VirtualMindTrial: AN INTELLIGENT QUESTIONNAIRE SYSTEM FOR CLINICAL TRIAL RECRUITMENT

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VirtualMindTrial: AN INTELLIGENT QUESTIONNAIRE SYSTEM FOR CLINICAL TRIAL RECRUITMENT

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ABSTRACT

The recruitment of human subjects for clinical trials research is a critically important step in the discovery of new cures for diseases. Volunteers are subjected to an elaborate questionnaire process in current recruitment methodologies. Although the questionnaire process is extremely important in clinical trial recruitment, it is inefficient due to redundancy and lack of a systematic approach. Ideally, questionnaire generation and implementation must be guided by intelligent heuristics that minimize redundancy and inconsistency.

In this thesis, an intelligent approach to questionnaire flow called VirtualMindTrial is proposed. Given a set of textual inclusion/exclusion clinical trial eligibility criteria and data available from diverse sources such as Microsoft HealthVault, VirtualMindTrial is able to 1) filter known criteria, 2) add associative criteria based on selected criteria, 3) form a neighborhood of patients who satisfy similar criteria, and 4) generate a dynamic questionnaire flow for screening patients. The questionnaire has been implemented using a visual 3-D environment to help volunteer subjects experience a realistic screening process. Experimental results demonstrate the effectiveness of our system in terms of dynamic questionnaire flow generation and in enhancing the user experience with virtual worlds. A visual prototype system has been developed as part of

the thesis to illustrate the enhanced efficiency and quality of screening patients with psychiatric disorders for clinical research.

The faculty listed below, appointed by the Dean of School of Computing and Engineering, have examined a thesis titled "VirtualMindTrial: An Intelligent Questionnaire System for Clinical Trail Recruitment" presented by Nikhilesh Katakam, candidate for the Masters of Science degree, and certify that in their opinion it is worthy of acceptance.

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LIST OF ABBREVATIONS

VERT	Virtual Reality Exposure Therapy
VRT	Virtual Reality Therapy
VR	Virtual Reality
GAD	Generalized Anxiety Disorder
PHR	Patient Health Record
SAD	Social Anxiety Disorder

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The views and conclusions contained herein are those of the author's and should not be interpreted as necessarily representing the official policies or endorsements, either expressed or implied, of the University of Missouri - Kansas City.

CHAPTER 1

INTRODUCTION

1.1 Research Motivation

The recruitment of human subjects for clinical trials research is a critically important step in discovery of new cures for diseases. Recruitment via the traditional methods of phone-based and face-to-face interviews is inefficient. There is considerable scope for improving on the current paradigm for recruiting. Volunteers are subjected to an elaborate questionnaire process in current recruitment methodologies. Although the questionnaire process is extremely important in clinical trial recruitment, it is inefficient due to redundancy and lack of a systematic approach. Ideally, questionnaire generation and implementation must be guided by intelligent heuristics that minimize redundancy and inconsistency.

Redundancy is one of the factors resulting in the high recruitment cost of clinical trials. Ideally, one should be able to eliminate unsuitable patients or volunteers before initiating expensive screening and evaluation. However, this is often discovered only after considerable time and effort have been invested by both the volunteer subjects and the clinical trial personnel. Currently, subjects are recruited for clinical trials on a just-in-time basis. Ideally, one should have prescreened the subjects available for trials who have already indicated an interest in volunteering. If detailed information regarding their medical conditions is already available, and can be searched with a high degree of specificity, it would increase the probability of obtaining subjects for clinical trials.

Virtual Worlds have a great potential to help improving the clinical trial recruitment process and overcoming the limitations [36]. Virtual Worlds represent an exciting and emerging frontier. Virtual worlds make it possible to create virtual objects, actors, and environments where information can be virtually exchanged and processed. The underlying technology makes it possible to carry out unique virtual worlds by transcending physical barriers of space and time. The simulation of clinical trial process using these technologies is particularly valuable in screening patients for a study. In future, experiences of virtual clinical systems can be seamlessly integrated with the real clinical trial experiences.

1.2 Problem Statement

In this thesis, an intelligent approach to questionnaire flow called VirtualMindTrial is proposed. Given a set of textual inclusion/exclusion clinical trial eligibility criteria and data available from diverse sources such as Microsoft HealthVault, VirtualMindTrial is able to 1) filter known criteria, 2) add associative criteria based on selected criteria, 3) form a neighborhood of patients who satisfy similar criteria, and 4) generate a dynamic questionnaire flow for screening patients.

A visual prototype system has been developed as part of the thesis to illustrate the enhanced efficiency and quality of screening patients with psychiatric disorders for clinical research. The visual 3-D environment helps volunteer subjects experience a realistic screening process.

1.3 Thesis Outline

In Chapter 2 we present the related systems that use the potential of virtual environments for treating psychiatric disorders and also describe other online based systems for clinical research. Chapter 3 describes the VirtualMindTrial framework. Chapter 4 introduces the VirtualMindTrial

system architecture in detail. Chapter 5 demonstrates the online and virtual environment models for the proposed system. Chapter 6 shows the evaluation and experimental results of measuring the performance of VirtualMindTrial. Chapter 7 concludes this thesis and provides information for future work for this system.

CHAPTER 2

RELATED WORK

In this chapter we will review several systems which provide significant contribution in the areas of clinical trial recruitment, intelligent questionnaire generation and use of virtual worlds for health care. In Section 2.1 we discuss several web based online systems for improving clinical trial recruitment. In Section 2.2 we illustrate several intelligent questionnaire generation systems that help in creating a questionnaire set from a given input and in Section 2.3 we explain several different systems that use virtual world technologies in improving health care domain.

2.1 Web Based Systems in Health Care

There has been some progress in the standardization of different aspects of clinical trials – trial registry, trial authoring [18], and clinical guidelines [32]. There is a major ongoing effort in standardizing the BRIDG[1] model for clinical trials. The Volunteer for Vanderbilt Research Program [13] is a good illustration of the benefits of using even a basic website for volunteer initiated recruitment. TrialX [20] is one of the more advanced online trial search systems based on semantic matching of trials with personal health records. Fink et al. [7] introduced an interactive web-based system which helps physicians in finding cancer patients and match them to relevant clinical trials. The interface helps clinicians to add new clinical trials and appropriate selection criteria for each trial, thereby providing means to extend their knowledgebase. Embi et al. [6] present a clinical trial alert system which notifies the physician when it finds an eligible patient for an ongoing clinical trial.

[1] http://www.bridgproject.org (Accessed date: Aug. 31, 2010)

2.2 Intelligent Questionnaire Generation systems

Goto et al. [10] demonstrate a system which helps in automatically generating multiple choice cloze questions from English texts. Quiz Pack [8, 2, 3] is an intelligent tutoring system which helps in generating a dynamic parameterized quiz for programming related subjects. Zitko et al. [39] describe a system for dynamically generating questions of a test based on previously formalized domain knowledge.

2.3 Virtual Worlds in Health Care

Virtual worlds go a step beyond web-based systems in offering an immersive and informative personalized experience, with the option to be anonymous. Virtual world platforms such as Second Life have been used in health care. The IBM's Virtual health care island [14] is a futuristic representation of the challenges and opportunities facing today's health care industry. It also shows how Information Technology can help in improving global health care delivery. The Plumbing Advise project [30] demonstrates a futuristic hospital environment equipped with various features such as Wi-Fi, Cisco real estate framework for health care and much more.

Medical Simulation in the Virtual World of Second Life by MUVErs [17] simulates medical treatment procedures such as measuring the patient's heart rate, intravenous administration and supplying oxygen. Second Life for E-Health - Laval 08 [9] aims at providing patients suffering with mental disorders integrated therapy with online support sessions. Game-based learning for Virtual Patients in Second Life [31] shows scenarios taking place in a day to day hospital environment. Patients get to learn medical procedures through games. 3D Emergency Preparedness Training [16] simulates various actions that people need to take in case of

emergency. Some of the scenarios mentioned are calling emergency services in case of an accident.

Virtual Reality Exposure Therapy (VRET) is a process where a person is exposed to specific feared situations or objects that trigger anxiety [11]. In [15] Virtual Reality Therapy (VRT) system is used in treatment of subjects diagnosed with acrophobia, a disorder that is characterized by marked anxiety upon exposure to heights and avoidance of heights. As a part of this study, the subjects who were suffering from fear of heights were exposed to a virtual scene of a bungee - jump tower in the middle of a large city. The results proved that using such virtual reality (VR) environments could help in overcoming acrophobia.

Many VRET systems are shown in [5, 27, 26, 28, 25] for treating subjects with posttraumatic stress disorder. Riva et al. [24] illustrates the concept of Interreality which helps in linking the virtual world behavior to that of the real world and vice versa. This is achieved with the help of 3D shared virtual worlds using bio sensors, activity sensors personal digital assistants and/or mobile phones. NeuroVR [27], an open-source software, is used in the assessment and treatment of several anxiety disorders using virtual worlds. Riva et al. [22, 23] make use of bio feedback enhanced virtual reality to facilitate the relaxation process by presenting subject with key relaxing images. This helps in the treatment of Generalized Anxiety Disorder (GAD). VR-ENGAGE is a VR game that has been constructed for teaching students in a motivating way [35].

Table 1 shows a feature comparison table that compares the features provided by the existing virtual world projects discussed above to that of VirtualMindTrial. As we can see from Table 1, most of the systems lag in providing a gesture based interaction, providing audio enhancements

and presenting a game based approach for the patients. The VirtualMindTrial system proposed in this thesis provides all the feature listed, and helps patient's achieve a high level of interactivity while using the virtual worlds.

Table 1: Feature Comparison Table for Different Virtual Worlds

Papers	VRET	Gesture Based Interaction	Online Community	Audio Enhancements	Game Based Approach
[14, 30, 17, 9, 31, 16]	No	No	Yes	Partially	No
[5, 27, 26, 28, 25, 24, 11, 15]	Yes	Partially	No	Yes	No
[27,22,23]	Yes	Yes	No	Yes	No
VREngage[35]	No	No	No	Yes	Yes
VirtualMindTrial	Yes	Yes	No	Yes	Yes

Chapter 3

VirtualMindTrial FRAMEWORK

3.1 Introduction

The VirtualMindTrial framework provides an intelligent approach for generating questionnaire flows. Given a set of textual inclusion/exclusion clinical trial eligibility criteria (The medical or social standards determining whether a person may or may not be allowed to enter a clinical trial [4]) and data available from diverse sources such as Microsoft HealthVault [19], VirtualMindTrial framework is able to 1) filter known criteria, 2) add associative criteria based on selected criteria, 3) form a neighborhood of patients who satisfy similar criteria, and 4) generate a dynamic questionnaire flow for screening patients.

The VirtualMindTrial framework contains six major components namely Criteria Merging, Criteria Filtering, Criteria Association, Patient Neighborhood Formation, Domain Modeling and Dynamic Questionnaire Flow Generation. Figure 1 illustrates the components of VirtualMindTrial framework. In this section we give a brief description about the functionality and importance of each component.

Criteria Merging: The Criteria Merging component is responsible for combining common criteria among multiple selected studies and segregating the remaining criteria. Through this component VirtualMindTrial is able to extend its support from a single study model to a multi study model. A single study model contains criteria from only one study, while a multi study model contains criteria from multiple studies. A multi study model helps in parallel diagnosis of

multiple studies. (Additional details of the Criteria Merging component will be discussed in Section 3.2).

Criteria Filtering: The Criteria Filtering component take's patient health records (PHR) from diverse sources as input and partitions the criteria into known (which can be determined by the given patient input) and unknown (which cannot be determined by the given patient input) groups. The known subset of criteria is further grouped into fully known and partially known groups. (Additional details of the Criteria Filtering component will be discussed in Section 3.3).

Patient Neighborhood Formation: In this step a neighborhood of patients who satisfy similar criteria are identified and grouped together as a cluster. The questions generated in the latter stage are associated to all the patients in this cluster. This way VirtualMindTrial framework extends from a single patient model to a multi patient model. (Additional details of the Patient Neighborhood Formation will be discussed in Section 3.4).

Criteria Association: The Criteria Association component helps in enhancing the criteria by automatically adding associated or related criteria to the existing unknown criteria set obtained after criteria filtering. (Additional details of the Criteria Association will be discussed in Section 3.5).

Domain Modeling: The VirtualMindTrial knowledge base contains a large collection of diagnosis questions. These questions are based on several different standards specific to a disorder. The Domain Modeling helps in enhancing the questionnaire set by adding diagnosis

related questions from the knowledge base. (Additional details of the Domain Modeling will be discussed in Section 3.6)

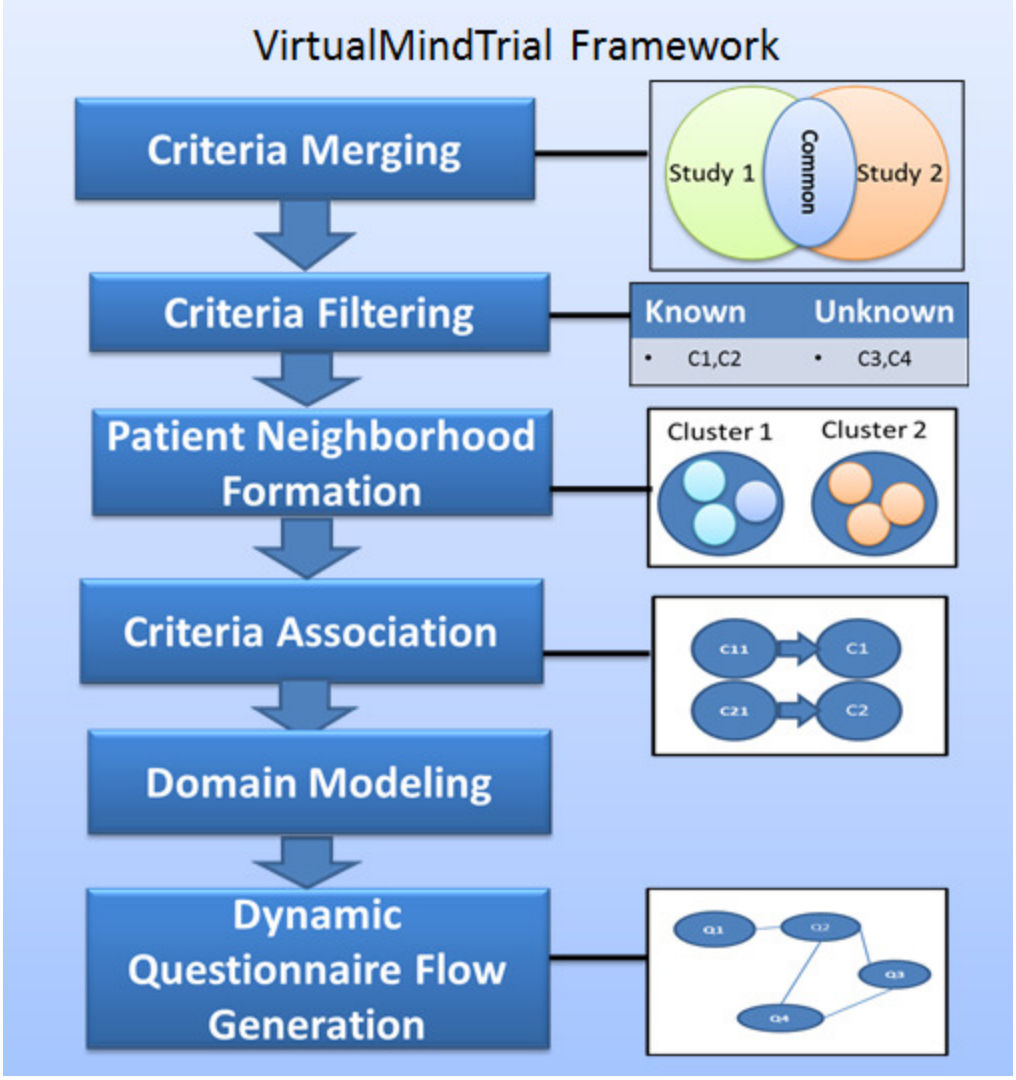


Figure 1: VirtualMindTrial Component Diagram

Dynamic Questionnaire Flow Generation: In this step, each unknown criterion is converted into a question to form a questionnaire graph. A questionnaire graph is a directed acyclic graph

containing questions from multiple studies. Each node in the questionnaire graph represents a question and each edge carries the weight of its previous outgoing node. Once the questionnaire graph is formed, essential threshold parameters are calculated which help in determining the patients path through the graph. (Additional details of the Dynamic Questionnaire Flow Generation will be discussed in Section 3.7).

As we can see from Figure 1, a set of grouped criteria is given as input to the Criteria Merger component, which then filters and combines criteria from multiple studies. This combined set of criteria is further filtered by obtaining data from the PHRs. The filtered criteria are further enhanced by adding associative criteria. These associative criteria are provided either by our associative rule mining engine or as a service. If there is a need to diagnose patients with a specific disorder, the domain modeling component adds diagnosis related questionnaire based on certain standards. Finally, the enhanced set of criteria is converted into a questionnaire graph which is used to screen the patients.

