of five randomized control trials (RCTs) with respect to symptoms of depression in epilepsy patients (13). The study used data from 453 patients with 232 in self-management intervention and 221 patients in usual or wait-list control. Using a series of t-test, the study characterized the changes in PHQ-9 scores over a period of time and a mixed model analysis was done to evaluate the association between baseline variables and changes in PHQ-9 scores over time.

Insight Epilepsy Informatics Platform

The Insight architecture consists of a set of modules that support three primary functions: (1) study selection based on inclusion/exclusion criteria, (2) cohort query formulation using a domain ontology-driven visual query interface, and (3) integrated statistical analysis. The current version of Insight has been developed using the Django web application framework (the previous version of Insight used the Ruby on Rails (17)). The use of Django web framework uses the

Python programming language, which has a large number of libraries and modules that support variety of data processing and analysis tasks, including statistical methods. The architecture of Insight allows it to integrate and manage data from multiple studies with the use of either software modules for data pre-processing and conversion to a common data model following the well-known Extract Transform Load (ETL) approach. We note that as part of the data processing step, multiple terms in the study data are annotated using an epilepsy domain ontology, which enables Insight to support ontology-driven query execution.

Figure 1shows the current architecture of Insight that uses the Model View Template (MVT) approach with data accessed via an object relational data Model, the Insight user interface supported by the View component, and the user interaction with various features of the software mediated by the Template [Django]. The Insight platform is accessed via a Web browser with role based access control (RBAC) with users assigned to different user groups. The access privileges of a user are based on the specific study protocol that is approved by the MEW DB steering committee, which reviews and accepts or declines a proposed study to access the integrated datasets. Users follow a three-step process to identify specific research studies based on their inclusion-exclusion criteria, followed by creation of a study cohort using an intuitive query formulation process, and the study cohort data in finally analyzed using appropriate statistical methods in the data analysis module.

During the first step for study selection, users can select appropriate inclusion and exclusion criteria from a drop-down menu and the specific research studies that conform to the selected inclusion/exclusion criteria are listed for users to review. Users can also choose to select all studies in the MEW-DB for the second phase of cohort query. During the second phase, users can compose a patient cohort query using any of the Tier-1 and Tier-2 variables (described in the previous section above) using a drop-down menu and assign specific values to query variables, for example age between 20-40 years or Patient Health Questionnaire-9 (PHQ-9) score of -5. The selected variables, which are mapped to the Epilepsy and Seizure Ontology (EpSO) (22), are used to compose the patient cohort query followed by "query unfolding". The query unfolding uses ontology reasoning to include all the subclasses of a term in the user-defined query, which ensures that the query results are exhaustive. EpSO is a domain ontology that has been developed to model multiple aspects of epilepsy, including seizure semiology, medication, and etiology (for detailed description of EpSO we refer to (22)). Users can view the results of the cohort query in the Insight visual interface or download it for statistical data analysis.

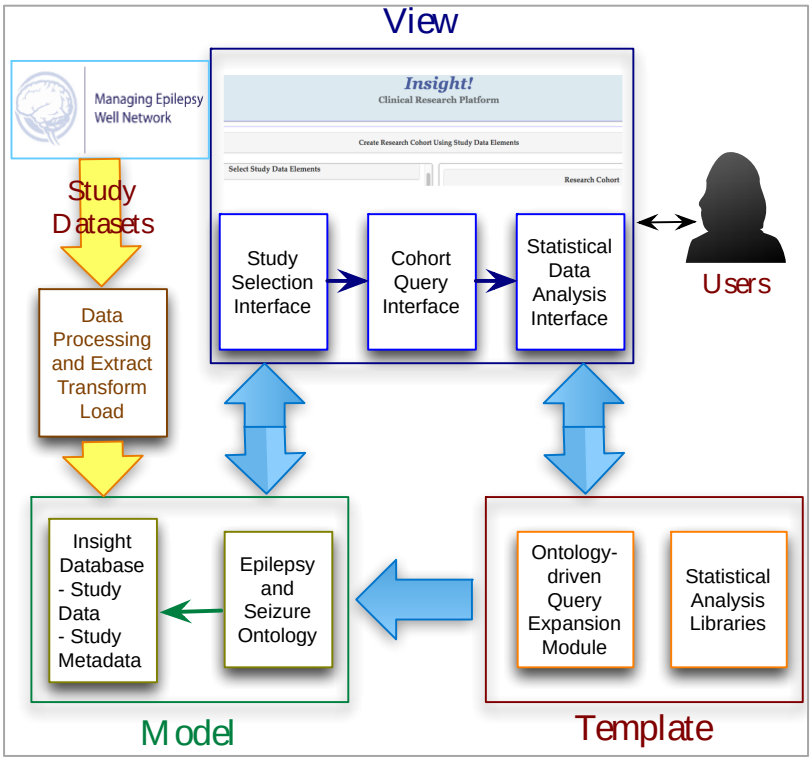

Figure 1: The Model View Template (MVT)-based system architecture of the Insight platform with description of their subcomponents

However, there are many challenges associated with use of statistical data analysis after downloading the patient cohort data, including re-formatting the data into a format that is required by a given statistical tool (e.g., Mann-Whitney U test and chi-squared test). In addition, downloading and transferring the patient cohort data between different computing platforms that have relevant statistical data analysis tools is cumbersome and significantly increases the time required for statistical analysis. An intuitive approach to address this challenge is to enable users to perform various statistical analysis in the Insight platform itself, which would eliminate the need to download and process the patient cohort data. Therefore, we implemented a new integrated statistical data analytics module in Insight to streamline and effectively reduce the time required to analyze patient cohort data.

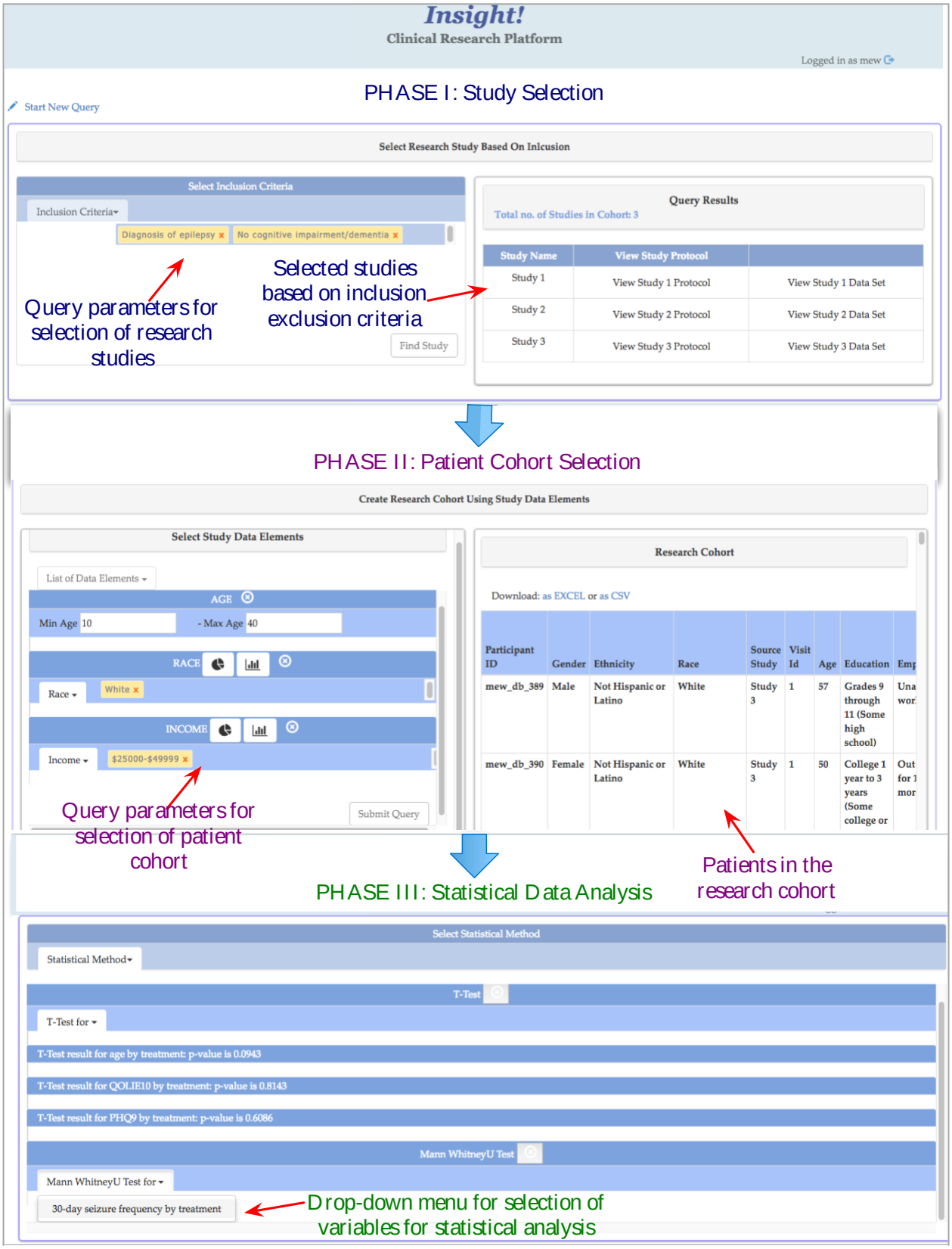

Figure 2: The three components of the Insight platform, namely: (1) Study Selection; (2) Patient Cohort Selection; and (3) Statistical Analysis component