3.2 Criteria Merging

The Criteria Merging is the first step in the VirtualMindTrial framework. In this step, a set of textual inclusion/exclusion clinical trial eligibility criteria is given as input to the VirtualMindTrial's merging engine. The merging engine scans through each criteria and groups them according to their study. If a criterion is present in multiple studies, only one instance of it is retained to the original list and is mapped to all the studies it falls under. The end result of this step is a unified criterion set where each criterion is associated to one or more studies. This component helps in eliminating duplicate or redundant criteria when dealing with multiple studies. Figure 2 illustrates the criteria merging scenario.

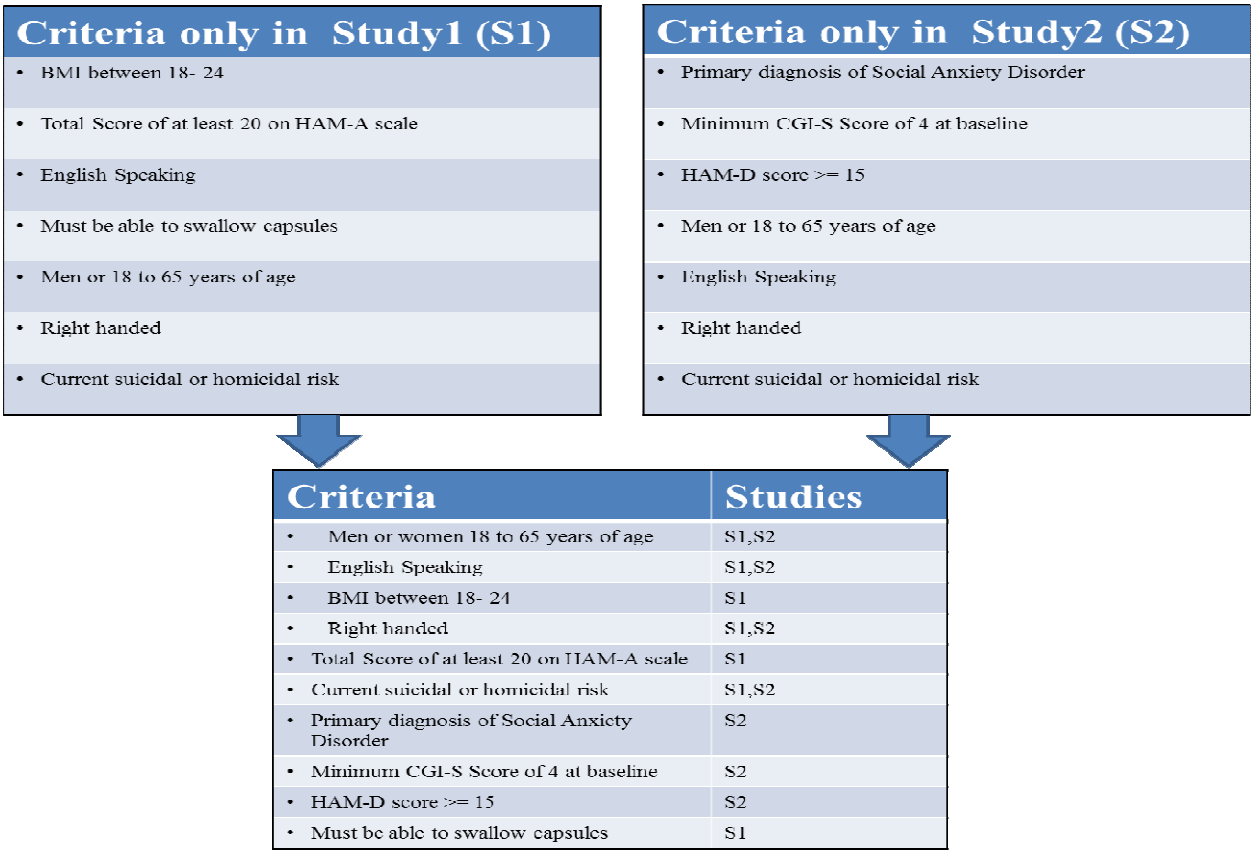


Figure 2: Criteria Merging Based on Study

After merging the criteria, we calculate the total score (S(total)) of the merged criteria set by summing the individual score of each criteria. This total would be used in later stages to determine how much percentage score the patient has obtained for each study. A detailed explanation about how we assign a score to each criterion is discussed in chapter 4.

3.3 Criteria Filtering

3.3.1 Introduction

Criteria filtering is the most important step in the VirtualMindTrial framework where known criteria are filtered out from the given input list of inclusion/ exclusion clinical trial eligibility

criteria. Given a PHR from diverse sources, the criteria filtering engine divides the criteria into two groups, known and unknown. The known set of criteria's is further grouped into fully known and partially known subgroups. These groupings are based on the information present in the PHR.

Figure 3 illustrates a flow diagram for criteria filtering. A unified criteria set (S) obtained after criteria merging is passed as input to the filtering engine. The filtering engine then scans through each criteria C_i in 'S' and performs a check to see whether the selected PHR has any information related to C_i, if the information exists and provides strong evidence for satisfying C_i, C_i is added to the fully known criteria set. On the other hand if information matches C_i partially it is added to the partially known set, if none of the above cases succeed C_i is added to the unknown criteria set.

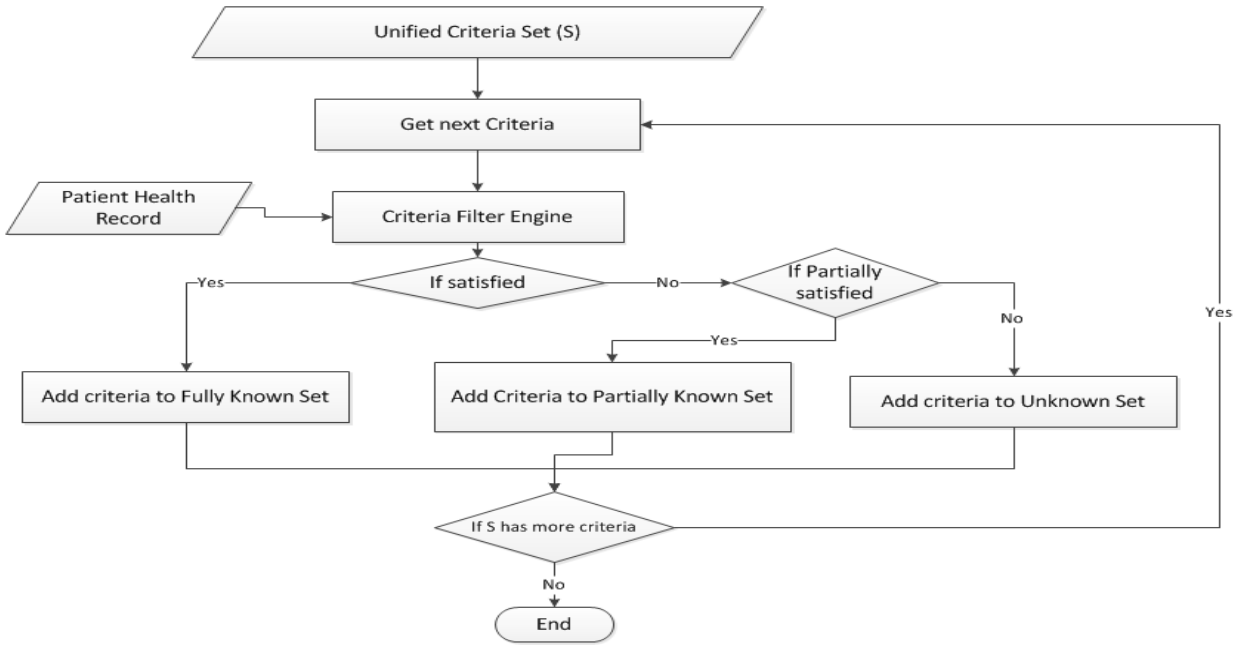


Figure 3: Criteria Filtering Flow Diagram

Once the criteria has been partitioned into known and unknown sets, the know set of criteria is eliminated from the input criteria and only the unknown set of criteria is passed on to the next module thereby eliminating redundancy and improving the efficiency of criteria.

Figure 4 illustrates an example scenario for criteria filtering. As we can see, the PHR contains information about the patient's age, gender, height and weight to calculate the BMI, HAM-D test score results and primary language of the patient. When this health record is passed as input to the filtering engine along with the criteria set, the filtering engine identifies that criteria C1, C2, C3 & C9 could be determined from the given patient input. Further, the criteria C1 and C2 are satisfied fully based on the information present in the health record and are added to the fully known criteria set.

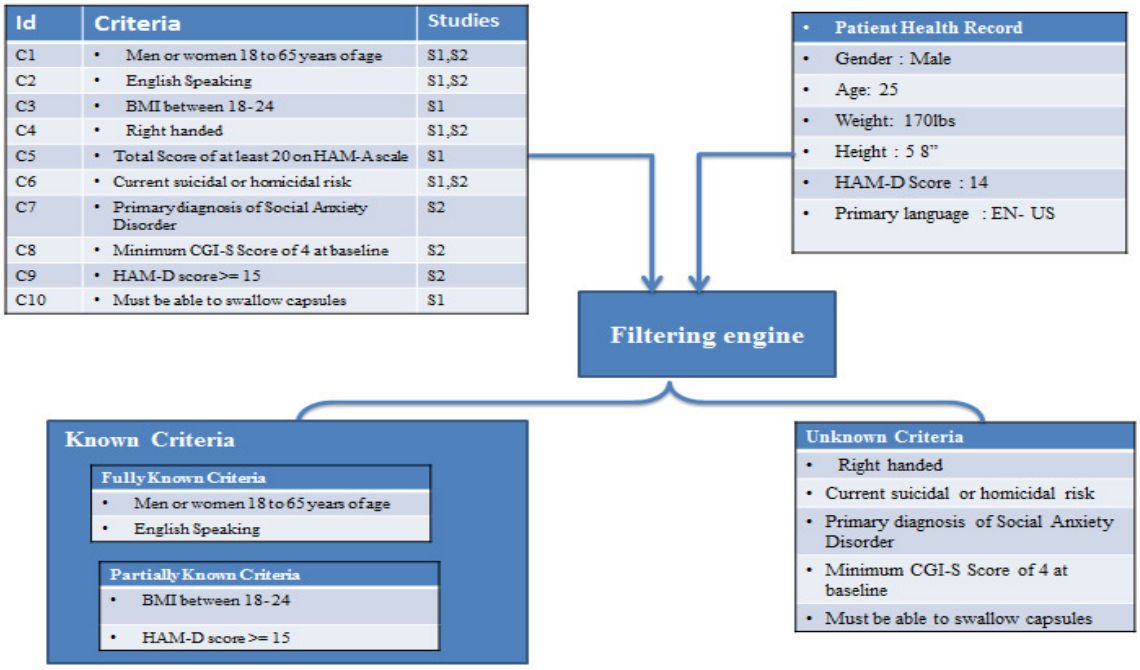


Figure 4: Criteria Filtering

On the other hand, the health record provides partial evidence for matching the criteria C3 and C9, for example, considering the criteria C3, when we calculate the BMI based on the height and weight measurement given in the PHR, we get a BMI value of 25.8 (approximate value) which does not fall in the BMI range (18-24) required for criteria C3. However, since the calculated BMI falls very close (± 5) to the required BMI range we consider the criteria C3 as a partial match and add it to the partially known set. All the other criteria, which could not be satisfied either fully or partially, are considered as unknown criteria and are added to the unknown criteria set.

3.3.2 Assigning Scores to the Criteria Groups

Once we partition the criteria into known and unknown sets, we calculate the total score for the know criteria set (S (known)) and the unknown criteria (S (unknown)) set by obtaining the original criteria scores. Since known criteria set is further grouped into fully known and partially known, the actually score of the criteria varies based on the group it belongs to. For example, if criteria is in the fully known set, we add its original score to S(known). On the other hand when the criteria is in the partially known set we add a partial score for the criteria to S(known).

We calculate the partial score of partially known criteria by using the formula shown in Figure 5. Here X is the original score for the criteria, V1 is the lower bound or an upper bound value of the criteria, V2 is the actual value of the criteria, MaxV is the upper bound of the criteria and MinV is the lower bound of the criteria. The value of V1 depends on V2, i.e., if V2 is less than MinV, then V1 is equal to MinV else if V2 is greater than MaxV, then V1 is equal to MaxV.

$$\text{Partial Score} = X - \frac{Abs(V1-V2)}{(Max\,V - Min\,V)} * 100$$

X = Actual Criteria Score
V1= Lower Bound or Upper Bound Value of a Criteria
V2= Actual Value of a Criteria
MaxV= Upper Bound of the Criteria
MinV= Lower Bound of the Criteria

Figure 5: Formula for Calculating Partial Score

An example scenario to show partial score calculation is illustrated in Figure 6 and Figure 7. The input for each example is a partially satisfied criterion, patient health record, and the actual score of the criteria. As we can see from the Figure 6, when the age of patient (which is 17) falls below the lower bound of the criteria (which is 18), the value of V1 is set to the lower bound value of the criteria.

Input

Criteria
Men or women Aged 18 to 65

Patient Health Record
• Gender : Male
• Age: 17

Actual Score = 100
Upper Bound =65
Lower Bound= 18
Criteria Value= 17

Since Criteria Value < Lower Bound

$$\text{Partial Score} = 100 - \frac{Abs(18-17)}{(65-18)} * 100$$

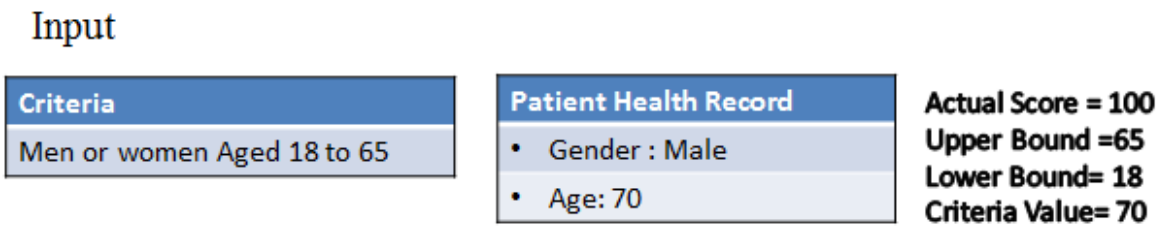
$$= 100 - 2.12$$

$$= 97.88$$

Figure 6: When Criteria Value is Less than the Lower Bound

On the other hand in Figure 7, when the patient age falls above (70) the upper bound value of the criteria(which is 65), the value of V1 is set to the upper bound value of the criteria.

After calculating the scores for each partially known criteria and fully know criteria we add them to get the total calculated score for the known criteria . We then subtract this score from the S(known) to the total score already satisfied by the patient based on the information given in his health record.The value of S(unknown) is the maximum possible score for the quiz that is generated in the final stage.



Since Criteria Value > Upper Bound

$$\text{Partial Score} = 100 - \frac{Abs(65-70)}{(65-18)} * 100$$

$$= 100 - 10.6$$

$$= 89.4$$

Figure 7: When Criteria Value is Greater than the Upper Bound

We make an assumption that partially score for a partially known criteria could be calculated only of those criteria which have fixed integer range. For all the other partially known criteria we assume that the partial score is give as input form our system.

3.4 Patient Neighborhood Formation

3.4.1 Introduction

The patient neighborhood formation helps in identifying patient groups who have satisfied similar type of criteria.We have adopted the collaborative filtering technique in forming the neighborhood for a given patient. Through this step, criteria selected for a give patient can be associated to all his neighbors, enabling VirtualMindTrial framework to handle multiple patient scenarios.

Figure 8 illustrates a scenario where a neighborhood of patients is formed based on the criteria satisfied by each patient. In the next sections, a detailed procedure for collaborative filtering algorithm is explained.