Statistical Data Analytics Module Development

The Insight platform supports multiple statistical methods that can be applied to the patient cohort data. To apply statistical methods on the patient cohort data, a new statistical data analysis module was developed and implemented. Using the patient cohort data after execution of the two phases of Study Selection and Cohort Query, which have been described in details earlier (17), the statistical analysis module uses a similar user-friendly approach for invoking the a set of statistical methods on the results of the cohort query.

The implementation of the statistical methods involves three aspects: (1) storage and modification of data in a common model; (2) user interface features for invocation of statistical methods; (3) visualization of results of statistical data analysis. In the first phase, the results of the patient cohort query are stored as a "view" in the Insight database, which allows fast access to the data during subsequent statistical data analysis. In addition, the database view is also used to support download functions for users. In the second phase, the Insight statistical data analysis module interface is used to conduct the statistical analysis. The statistical functions in Insight are implemented using a modular approach, which allows new statistical modules to easily added. At present, Insight supports multiple statistical analysis methods, including variance, t-test, chi-squared test, and Mann-Whitney U test. As discussed earlier, these statistical methods are used in all the three research studies involving use of the MEW-DB integrated data.

Figure 2 shows the creation of the patient cohort using the first two components of the Insight platform (Study Selection and Cohort Query). Figure 2 shows the application of statistical methods on the patient cohort data using the Insight interface features, where a user can select specific statistical method to be applied to the data. For a given statistical method, the Insight interface automatically populates the subcategories of the drop-down menu with appropriate variables selected from the patient cohort data (output of the second component of Insight described earlier). This adaptive population of drop-down menu allows users to quickly select cohort-specific variables to be analyzed using a statistical method, which is both efficient as well as user-friendly. Once the statistical method and appropriate study variables are selected and applied, the output results are listed for viewing by the user. The results of the analysis can also be downloaded also by the user.

Evaluation of Data Analytics in Insight

The objectives of our evaluation are two-fold: (1) the first goal is to evaluate the usability of the Insight platform using two approaches, namely a "user satisfaction survey" and "first click testing"; and (2) the second goal is to evaluate the time performance of the statistical modules with respect to different datasets. The usability evaluation of the Insight platform was conducted with two team members of the MEW project who have performed several tasks on the MEW DB, including data processing and statistical analysis. We propose to perform a comprehensive user evaluation study of the Insight platform with a focus group consisting of participating MEW network members in the future. The details of two methods used for usability evaluation are:

1. **First click testing**: This method is used to evaluate the effectiveness and efficiency of the user interface in terms of enabling users to accomplish their tasks. We defined four tasks for users to complete by using the Insight user interface for the statistical data analysis, namely: (a) computation of t-test over a select cohort; (b) computation of Mann-Whitney U test over specific study variable; (c) computation of mean; and (d) computation of variance of study variables in a given cohort. This testing measures the number of clicks performed by the users in completing a given task, which may involve selecting the correct or incorrect set of options in the user interface. Intuitively, users who select the correct sequence of options in the user interface complete their tasks with a minimal number clicks and on time.
2. **User satisfaction survey**: In addition to the first click test, we also performed a broader user satisfaction survey with the objective of evaluating: (a) whether users can locate relevant information easily; (b) whether the results of their queries are easily accessible as well as visualized; (c) a comparative evaluation of the Insight interface with respect to existing tool; and (d) the likelihood of users recommending the Insight platform to other users for cohort data analysis.

The response of the users was recorded on a graded scale of 1-10 points with 1 corresponding to lowest value and 10 corresponding to highest value. The performance evaluation test used data from all the three studies that used the MEW DB data (described earlier), which demonstrate the scalability of the Insight platform with different size of datasets.

Results

The results are shown in Figure 3 show the results of the two user evaluation surveys for the Insight platform.