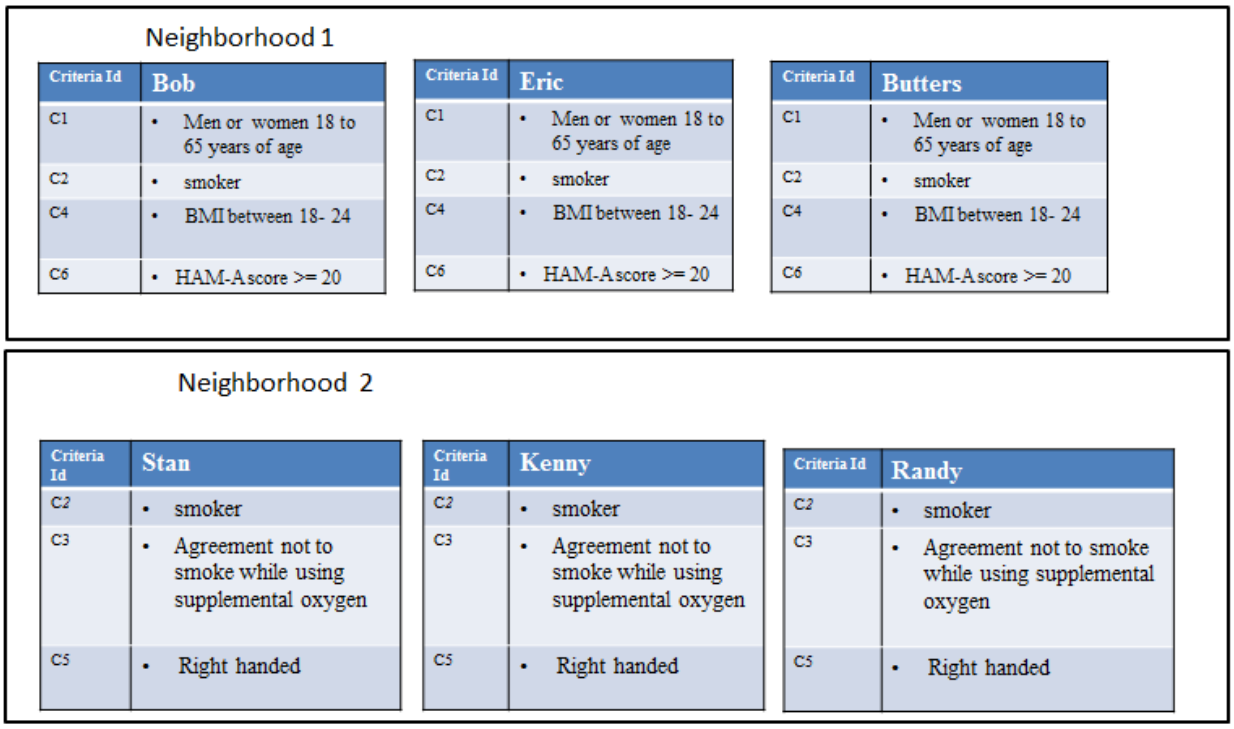


Figure 8: Patient Neighborhood Formation

3.4.2 Patient-Criteria Matrix Representation

The patient-criteria matrix representation is the first step towards the neighborhood formation. Here we construct an 'M x N' matrix of 'M' patients and 'N' criteria. Each row represents a patients and each column represents a criteria. For any given row R, $r_{i,j}$ (i^{th} row j^{th} column element) determines the actual / partial score of ith patient on jth criteria. Figure 9 illustrates an example patient-criteria matrix.

	C1	C2	C3	C4	C5	C6
Bob	100	80	0	100	1	90
Stan	0	100	100	0	70	10
Eric	100	82	0	96	6	95
Randy	5	99	99	2	74	7
Butters	100	80	4	90	7	90
Kenny	10	90	98	5	70	4

Figure 9: Patient-Criteria Matrix Representation

3.4.3 Cosine Similarity Based Neighborhood Formation

In this step the similarities between two patients in calculated using the cosine measure. The cosine measure [29] between two vectors *a* and *b* can be computed by the formula shown in Figure10.

$$\text{Cos}(a, b) = \frac{a \cdot b}{\|a\| \ \|b\|} = \frac{\sum a_i * b_i}{\sqrt{\sum a_i^2} * \sqrt{\sum b_i^2}}$$

Figure 10: Cosine Measure between Two Vectors

Here each vectors *a* and *b* represent a patient row from the patient-criteria matrix. Once the cosine similarity between two patients is calculated, it is compared with a neighborhood threshold. If the cosine measure is greater than or equal to the neighborhood threshold the patients are grouped as neighbors else we conclude that they do not form a good neighborhood.

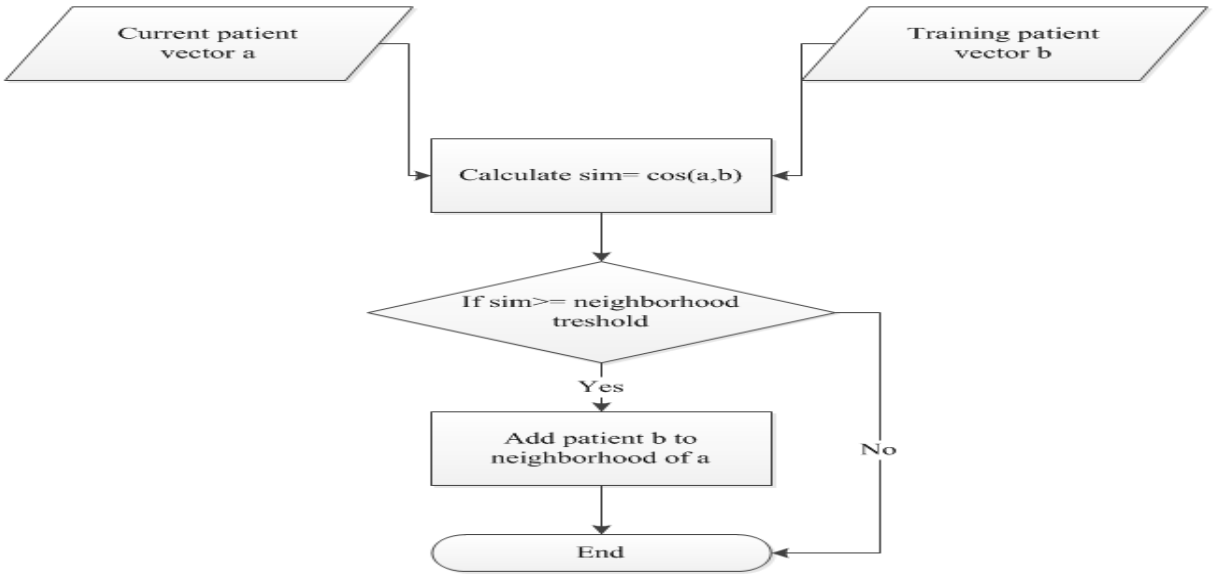


Figure 11: Cosine Similarity Measure Flow Diagram

Figure 11 illustrates the flow diagram for cosine similarity measurement. The cosine similarity between the current patient and every other patient in the patient- criteria matrix (excluding the current patient) is calculated and a neighborhood set for the current patient is formed at the end of this step. The quiz generated for the current patient (P) in the next step, would be associated to all the patients in the neighborhood of P.

3.5 Criteria Association

Criteria Association enhances the unknown criteria obtained after criteria filtering, by identifying and adding associated or related criteria. Each criterion from the unknown set is given as input to

the association engine, which then performs a look up to find any associate criteria to the current criteria. We have used the apriori rule mining algorithm using the weka tool for finding the associative mappings between the criteria. Information about the associative mappings between criteria could be obtained via web service providers. If an associated criterion is found, the association engine performs a check to see whether this criteria is already present in the unknown list, if it not present the corresponding criteria is added to the unknown criteria list else it is simply discarded. Figure 12 show the flow diagram for criteria association

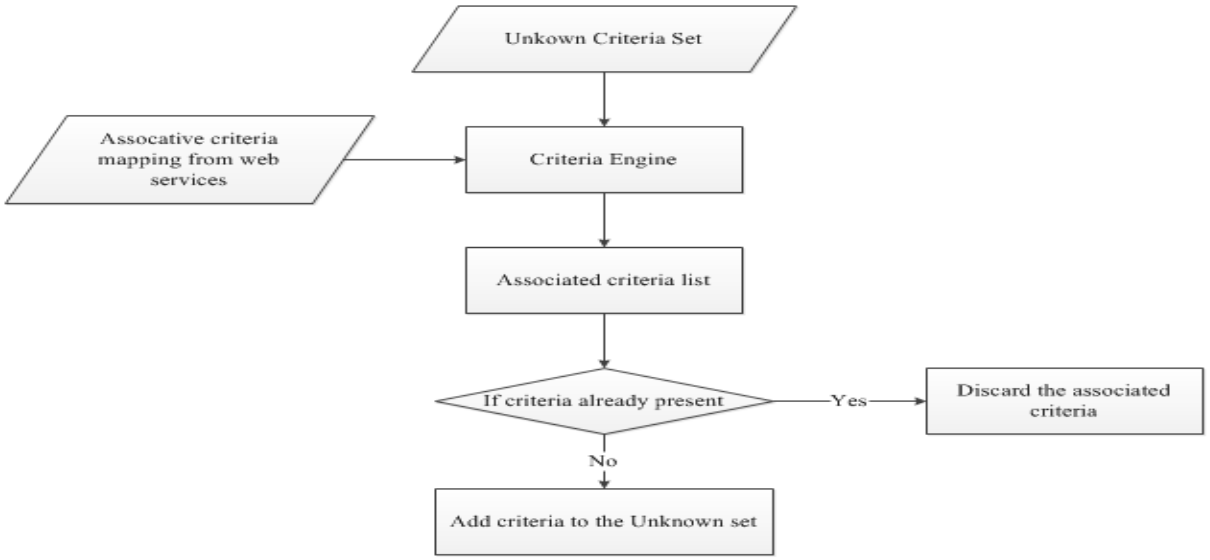


Figure 12: Criteria Association Flow Diagram

An example scenario illustrating criteria association can be seen in Figure 13. As we can see from the Figure 13, when a criteria “smoker” is in the list of unknown criteria, the associative engine finds a related criteria “Agreement not to smoke while using supplemental oxygen” and adds it to existing list. Similarly, for the criteria “pregnant” in the unknown criteria list, the

associative engine finds a related criteria “Negative serum pregnancy test for women with child bearing potential” and adds it to the list.

Criteria Association helps in automatically adding or enhancing criteria that a recruiter might have accidentally overlooked. The recruiter will always have the provision to remove the automatically added associated criteria, if he/she feels, is unnecessary for the study.

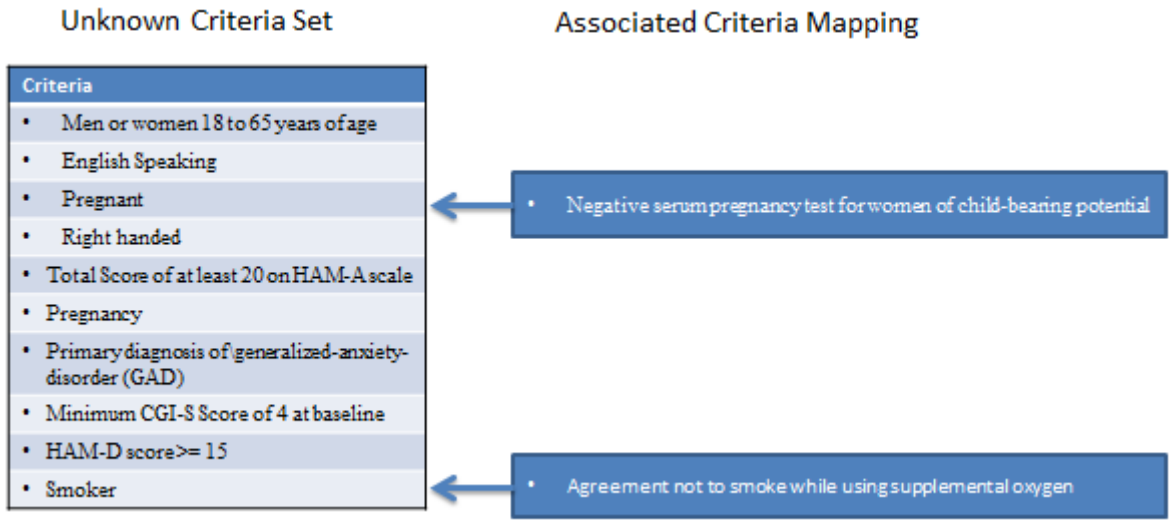


Figure 13: An Example Scenario Illustrating Associative Criteria Mapping

3.6 Domain Modeling

VirtualMindTrial knowledge base contains a large collection of diagnosis questions. These questions are based on several different standards specific to a disorder. The Domain Modeling helps in enhancing the questionnaire set by adding diagnosis related questions from the knowledge base.

Before the criteria are converted into questions, the domain modeling component scans through each criteria from the unknown list and searches for any criteria that requires patients to be

diagnosed with a certain standard. If such criterion exists in the unknown list of criteria, the domain modeling component automatically adds additional questions from our knowledge base. These questions help in diagnosing patients based on different standards associated with each study. The questions in the knowledge base have been created by comparing each standard associated with the study. Table 2 shows a list of diagnosis questions related to generalized anxiety disorder (GAD) that have been formed based on the comparison of several different standards such as MINI 500, GAD-7, HAM-A, HAMD-7, IUS and Penn State Worry Questionnaire.

3.7 Dynamic Questionnaire Flow Generation

Dynamic questionnaire flow generation forms the final step in the VirtualMindTrial framework. It is responsible for converting the unknown criteria's into a questionnaire graph. The questionnaire flow algorithm is responsible for determining the graphs path. The main aim for this algorithm is to compute the success ratio while traversing through the questionnaire graph. After traversing through certain number of nodes in the graph the algorithm performs a check to determine if the success ratio meets the threshold ratio for satisfying the study. If the condition is met, we traverse to the next node in the graph; else all the corresponding nodes in the graph are discarded.

Figure 14 illustrates an example where the set of unknown criteria obtained after criteria association being converted into a questionnaire graph. As we can see from the Figure 14, each criterion is converted into a question. Each question is assigned a weight for calculating patients score. The graph path for each patient in a neighborhood depends upon the information present in the PHR.

Figure 15 illustrates a scenario where the questionnaire flow algorithm determines the graph path based on the threshold. As we see in step (b) of Figure 15 when the success ratio at node Q3 is greater than or equal to minimum threshold (which are specified by the recruiter who is designing the study) we traverse through the next nodes Q4 and Q5, on the other hand in step(c) we can see that since the success ratio at node Q3 is less than the minimum threshold we discard nodes Q4 and Q5.

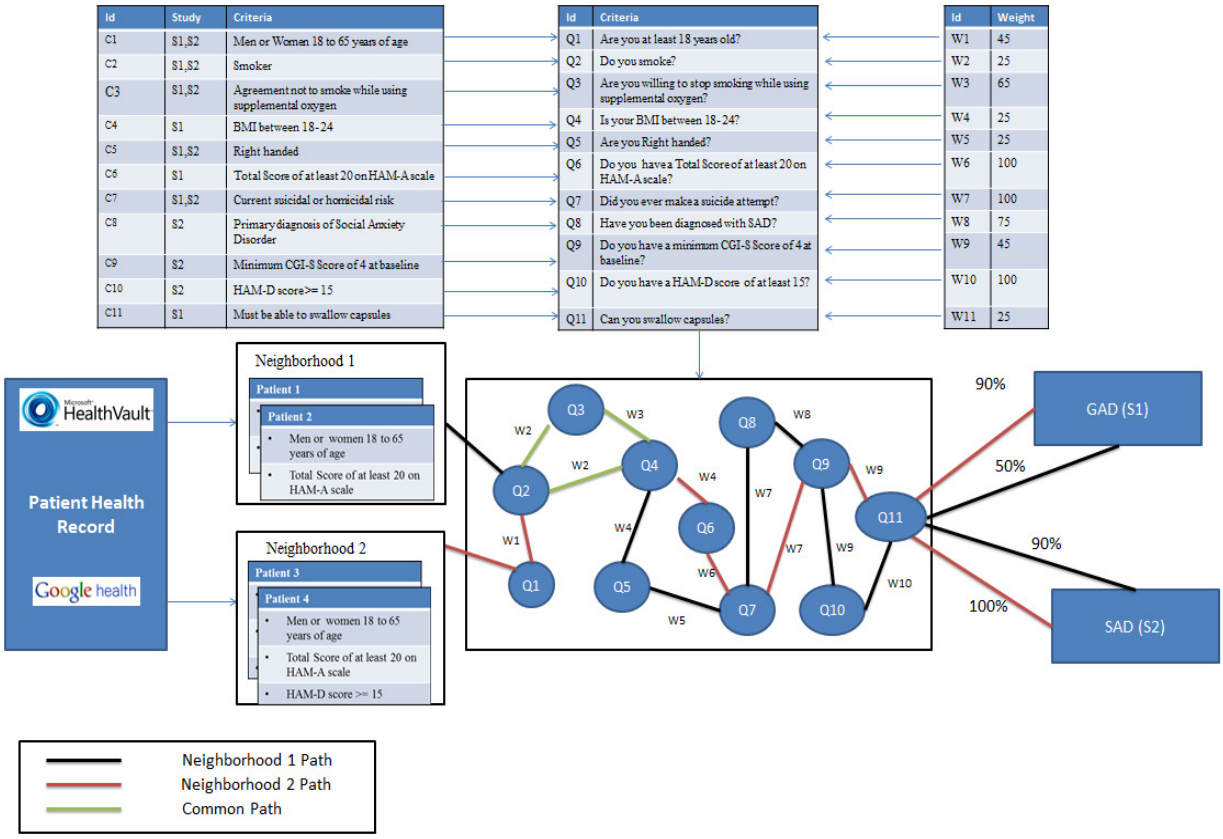


Figure 14: Questionnaire Graph

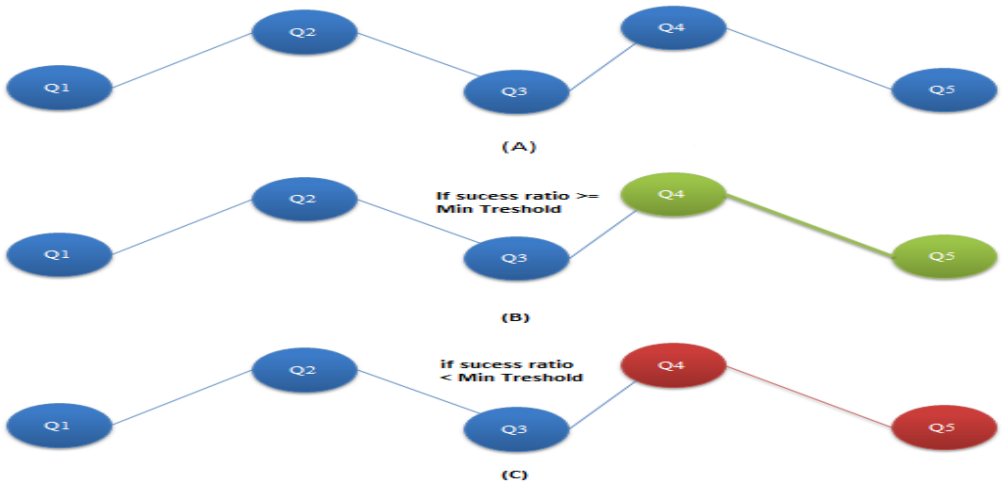


Figure 15: An Example to Show the Path Calculation for the Questionnaire Graph

Table 2: Comparison of Different GAD Standards

Question 1	
Standard	Original Question from MINI
	Have you worried excessively or been anxious about several things over the past 6 months?
GAD-7	Feeling nervous, anxious or on edge.
HAM-A	Anxious Mood
HAMD-7	• Tension, Nervousness. • Physical Symptoms of Anxiety.
Penn State Worry Questionnaire (PSWQ)	• If I do not have enough time to do everything, I do not worry about it. • My worries overwhelm me. • I do not tend to worry about things. • My situations make me worry. • (Q's 9-16 from PSWQ)
IUS	• My mind can't be relaxed if I don't know what will happen tomorrow • Uncertainty makes me uneasy, anxious, or stressed. • Uncertainty makes life intolerable. • I always want to know what the future has in store for me.
Question 2	
Standard	Original Question from MINI
	Are these worries present most days?
GAD-7	(Not applicable)

HAM-A	(Not applicable)
HAMD-7	(Not applicable)
Penn State Worry Questionnaire (PSWQ)	(Not applicable)
IUS	(Not applicable)
Question 3	
Standard	Original Question from MINI
	Do you find it difficult to control the worries or do they interfere with your ability to focus on what you are doing?
GAD-7	Not being able to stop or control worrying.
HAM-A	Anxious Mood
HAMD-7	Interest, Pleasure, Level of Activities.
Penn State Worry Questionnaire (PSWQ)	As soon as I finish one task, I start to worry about everything else I have to do.
IUS	• When it's time to act, uncertainty paralyses me. • When I am uncertain, I can't go forward. • When I am uncertain I can't function well. • Uncertainty stops me from having a firm opinion. • Being uncertain means that a person is disorganized.
When you were anxious over the past 6 months, did you, most of the time : (This is the common prefix for all the following questions)	
Question 4	
Standard	Original Question from MINI
	Feel restless, keyed up or on edge?
GAD-7	Being so restless that it is hard to sit still.
HAM-A	Depressed Mood
HAMD-7	• Tension • Nervousness.
Penn State Worry Questionnaire (PSWQ)	I know I should not worry about things, but I just cannot help it.
IUS	• Uncertainty makes me vulnerable, unhappy, or sad. • Ambiguities in life stress me. • My mind can't be relaxed if I don't know what will happen tomorrow.
Question 5	
Standard	Original Question from MINI
	Feel tense?

GAD-7	Feeling afraid as if something awful might happen.
HAM-A	• Tension • Fears
HAMD-7	• Tension • Nervousness.
Penn State Worry Questionnaire (PSWQ)	• When I am under pressure I worry a lot. • I am always worrying about something.
IUS	• I must get away from all uncertain situations. • Unforeseen events upset me greatly. • It frustrates me not having all the information I need.
Question 6	
Standard	Original Question from MINI
	Feel tired, weak or exhausted easily?
GAD-7	Trouble relaxing.
HAM-A	Somatic (muscular)
HAMD-7	Energy Level
Penn State Worry Questionnaire (PSWQ)	(Not applicable)
IUS	
Question 7	
Standard	Original Question from MINI
	Have difficulty concentrating or find your mind going blank?
GAD-7	Worrying too much about different things.
HAM-A	Intellectual
HAMD-7	Interest, pleasure, Level of Activities.
Penn State Worry Questionnaire (PSWQ)	(Not applicable)
IUS	• When it's time to act, uncertainty paralyses me. • When I am uncertain, I can't go forward. • When I am uncertain I can't function well. • The smallest doubt can stop me from acting.
Question 8	
Standard	Original Question from MINI
	Feel irritable?
GAD-7	Becoming easily annoyed or irritable.
HAM-A	Anxious Mood, Behavior at interview

HAMD-7	(Not applicable)
Penn State Worry Questionnaire (PSWQ)	(Not applicable)
IUS	• I can't stand being undecided about my future. • Ambiguities in life stress me. • Uncertainty makes life intolerable.
Question 9	
Standard	Original Question from MINI
	Have difficulty sleeping (Difficulty falling asleep, waking up in the middle of the night, early morning wakening or sleeping excessively)?
GAD-7	(Not present in GAD-7)
HAM-A	Insomnia
HAMD-7	(Not applicable)
Penn State Worry Questionnaire (PSWQ)	(Not applicable)
IUS	• Uncertainty keeps me from sleeping soundly.

Chapter 4

VirtualMindTrial SYSTEM ARCHITECTURE

4.1 Introduction

The architecture of VirtualMindTrial is two phased. Phase-I mainly focuses on converting the selected criteria into a set of questionnaire, while Phase-II deals with visualization of the questionnaire using a visual 3-D environment to help volunteer subjects experience a realistic screening process. The VirtualMindTrial database, web services [34] and gesture recognition API's [37] also form the core components of the VirtualMindTrial architecture.

Figure 16 shows the overall architecture of the VirtualMindTrial. In this section we give a brief description about the functionality and importance of each stage.

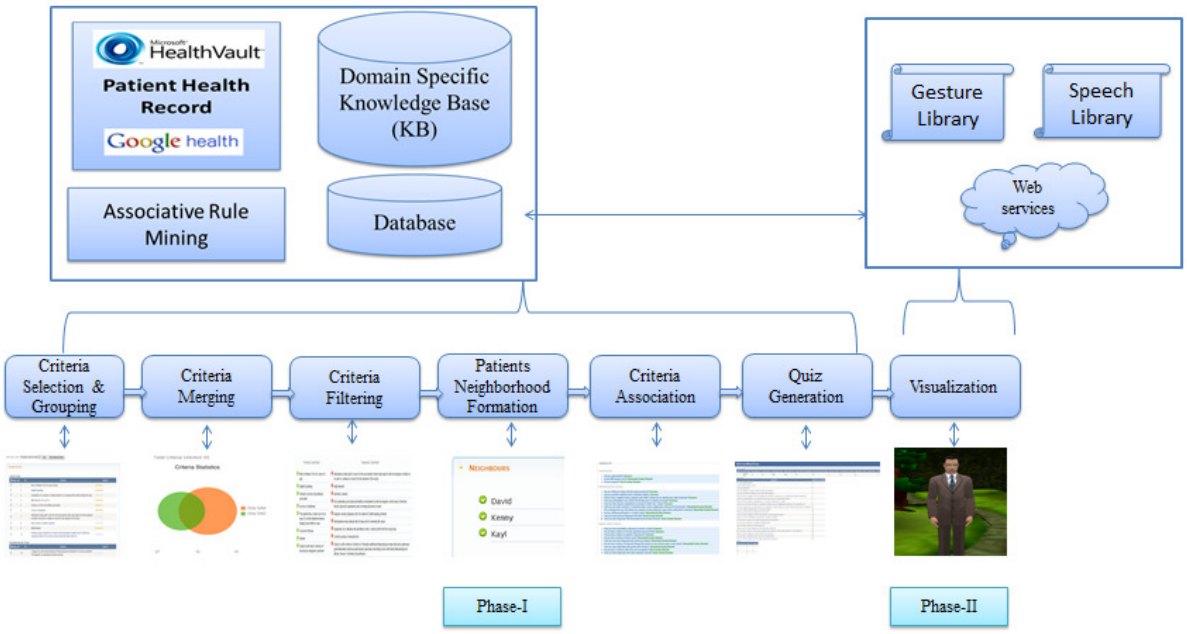


Figure 16: VirtualMindTrial Architecture

Criteria Selection and Grouping: The VirtualMindTrial database contains a large collection of inclusion and exclusion criteria. These criteria help in determining whether a patient should or should not be included in a study. These criteria can be further grouped based on their study and category (i.e. general, recruitment specific and diagnosis specific) they fall into. The VirtualMindTrial architecture makes and assumption that this grouping is already done and stored in our database.

After grouping the criteria, each selected criteria by the recruiter, is taken as input and is saved for further processing.

Criteria Merging: Once the recruiter selects the criteria, we scan through each of the selected criteria and identify which criteria are common and which criteria are specific to a single study and save these results for further processing.

Criteria Filtering: In criteria filtering we scan through the patients input and filter all the satisfied criteria from the list of selected criteria. The remaining criteria are further grouped as unknown criteria i.e. the criteria whose group could not be determined by the given patient input.

Patient Neighborhood Formation: After filtering out known criteria based on selected patients input, we scan through each patient in our database and identify which patient have satisfied similar criteria to the current patient and form a neighborhood group of all these patients. As explained in chapter 3 we make use of collaborative filtering algorithm to achieve this.

Criteria Association: Once the neighborhood is formed, we add associative or related criteria to the existing criteria that have not been selected by the recruiter.

Quiz Generation: This is the final stage in phase-I where all the unknown set of criteria are converted into a question set which help in determining the patients eligibility for a particular study. A quiz containing this question set is created and is assigned to every patient in the neighborhood.

Visualization: Once the final quiz is created, this quiz is conducted on patients using a visual 3-D environment built using Alice3 beta [1] to help volunteer subjects experience a realistic screening process.

Databases: The databases form an essential component in the VirtualMindTrial architecture. This contains information about criteria i.e. the study, type and groups they belong to. It also serves as a question repository where questions and criteria are mapped using an N:N relationship. The database also contains information about patient health record obtained via diverse sources such as Microsoft HealthVault and Google Health [12]

Web Services: The web services help in providing associative mapping to each criterion in our database. Apart from this they serve as a bridge between the virtual worlds and real world question base.

Gesture Recognition API: The Gesture Recognition API plays an important role in the VirtualMindTrial architecture. It provides and intuitive way to interact with the virtual 3D environment. We make use of the WiiGee open source gesture libraryfor training and recognizing the gestures. Patients perform a gesture using a Wii remote controller [38]. The Wii Gee library recognizes this gesture and helps us in taking necessary action.

Speech Library: To make the virtual environment more interactive we have used Mac OSX built in text to speech conversion libraries. This help in converting any interaction in the virtual environment to associated speech.

4.2 Criteria Selection and Grouping

4.2.1 Introduction

Criteria selection and grouping is the process of retrieving criteria from the database, based on study (i.e. generalized anxiety disorder, social anxiety disorder) and further grouping them based on their type (i.e. inclusion, exclusion) and category they fall into (i.e. general, recruitment specific and diagnosis specific).

Once this grouping is done we present a set of matching criteria to the recruiters to make a selection relevant to the study.

4.2.2 Database Model

Figure 17 shows a normalized structure of how the criteria are organized in the database Due to its extremely normalized model; the VirtualMindTrial database helps us achieve the above mentioned grouping with simple SQL calls to the database.

As we can observe from Figure 17, each criterion is associated with a category, type and study. Further, we can also observe that there is an N: N mapping between the criteria and study tables which signifies that a single criteria can be associated or mapped to multiple studies and vice versa.

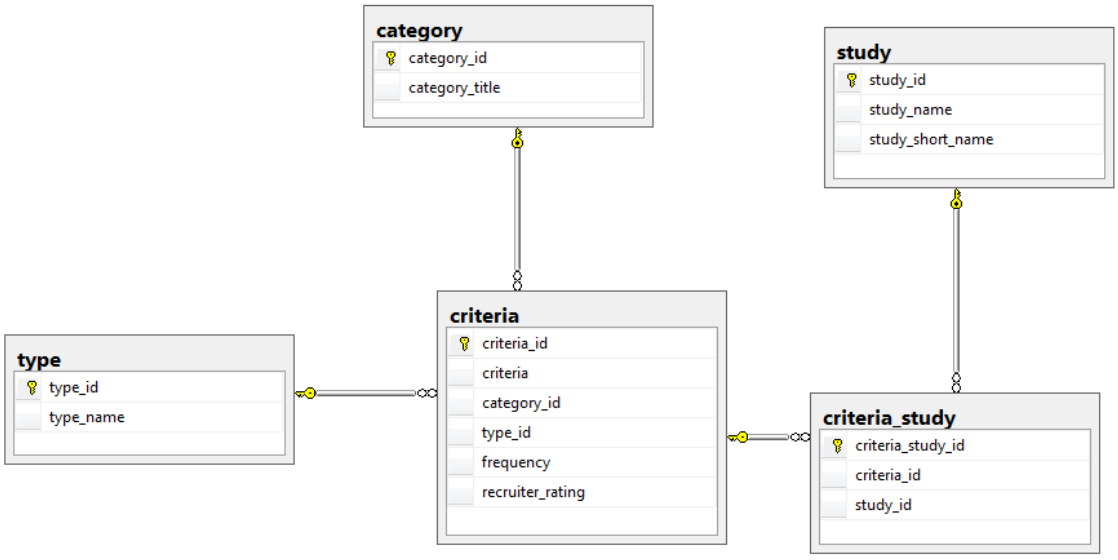


Figure 17: Normalized Structure of the Criteria Table

Associated with each table is a primary key which helps in uniquely identifying a record in that table and also participate in a primary key – foreign key relationship with other tables.

4.2.3 Criteria Frequency & Rating

The importance of each criterion can be determined using two fields “frequency” and “recruiter rating”. The frequency of each criterion is determined by the number of occurrences of the criteria in multiple studies for a single disorder. We assume that this is already known. On the other hand recruiter can manually rate the importance of criteria according to their needs. This rating would be on a five point scale starting from one to five. Initially all criteria are given a rating of five, and each criteria are treated with equal priority. Once a recruiter rates the criteria, their rating would be stored into the recruiter rating field of the corresponding criteria. By default the system considers the recruiter rating for determining the importance of the criteria, in its absence the frequency of the criteria is used to determine the importance of the criteria.

Once the frequency or recruiter rating for the criteria is known, the total score for the selected criteria is calculated. This is done by assigning a score range between twenty five to hundred for each frequency or rating. Table 3 displays the frequency or rating ranges associated scores.

The frequency ranges that are mentioned here have been formed after carefully observing a total of sixty six criteria which include criteria from two studies.

Table 3: Frequency and Rating Scores

Frequency	Rating	Score
1 to 9	1	25
10 to 29	2	45
30 to 99	3	65
100 to 299	4	85
Above 300	5	100

4.3 Criteria Merging

Criteria merging is a simple process where we determine whether a criteria is common criteria among multiple selected studies or an individual criteria particular to a single study.

This helps in filtering out common criteria among multiple studies and creates a union of all the criteria based on the studies they belong to. As we can see from the Figure 18 two individual

criteria sets have been combined into a unified set where duplicate criteria C1 and C3 have been merged.

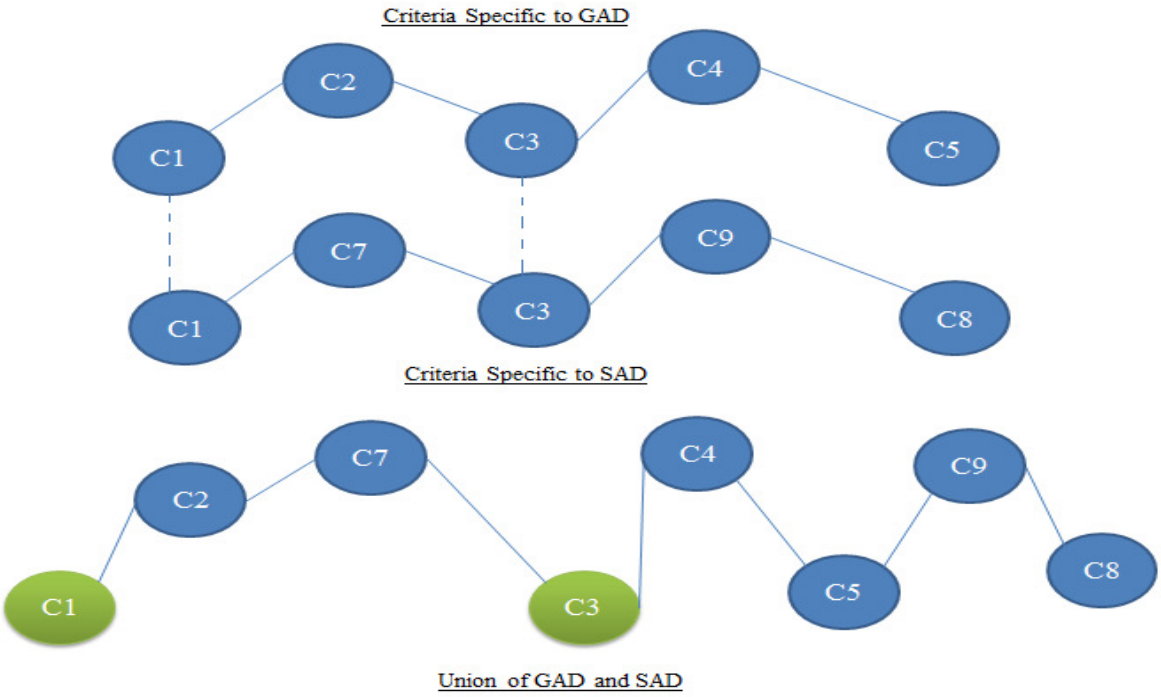


Figure 18: Criteria Merging Scenario

4.4 Criteria Filtering

4.4.1 Introduction

Criteria Filtering is the process of filtering out a set of criteria which have already been satisfied by the patients. The underlying assumption is that, associated with each criterion there is a filter query in our database which helps in determining whether or not a user has satisfied a particular criteria. We also assume that we have user information in our database which is collected from multiple data sources such as Microsoft HealthVault, Google Health or manually provided by the patient himself.