First click testing. The results for the first click testing (Figure 3(A)) show that both the users performed extremely well in terms of selecting the correct options in the interface to complete the four tasks (described in the previous section above). The first question asked the users whether they were able to complete the four tasks in the first attempt and both the evaluation results show that both the users completed the tasks in their first attempt. The second question validated the design principle of the user interface that users should be able to reach a final selection option with minimal number of clicks. Both the users agreed strongly (user rating score of 10) in the third question that the drop-down menu showed only the relevant study variables for a give statistical data analysis method. The two users gave a rating of 10 and 9 (corresponding to user 1 and user 2) in the fourth question for the difficulty level associated with locating a specific statistical data analysis method in the user interface. Finally, both the users agreed that the Insight platform was very easy to use to perform statistical analysis as compared to existing statistical packages such as SAS. However, one of the users noted that at present the Insight platform did not support a large number of statistical data analysis methods, which we aim to address in the future with implementation of additional statistical data analysis methods.

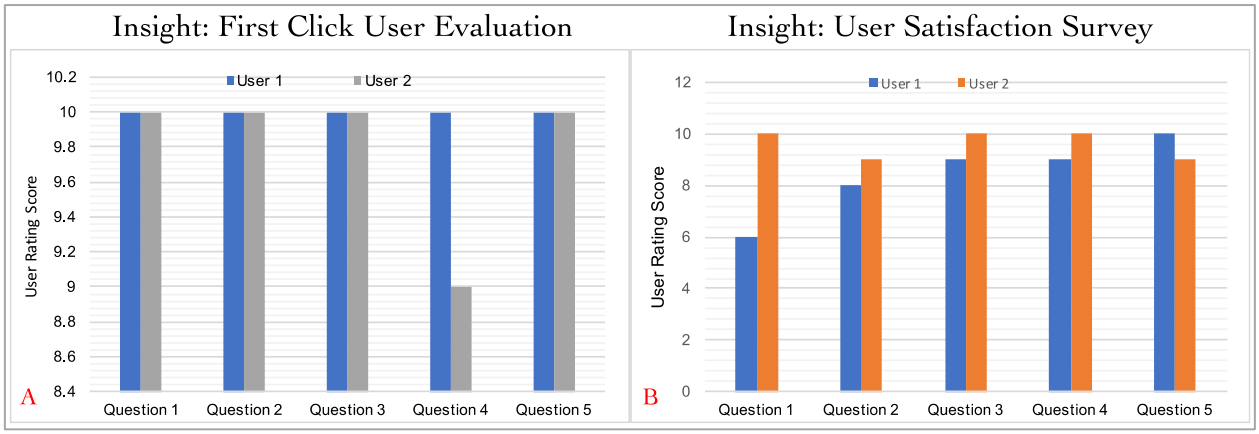

Figure 3: The results of the user evaluation of the Insight platform are shown using two approaches: (A) First Click user evaluation; and (B) User satisfaction survey with two users who are familiar with the MEW DB

User Satisfaction Survey. Figure 3(B) shows the results of the user satisfaction survey consisting of 5 questions covering the navigation, visualization, effort required to complete tasks, and whether they would recommend the Insight platform to other MEW DB users. One of the users noted that the Insight platform was "fairly easy (to use) after demonstration" and it would have been more difficult to use without a demonstration. We agree with this assessment and we aim to create comprehensive user manual for the Insight platform that will allow first time users to quickly learn the different components of the platform. Both the users agreed that it was relatively easy to select specific statistical analysis method the associated study variable in the second question. Similarly, both the users strongly agreed that results of the three Insight platform