After criteria merging, the unified set of criteria is passed on to criteria filtering stage. Here the recruiter selects a patient to filter out all the criteria satisfied by the patient. The filtering engines scans through each criteria in the database, obtains the filter query for that criteria and runs the filter on the selected patient. If a patient satisfies the criteria, it is added to known criteria set else it is added to the unknown criteria set.

The end result of criteria filtering, are two criteria subsets namely, known subset and unknown subset. Known subset contains criteria id's which have been satisfied by the patient and unknown subset is the set of criteria which could not be determined from the give patient input.

4.4.2 Criteria Filter Parser

Criteria Filter Parser forms the core component in the criteria filtering step. It is this stage which determines whether or not a patient has any information which helps in satisfying the criteria. It consists of two steps, perfect query match and partial query match. As stated in the above chapter, associated with each criterion are a set of query filters, which are stored in the database. Figure 19 shows the database mapping between criteria and its query table.

Figure 19: Criteria and Criteria Query Table Mapping

As we can see from the above figure, every criteria contains a perfect filter query(full_query) and a partial filter query (partial_query).

A perfect filter query, as the name implies matches the criteria perfectly. On the other hand a partial filter query matches the criteria partially. At first the criteria filter parser checks whether the current criteria satisfies the perfect filter query, if it does, it adds the criteria to the known criteria subset and fetches a new criteria, else it would fetch the partial filter query and performs a check to see if the criteria is matched partially. If none of them match, the criterion is put into unknown criteria set.

Figure 20 illustrates the flow diagram for the criteria filtering parser.

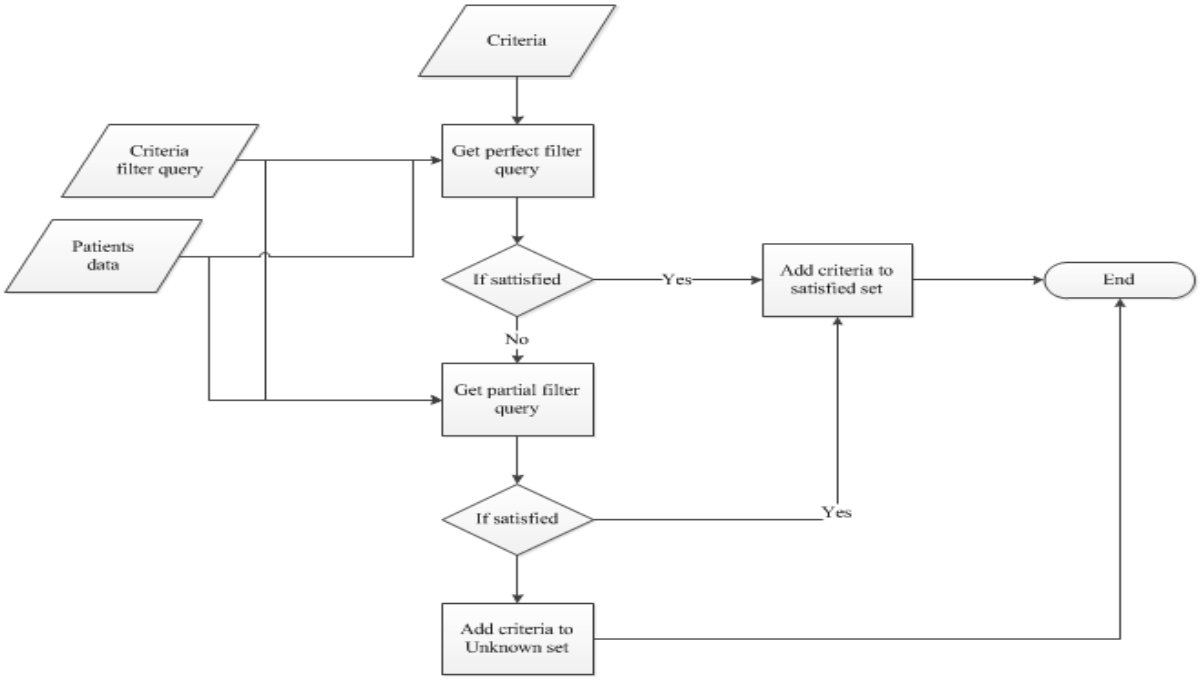


Figure 20: Criteria Filter Parser Flow Diagram

Figure 21 illustrates an example which shows the perfect filter query and a partial filter query for a given criteria. As we can see from Figure 21, for a criteria which requires all patients of age group eighteen to sixty five years old, a perfect filter query specifies the exact age group of eighteen to sixty five, while the partial filter query expands the age range bounds to fifteen to seventeen, thereby even considering all patients who have not fully satisfied the criteria but have partially satisfied it.

- Criteria:

"Men or women Aged 18 to 65"

- Perfect Filter Query:

```
SELECT CASE COUNT(*) WHEN 1 THEN 'True' WHEN 0 THEN 'False' ELSE 'False' END AS AgeRange
FROM users WHERE (age BETWEEN 18 AND 65)
```

- Partial Filter Query

```
SELECT CASE COUNT(*) WHEN 1 THEN 'True' WHEN 0 THEN 'False' ELSE 'False' END AS AgeRange
FROM users WHERE (age BETWEEN 15 AND 70)
```

Figure 21: An Example Showing a Perfect Filter Query and a Partial Filter Query

4.4.3 Patients Health Records

To test the perfect filter query or a partial filter query, the criteria filter parser requires knowledge or data about a patient. Patients Health Record are a set of tables which provides all the information about the patients, so that the criteria filter parser can successfully test the criteria filter query.

This data can be obtained via diverse data sources such as Microsoft HealthVault, Google Health or could be manually provided by the patients as well. Figure 22 illustrates associated tables in the database which store the patient health record.

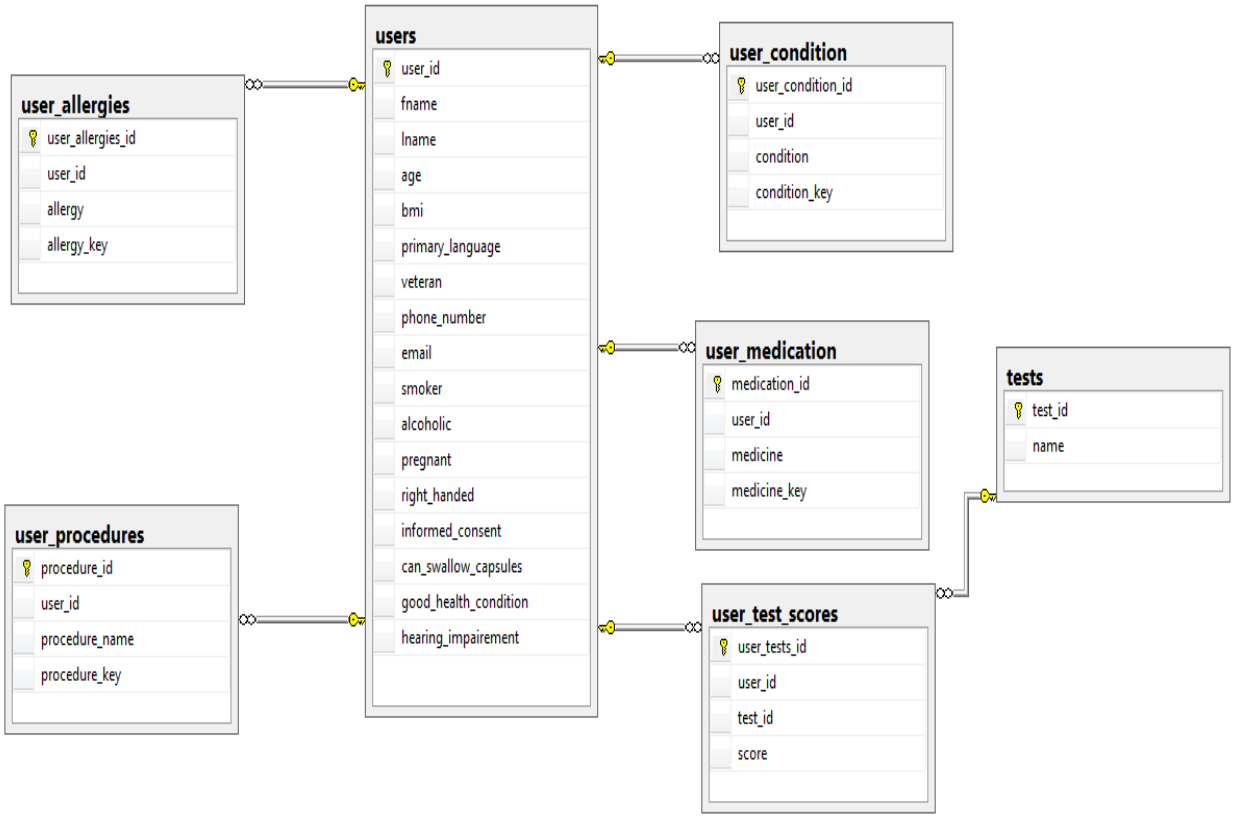


Figure 22: Patient Health Records

4.5 Patient Neighborhood Formation

Once the set of criteria is partitioned into known and unkown, VirtualMindTrial performs a check over the patient database to form a neighborhood of patients who have satisfied similar cirtiera.

In order to achieve this, VirtualMindTrial makes use of the collaborative filtering algorithm. Detailed explination about this algorithm is given in chapter 3. Once a neighborhood of patients is formed, the same set of questionnaire is applied to all the patients in the neighborhood group. This way the VirtualMindTrial architecture extends the question generation from a single patient model to a multi-patient model.

4.6 Criteria Association

4.6.1 Introduction

Criteria Association helps in enhancing the existing criteria by adding associative or related criteria. We scan through each criteria in the unknown criteria set obtained after criteria filtering and search for any related criteria that can be associated to it, if we find such a criteria we add that criteria to our unknown criteria set along with mapping information that helps in determining which criteria it is mapped to.

4.6.2 Criteria Association Database Mapping

Figure 23 shows the database tables which store the mapping information about a criterion. As we can see from the Figure 23 for every criteria_id in the criteria table there is an asso_criteria_id field in the associated_criteria table. Associated criteria information about a criterion can be obtained via the asso_criteria_id field. We assume that this mapping information is provided to us from various services.

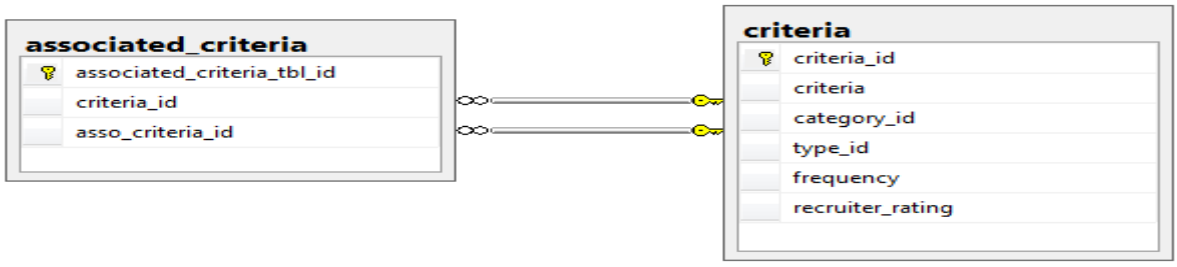


Figure 23: Associated Criteria Table

4.7 Quiz Generation

4.7.1 Introduction

The quiz generation phase forms the final step in the phase-I where the list of unknown criteria, which are formed after criteria association are converted into a questionnaire set. This questionnaire set is then combined to form a quiz. This phase consists of the following sub sections, criteria to question mapping, storing the patients quiz, and generating the quiz path.

4.7.2 Criteria to Question Mapping

For each criterion in the VirtualMindTrial database there is an associated question mapping available as shown in Figure 24. As we can observe there is an N: N relationship between the criteria and questions tables, which means that a single criteria can be mapped to multiple questions and vice versa. The criteria_question table acts as a mapping table which store mapping information about the criteria and its question. Associated to each question there are a set of options which are stored in the options table and are connected to the questions table via the question_option table. The “istrue” field in the options table determines whether an option is correct or incorrect.

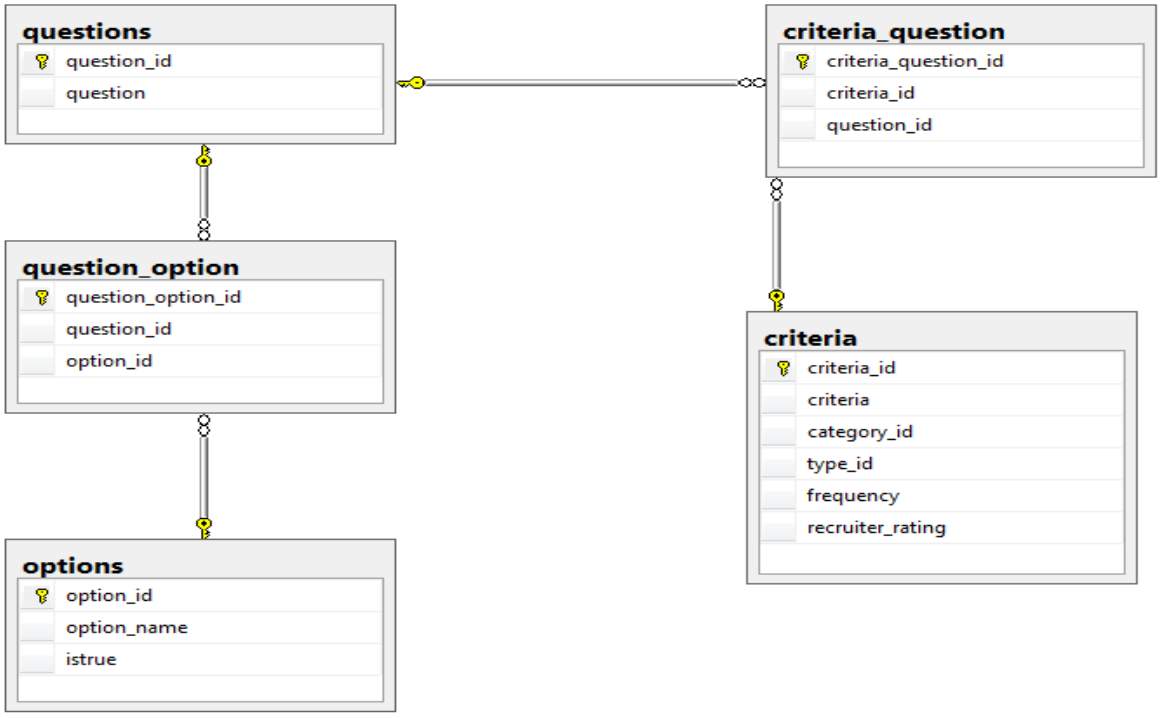


Figure 24: Criteria Mapped to Their Associated Questions

Although there is an N: N mapping between the question and its associated options the VirtualMindTrial module assumes that there is only a 1: N mapping between them. This signifies that for every question in the questions table there are N available options in the options table, but every option in the options table is mapped to only one question in the question table. N: N mapping is modeled to make it compactable for future work.

Using simple SQL queries, questions related to a criterion can be obtained from the database. Figure 25 shows an example query which generates a question along with corresponding options for a given criteria.

Input :

```
SELECT      questions.question, options.option_name, options.istrue
FROM        question_option INNER JOIN
              options ON question_option.option_id = options.option_id INNER JOIN
              questions ON question_option.question_id = questions.question_id INNER JOIN
              criteria INNER JOIN
              criteria_question ON criteria.criteria_id = criteria_question.criteria_id ON questions.question_id =
criteria_question.question_id
WHERE       (criteria.criteria_id = 1)
```

Output :

question	option_name	istrue
Are you atleast 18 year old?	Yes, I am atleast 18years old	True
Are you atleast 18 year old?	No, I am not 18 year old	False

Figure 25: SQL Query to Get the Question and its Associated Options for a Given Criteria

4.7.3 Storing the Patients Quiz

Once the criteria's are converted into questions from the above step, these questions are stored in the database for the further use. Before there are actually stored the recruiter need to specify a pass percentage threshold for every associated disorder they have chosen at the time of criteria selection process. This threshold will be used to determine the path or direction of the quiz.

Figure 26 shows the associated tables in the database used for storing the patients quiz. As we observe from the Figure 26 every quiz is identified by its quiz_id. There is an N: N mapping between quiz and its questions tables. The quiz_questions table acts as a mapping table between them. Also the relationship between quiz and users tables is N: N. Using the user_id and quiz_id attributes, all the question in a particular quiz can be obtained for a specific user.

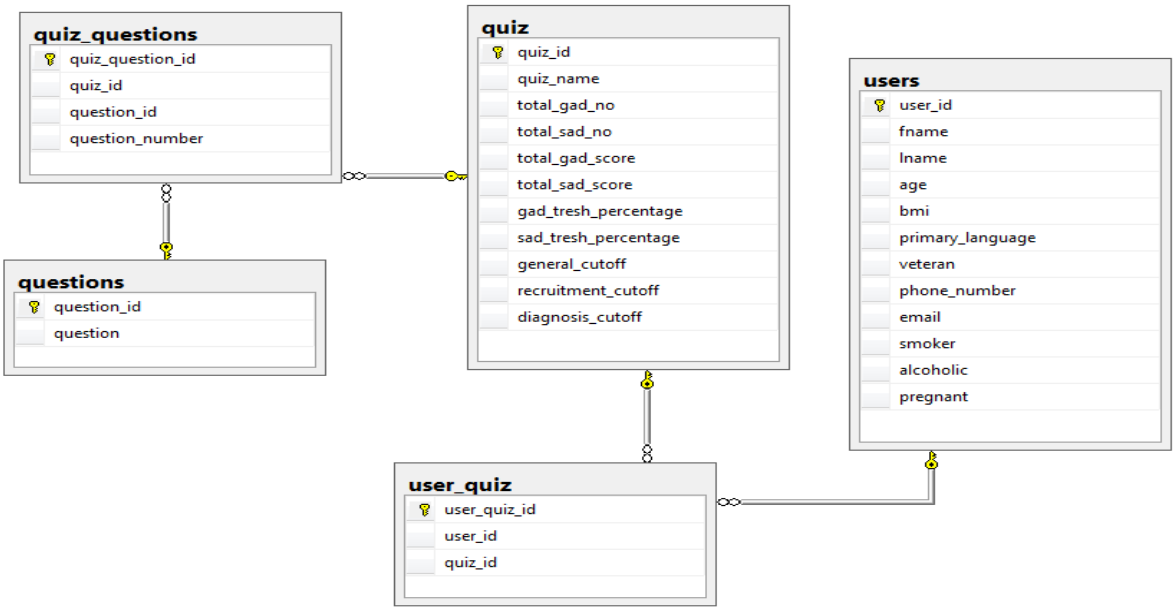


Figure 26: Schema for Storing Patients Quiz

4.7.4 Generating the Quiz Path

In this step we scan through the entire question set and segregate the questions based on the study they fall into. Since criteria can be mapped to multiple studies it is very likely that a question could also be mapped to multiple studies as well, as the question originates from the criteria. We identify such questions and group them as common question for all the selected studies.

Although this model is capable of handling multiple studies, in the database model shown in the Figure 26, we restrict our model to fit two studies namely “generalized anxiety disorder” and “social anxiety disorder”.

After classifying questions based on their study type we calculate the following quiz attribute: total number of questions in each study, total score of each study, and the general section, recruitment section and diagnosis section cutoff question numbers. These attributes are essential in generating the quiz path. The general section, recruitment section and the diagnosis section cutoff question numbers help in determining when each section end, these are used to change the scene settings during the visualization process.

Associated to each study say ‘x’ we calculate two additional attributes as we traverse to the question set. These are the current score of x and the remaining score of x. If there is a correct response to the question, the score associated with that question is added to the current score attribute of x. If the question is associated with multiple disorders then the current score attribute of each disorder is updated accordingly as shown in the flow diagram in Figure 27.

After each question is answered, irrespective of it being correctly answered or not, we subtract the questions score from the remaining score attribute of x. If a question is associated with multiple disorders, we update the remaining score attribute of all the associated disorders as well. Figure 28 shows the flow diagram for this process.

After the question number count of ‘x’ reaches a certain threshold, which in our case is half of the total number of questions in the disorder, we calculate the probability score of ‘x’ by adding the current score of the disorder and the remaining possible score for that disorder.

We then compute the maximum possible percentage for ‘x’ from this point by the following formula shown in Figure 29.

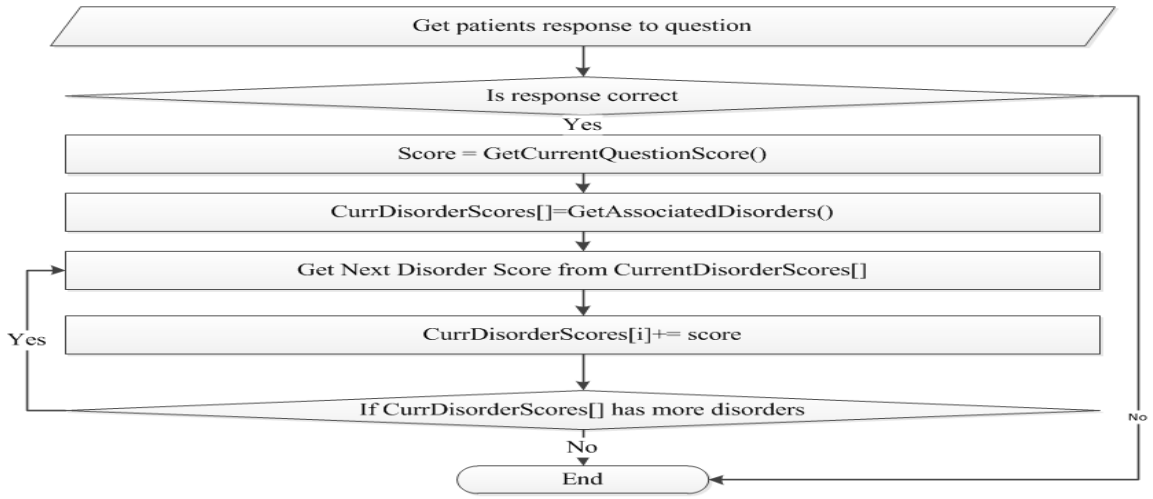


Figure 27: A Flow Diagram Showing how the Current Score of each Disorder is Calculated

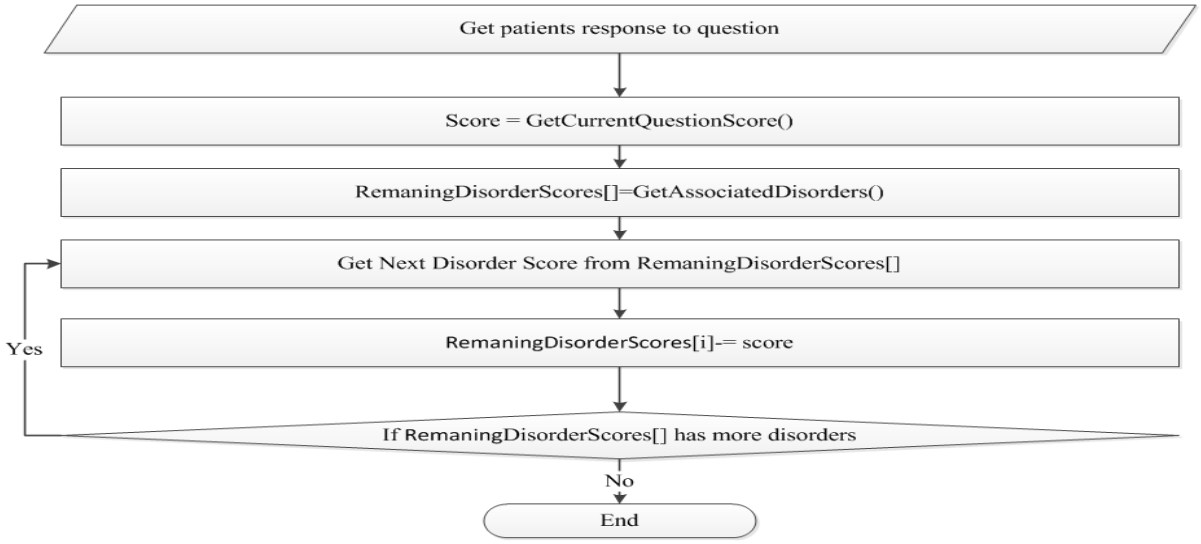


Figure 28: A Flow Diagram Showing how the Remaining Score of each Disorder is Calculated

$$\text{Maximum possible \%} = \frac{(\textit{Current Score} + \textit{Remaning Possible Score})}{\textit{Total Possible score for the disorder}} * 100$$

Figure 29: Formula to Calculate Maximum Possible Percentage

If this percentage is greater than or equal to the pass threshold percentage of ‘x’ we proceed further in the direction of the disorder else we simply discard the questions related to that disorder. We repeat this step until all the questions of ‘x’ have been answered.

With this approach at each stage we calculate the probability of success for proceeding in a certain path, and travel along that path only if the probability reaches certain threshold, thereby minimizing path length.

4.8 Visualization

Once the question set is formed and saved as a quiz, the patients respond to these questions using the virtual environments we have built using Alice. There are four stages setup for the patient’s namely general section stage, recruitment section stage, diagnosis section stage and result stage.

As we recall from the above section, the variables general cutoff, recruitment cutoff, and diagnosis cutoff help in determining when the stage settings should be changed.

In order to interact with our VirtualMindTrial database, for extracting quiz information, the visual model of VirtualMindTrial makes use of web services. These services provide essential methods which help in extracting quiz related information such as questions and options. Also they help in verifying whether the responses given by the patients are correct or incorrect and finally storing the quiz results back to our database.

Patient interacts with the virtual environment using gestures made by a Wii remote. We have used WiiGee an open source gesture recognition library for training and recognizing the gestures using a Wii remote. Once the gestures have been trained, they are loaded into the application via

the WiiGee library. Whenever the patient performs a gesture, WiiGee library identifies the gesture and helps us in taking necessary action.

Chapter 5

VirtualMindTrial INTERFACE

5.1 Introduction

There are two kinds of interfaces associated with VirtualMindTrial namely the web based interface and virtual environment based interface. In this section we walkthrough each interface and describe the details steps involved.

5.2 Web Based Interface

5.2.1 Introduction

The web interface is mainly used by the recruiters to generate a set of questions for one or more selected studies. The VirtualMindTrial web interface is a web application built using ASP.NET 3.5 technologies. In order to store information to and from the web interface we use a Microsoft SQL server express 2008 database as our backend. We used C# as our code behind programming language which acts as a controller for our web front end.

As discussed in the VirtualMindTrial architecture (Figure16) the web interface involves six stages starting from criteria selection to question generation. A detailed overview of each interface is discussed in the following sections.

5.2.2 Web Interface for Criteria Selection

The first step for the recruiter is to select a set of inclusion and exclusion clinical trial eligibility criteria for one or more studies. The patient should meet these criteria in order to be recruited for a study. Figure 30 shows the interface where recruiters can select criteria from multiple studies.

As we can see from Figure 30, the recruiter selects a particular study and then performs a search to obtain a list of inclusion and exclusion criteria for that study.

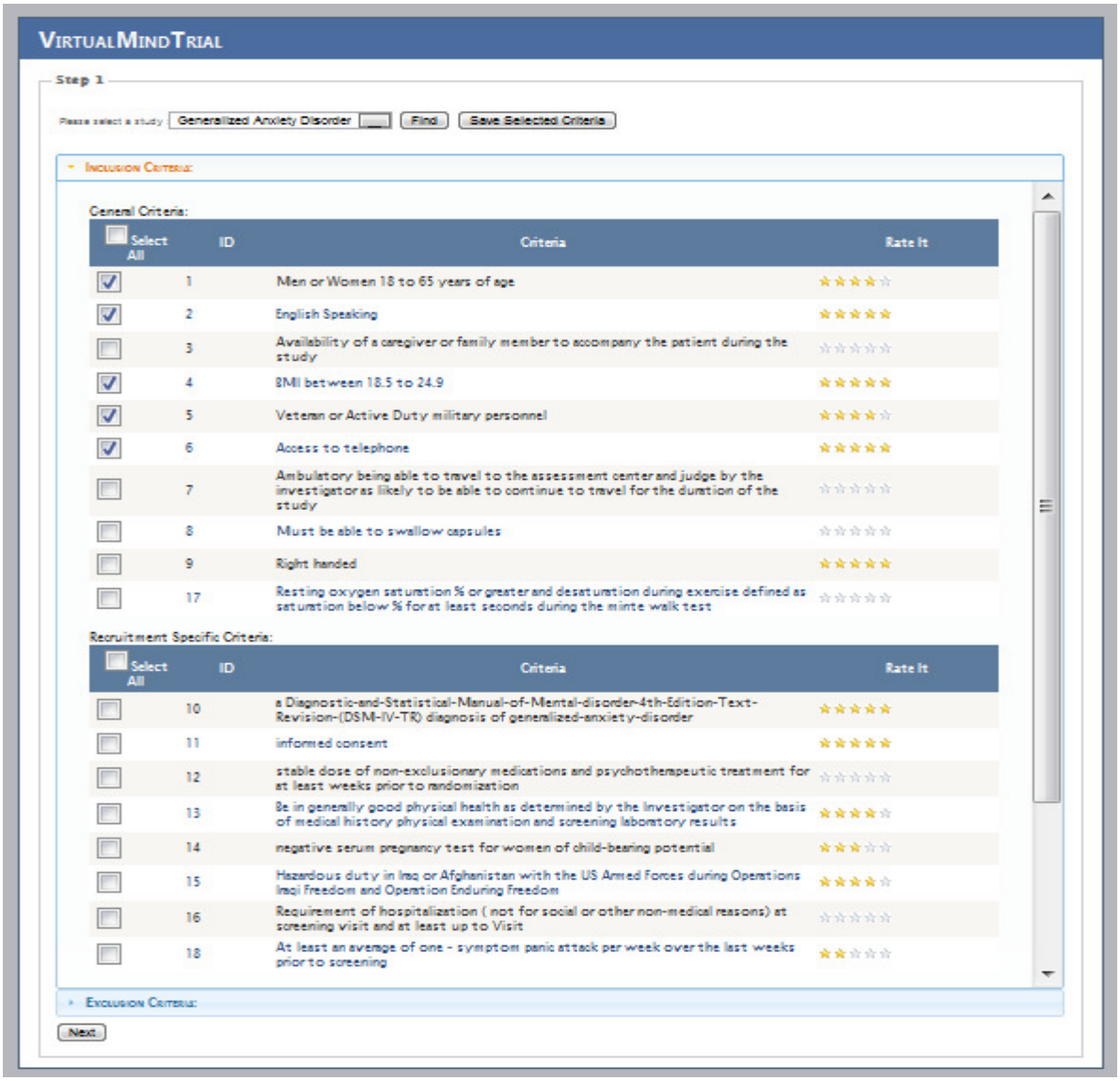


Figure 30: Web Interface for Selecting the Criteria

The criteia are further categorized into genral, recruitment specific and diagnosis specific sections before they are displayed to the recruiter. To select a criteria the recruiter simple needs to check the checkbox next to the criteria. If a recruiter wants to rate a particular criteia, they

simply need to select the rating star next to criteria. Once the selection is made, they need to click the save button inorder to save the slected criteria for further processing. The recruiter need to perform the same steps if they want to include criteria from another study. Once the recruiters complete selecting criteria from multiple studies, they need to click the next button to proceed to the next step.

5.2.3 Web Interface for Criteria Merging

Figure 31 shows the interface for criteria merging. As we can see from Figure 31, criteria from two studies have been merged and displayed to the user in pie chart format for better visualization. Further the statistics about criteria, based on their category (i.e. general, recruitment specific and diagnosis specific) and type (i.e. inclusion and exclusion) are also displayed to the recruiters.

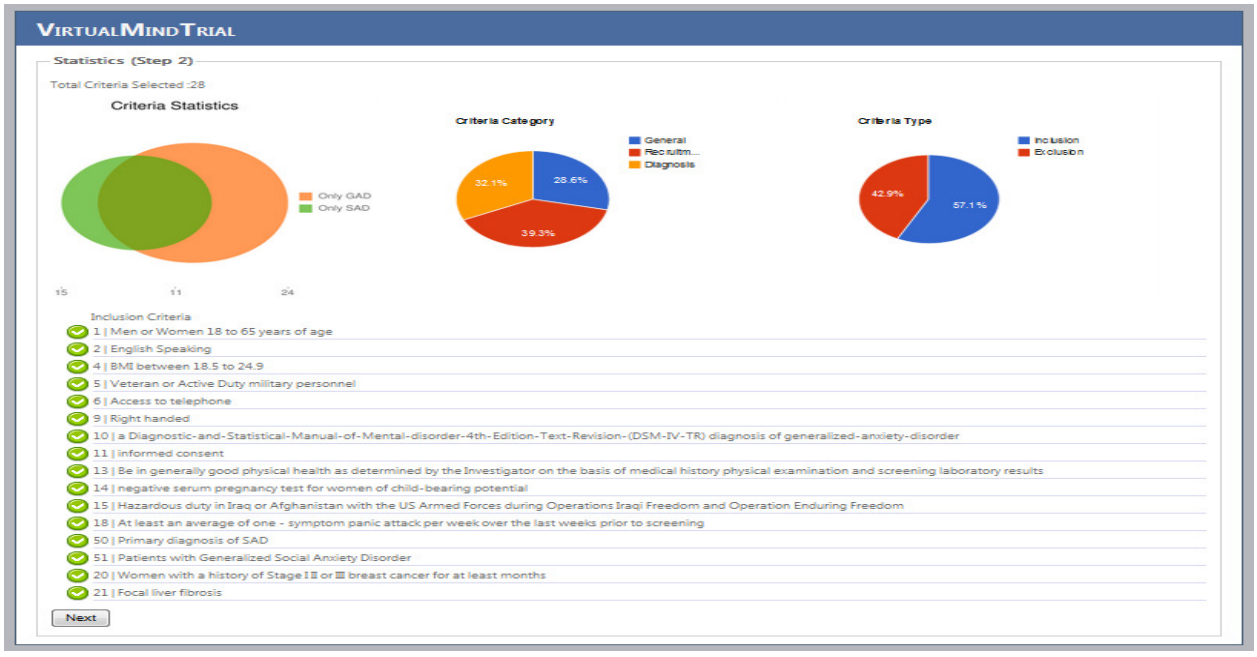


Figure 31: Web Interface for Criteria Merging

Once this step is complete, the recruiters need to press the next button to proceed to the next step.