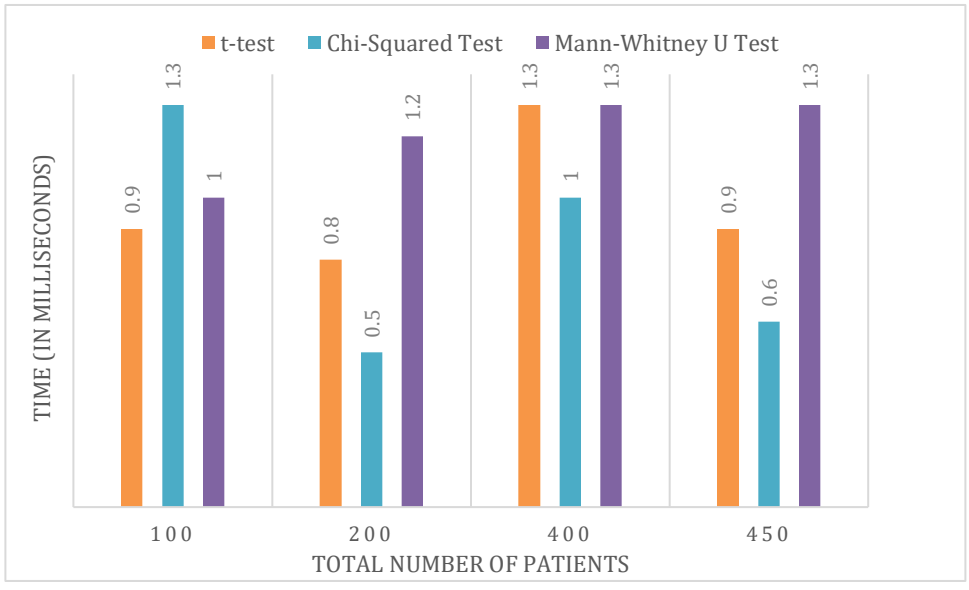

Figure 4: A comparative evaluation of the time performance of the Insight platform using four different sizes of patient data and three statistical test.

components (Study Selection, Cohort Selection, and Statistical Analysis) were clearly visualized in the third question. Although both the users strongly agreed that the Insight platform reduces the time and effort required to conduct statistical data analysis as compared to existing methods in the fourth question, one of the users noted that at present the Insight platform does not allow for more in-depth data analysis. We aim to work with the users to address this concern. Both the users strongly agreed in the fifth question that will recommend the Insight platform to other MEW DB users.

Performance evaluation for statistical analysis. To demonstrate the practical usability and scalability of the Insight platform, we used four datasets consisting 100, 200, 400, and 450 patients from Study 3 to compute three statistical tests, namely t-test, Chi-Squared test, and Mann-Whitney U test. Figure 4 shows the time performance of the Insight platform statistical analysis module in milliseconds for the four datasets and three statistical tests. The results show that performance difference between the four datasets is marginal for all the three statistical tests. For example, there is a difference of 0.2 milliseconds and 0.1 milliseconds between the 100 patient datasets and the 200 as well as 400 patient datasets respectively. Similarly, there is a difference of 0.1 to 0.4 milliseconds for the t-test. These results show that there is no significant impact on the time performance of the Insight platform in the MEW-DB as the number of patients increases. It is also interesting to note that the difference between the time performance of the three statistical tests is also marginal with difference in values ranging from 0.1 milliseconds (for 100 patients) to 0.7 milliseconds (for 200 as well as 450 patient datasets).

Discussion and Conclusion

This study demonstrated the significant utility of a focused ontology-driven informatics tool for epilepsy clinical research that offers functionalities spanning study selection, cohort identification, and integrated statistical analysis in the context of a multi-center national study on epilepsy self-management. We are not aware of other existing tools that offer a similar level of granularity and functionality that can be readily used in the MEW Network project. The utility of the Insight platform and in particular the statistical data analysis module lies in its potential to significantly improve the efficiency and effectiveness of data analysis procedure for users as the size of the MEW DB continues to increase in terms of the volume of data and the number of studies proposed to be conducted on the integrated data. Although there are multiple data integration and ontology-driven informatics tools that are available in the biomedical research domain, there are significant challenges associated with their adoption in highly specialized, specific disciplines of medicine. Therefore, we decided to develop the Insight platform as an epilepsy-focused informatics tool that meets the requirements of this domain with the use of a domain-specific ontology (EpSO) and specialized data processing, querying, and analysis features.

The availability of integrated functionalities, in particular the statistical analysis module in the Insight platform has several advantages as compared to the use of offline statistical analysis tools. For example, users do not need to download and transfer data across one or more computers that increases the risk to safe management of research study data, including de-identified study data as used in the MEW-DB. Therefore, the integrated functionalities for statistical testing in the Insight platform offers significant advantages in terms of ease of use as well as maintaining data access restrictions for users as compared to existing approaches of manual data transfer and analysis.

The primary objective of the Insight platform is to serve as an informatics tool that facilitates greater use of the MEW DB for analysis and evaluation of self-management techniques in epilepsy. To achieve this goal, we are implementing new features in the Insight platform, including the development of a Docker-based version, which will allow the Insight platform to be easily shared and installed by the MEW Network community. The Docker-based version will allow individual MEW researchers

The work reported in this paper has some limitation. For example, as highlighted by a user during the user evaluation the current version of the Insight platform does not support in-depth statistical analysis. In addition, the number of statistical tests currently available in the Insight platform are limited. Therefore, we plan to significantly increase the number of statistical tests available in the next version of the Insight platform. In addition, we propose to add extensive result visualization features in the next version of the Insight platform.

In conclusion, in this paper we presented an integrated data processing and analysis platform called Insight that can significantly facilitate epilepsy patient cohort studies in the MEW Network in the context of epilepsy self-management studies.

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