5.2.4 Web Interface for Criteria Filtering and Patient Neighborhood Formation

After the criteria has been categorized, in the next step the recruiter filters the criter by selecting a particular user. Here the sytem splits the criteria into known and unknown subsets. Further the known criteria are grouped into fully known and partially known subsets as shown in Figure 32. Each group (i.e. full known, partially known and unknown) is identified by a different icon as shown in Figure 33.

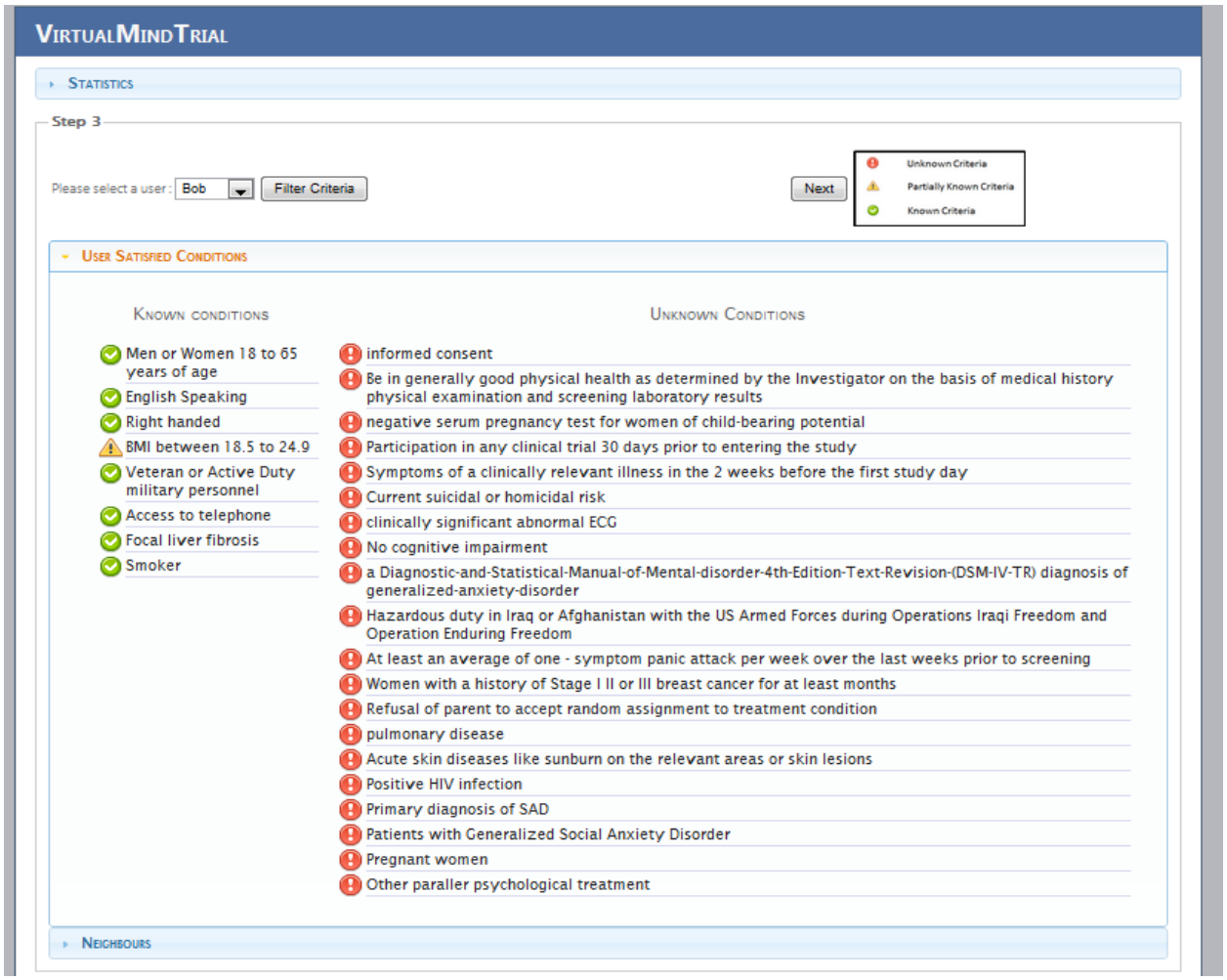


Figure 32: Splitting Criteria into Satisfied and Unknown Criteria

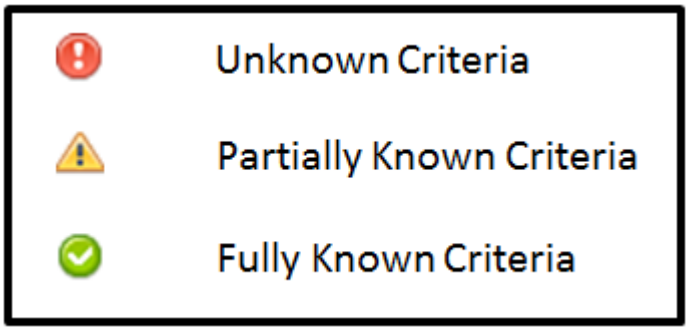


Figure 33: Icons for Identifying Criteria Groups

In order to find the neighbors for the selected patients the recruiters simple need to select the neighbors tab. A list of all neighbors for the current patient are then displayed to the recruiter as shown in Figure 34.

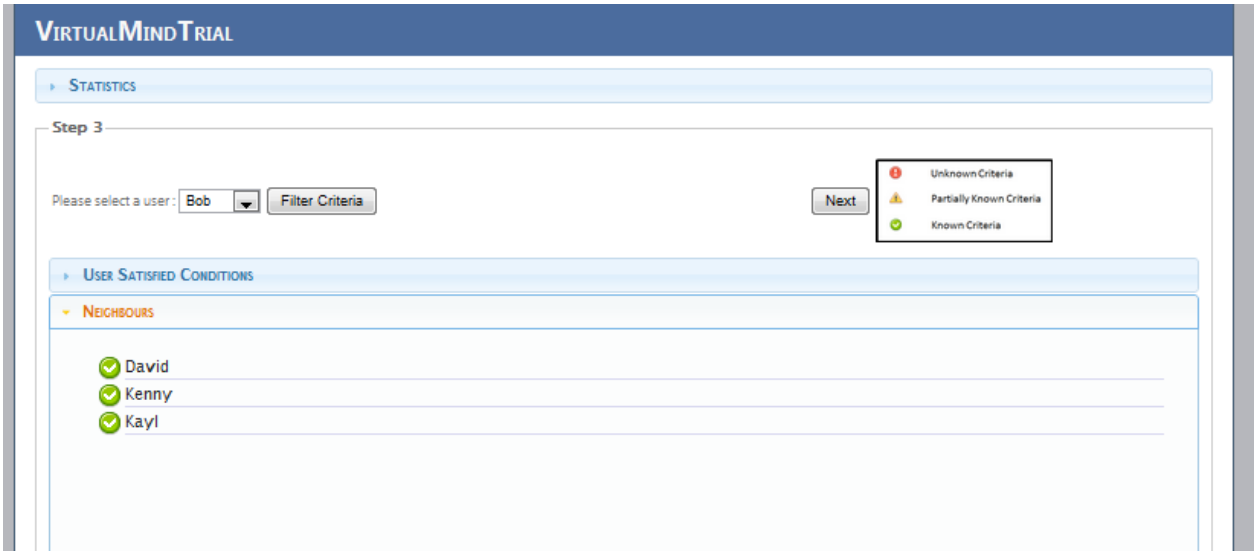


Figure 34: Forming Neighborhood for a Selected User

After partitioning the criteria and finding the neighborhood of patients, the recruiters need to click the next button to proceed to the next step.

5.2.5 Web Interface for Criteria Association and Question Generation

Figure 35 shows the web interface with a list of questions generated based on the unknown criteria from the previous step. As we can see from Figure 35 , any related or associated criteria are automatically added to the set of questions and are highlighted in orange color. Also, beside each question, a label describing which studies the question belongs to is displayed in green. If a question is common to multiple studies, it is labeled as common. The recruiters can reorder the questions as needed by simply dragging them and dropping them at the right place.

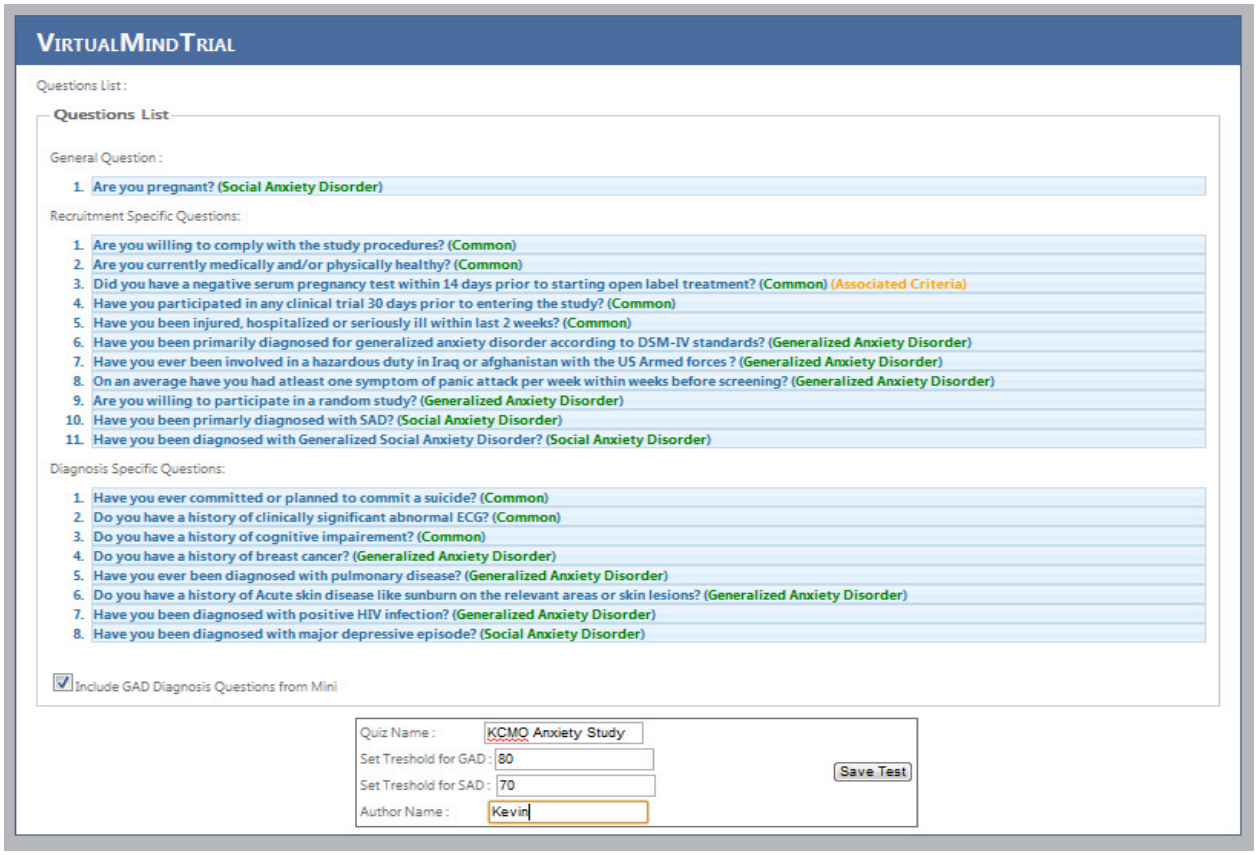


Figure 35: Web Interface for Question Generation

In Figure 35, we can observe a checkbox toward the bottom of the screen. If there is a need to add diagnosis questions for a study based on different standards, they get automatically added.

The recruiters can uncheck these set of question if they feel it is unnecessary for the study. Once these questions have been finalized by the recruiters, they specify the quiz name, pass percentage for each associated study as shown in Figure 36.

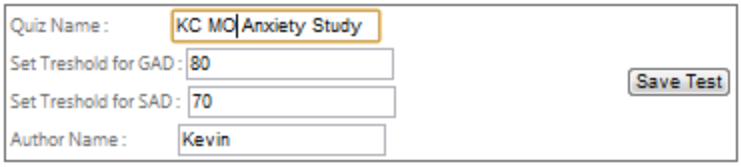


Figure 36: Web Interface for Specifying Quiz Parameters

Once these details are given the recruiters press the save test button to save the quiz. Figure 37 shows a screenshot of the quiz statistics.

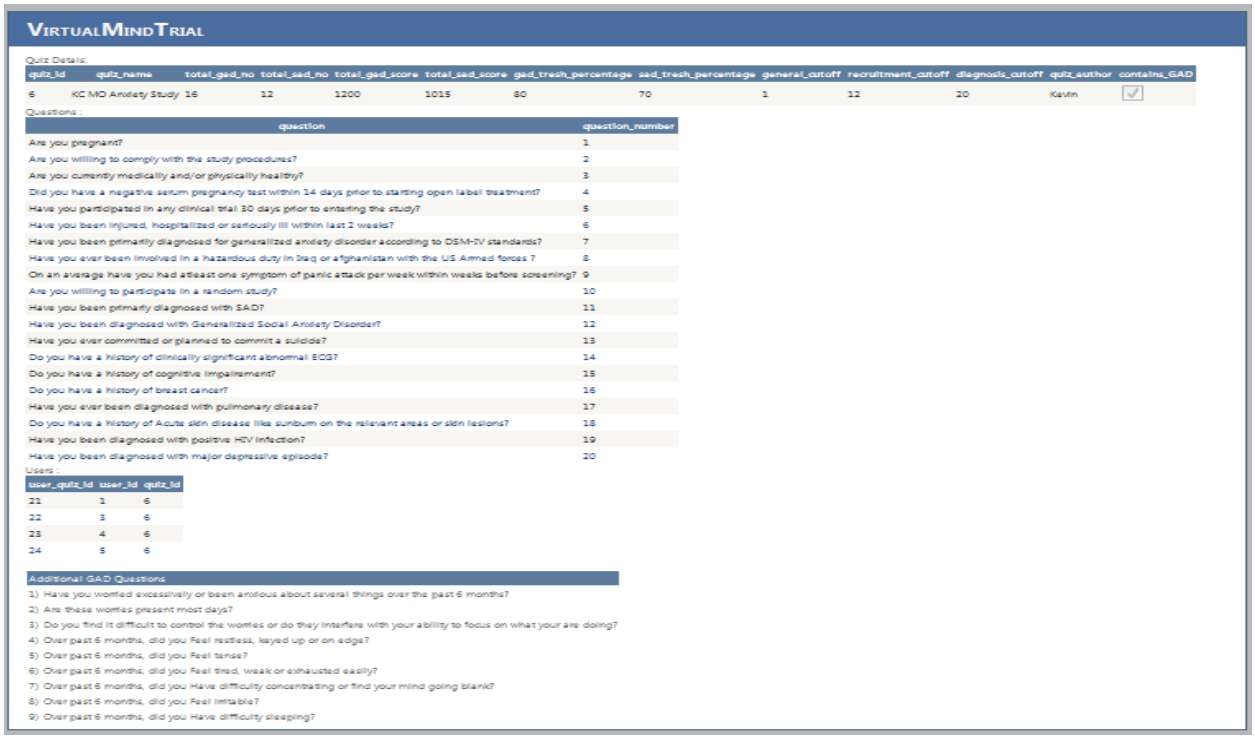


Figure 37: Web Interface Showing Quiz Statistics

5.3 Virtual Environment Based Interface

5.3.1 Introduction

The virtual environment based interface is mainly used by the patients to take the saved quizzes which determine their eligibility for a particular study. The virtual environment is built using Alice3 and then converted into java code using the Alice3 plugin for netbeans. The virtual environment consists of four sets or settings setup namely general setting, recruitment setting, diagnosis setting and final setting for displaying the results. Each of these sections is discussed below.

In order to interact with the virtual environment, patients use a Wii remote. The interaction is gesture based, i.e. patients answer the quiz questions by performing a gesture using the Wii remote. We have used WiiGee, an open source gesture recognition library for training and recognizing gesture.

5.3.2 Virtual Environment Setting for General Questions

Figure 38 shows the general environment setting for the patients. As we can see, this environment act's as an introductory setting stage, where patients are exposed to an open environment. A virtual recruiter shown in Figure 39 and a virtual patient shown in Figure 40 are present in this environment. Virtual recruiter greets the patients and takes general information about the patients. Each time a question is asked, a set of options for that question are also displayed. Although a question can contain multiple options, for simplicity sake we have restricted it to only two options. To select the first option, patients need to perform a right

gesture on the Wii remote and to select the second option patients need to perform a left gesture.

The patient's response is recorded and next question is loaded.

This process continues until all the general questions in the quiz are completed.

Figure 38: General Environment Setting

Figure 39: Virtual Recruiter

Figure 40: Virtual Patient

5.3.3 Virtual Environment Setting for Recruitment Questions

Upon completing the general section questionnaire, the virtual environment changes its set to a recruitment office setting as shown in Figure 41. As we can see, the appearance of both the virtual recruiter and patients also gets changed to suite the environment setting. The process for responding to question remains same as in the above section.

This setting would remain until all the recruitment specific questions in the quiz are completed.

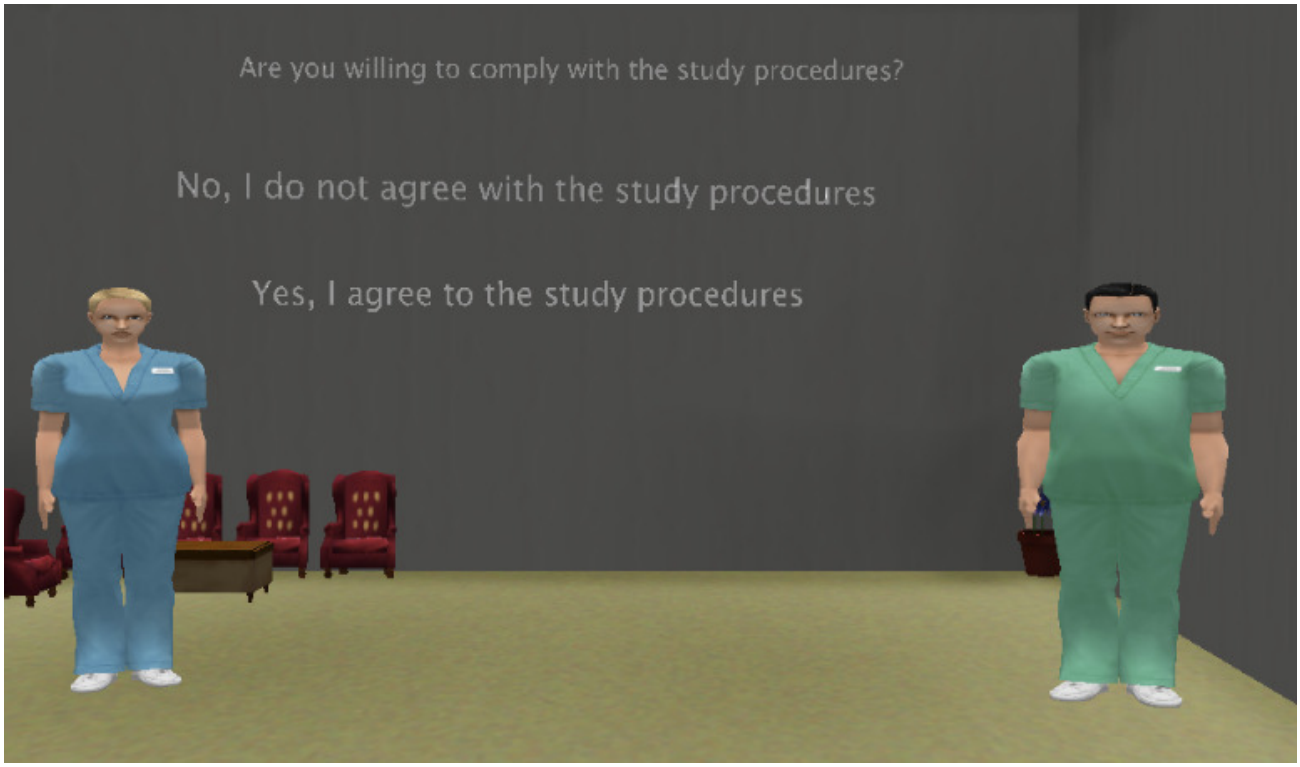


Figure 41: Recruitment Section Setting

5.3.4 Virtual Environment Setting for Diagnosis Questions

Upon completing the recruitment stage questions the set change to a diagnosis setting environment as shown in Figure 42. This environment looks more like a hospital, where the

patients would be asked diagnosis specfic question. We can also observe that the virtual recruiter and patients appreance changes to suite the environment.

5.3.5 Virtual Environment Setting for Final Setting

After the patients complete all the questions, the environment setting are changed to a final stage setting as shown in Figure 43. Here the virtual environment looks like our neighborhood community with the virtual recruiter and patient dressed in a casual outfit. In this stage the virtual recruiter gives a feedback of the entire quiz and determines patients quiz score for each study.

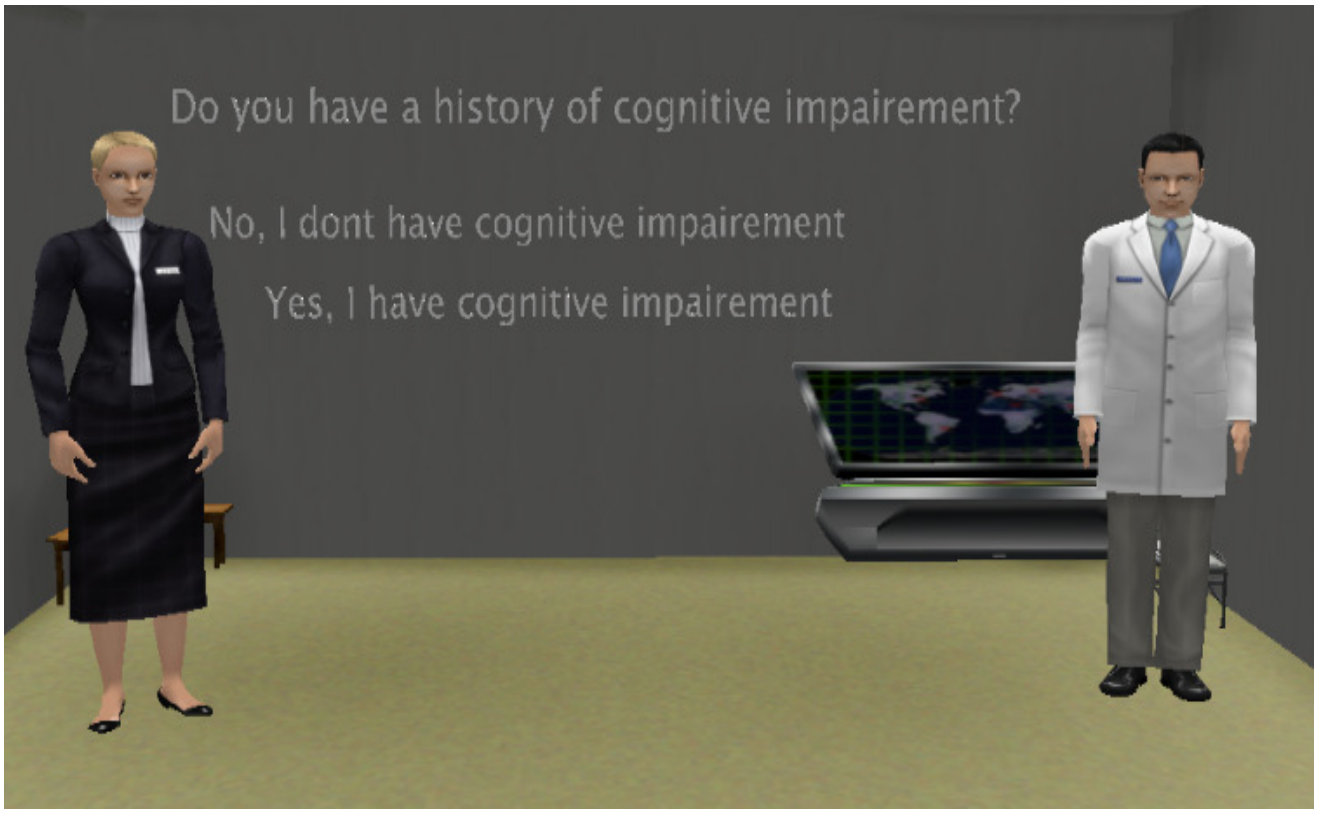


Figure 42: Diagnosis Section Setting

Figure 43: Final Stage to Display Quiz Result

CHAPTER 6

EVALUATION

6.1 Introduction

Evaluation plays an important role in this thesis work. It helps in determining the efficiency of VirtualMindTrial model and also measures the user's experience while taking the quiz through the help of virtual environments. Section 6.2 describes the experimental setup that is used for evaluating the performance of the system. Section 6.3 shows the evaluation results for the VirtualMindTrial web interface, particularly, it provides statistics of ten use cases where the systems performance is evaluated in terms of the number of criteria selected to the number questions generated, time it takes to generate a question set and number of neighbors formed in each use case. In section 6.4 we show the evaluation results obtained by conducting a survey on twenty one students, who take the quiz through the virtual and web interfaces, and provide their feedback about each interface. The survey is designed to compare the virtual and web interface in terms of fun, usability, user satisfaction, performance, comfort level and time.

6.2 Experimental Setup

The web application developed in this thesis was hosted on IIS 7 web server installed on a 64 bit Windows server 2008 R2 operating system running on a machine with processing speed of 2.40 GHz and 4.00GB of RAM. In order to develop the web interface, we used the visual web developer express edition IDE with C# as a code behind language. To store the data, we made use of the Microsoft SQL server 2008 express edition which was freely available.

For developing the virtual environment we used the Alice3 standalone application. Using the Netbeans plugin for Alice3 we converted the Alice project into a java application, which was run using the Netbeans IDE 6.7.1. This application was run on a Mac OS X snow leopard operating system with a processing speed of 2.13 GHz and 2.00GB of RAM.

6.3 Evaluation of VirtualMindTrial Web Interface

The VirtualMindTrial web interface is used by the recruiter for generating a quiz for diagnosing potential patients. This quiz can contain criteria from more than one study. To measure the performance of the web interface a set of ten use cases have been designed and for each use case the interface was tested on five different users. For each user we measure the total number of questions generated (A), given a set of selected criteria, time it took to generate these questions (B) and, number of neighbors formed for each user (C). We then compute the average of A, B, C individually in each use case. Table 4 show the results obtained after the above calculations

6.3.1 Experimental Results

Figure 44 shows a graph showing the total number of criteria selected to the Average number of question generated in each case. As we can observe, the total number of questions generated is less than the criteria selected in each use case.

Figure 45 shows the Average time taken to generate a question set in each use case. As we can observe from the graph the total time taken to generate questions in each use case is approximately 10.86 seconds on an average.

Table 4: Web Interface Evaluation Results Table

Use Case	Total Criteria Selected	Average No of Questions Generated	Average Time Taken (in Sec)	Average No of neighbors formed
1	20	14	11.7	10
2	20	9	10.8	5
3	20	10	11.2	6
4	20	16	9.0	7
5	20	13	10.6	11
6	20	11	11.5	12
7	20	12	11.3	8
8	20	15	10.6	6
9	20	14	10.8	7
10	20	11	11.1	8

Figure 46 shows the number of neighborhood formed in each use case. It can be observed that an average of 8 neighbors have been formed per use case.

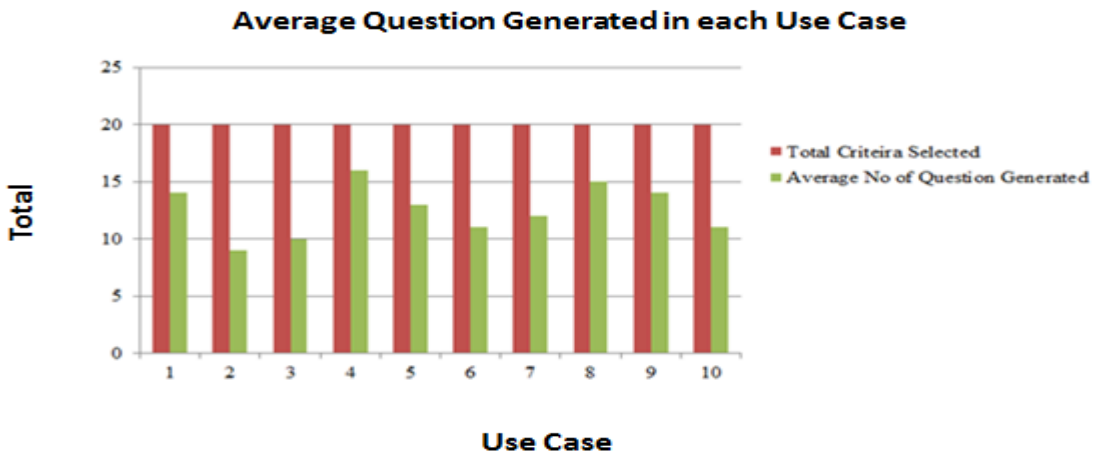


Figure 44: Comparison of Total Criteria Selected to the Number of Questions Generated

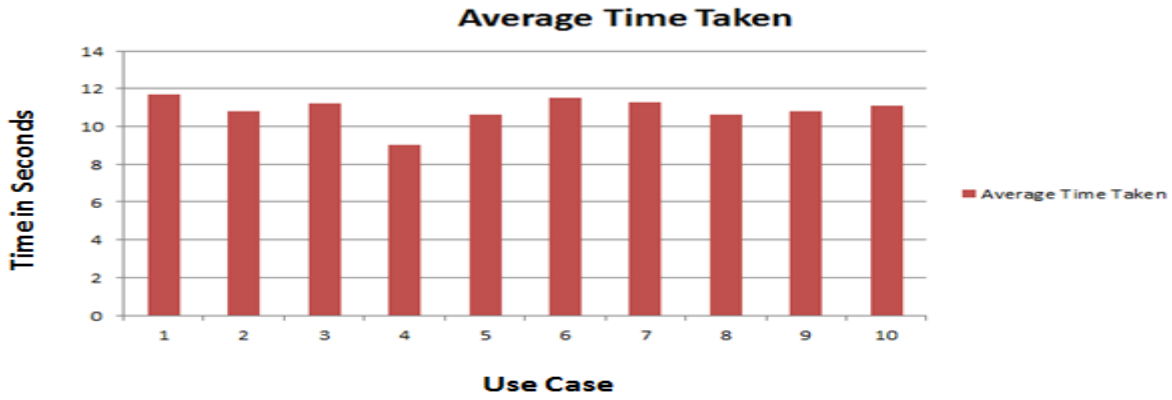


Figure 45: Time taken to Generate Questions in Each Use Case

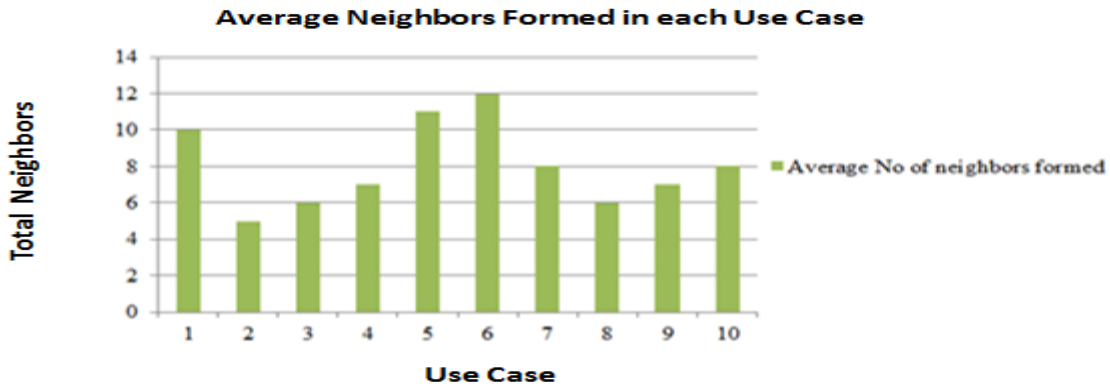


Figure 46: Average Number of Neighbors Formed

6.4 Evaluation of VirtualMindTrial Virtual Environment

6.4.1 Introduction

In order to determine the efficiency and performance of VirtualMindTrial's visual environment, we have designed an anonymous survey consisting of ten questions. The set of ten questions helps in gathering information about both the web and the virtual based quiz in terms of fun, usability, user satisfaction, performance, comfort level and time.

We have selected a total of 21 volunteers to participate in this survey. These volunteers are graduate students in the School of Computing and Engineering at the University of Missouri – Kansas City. The volunteers are in the age group of 22 to 25, out them 14 volunteers were male and 7 volunteers were female.

An online survey [25] was created using the Survey Monkey – A web application for creating online surveys. Figure 47 shows the list of question as a part of survey.

6.4.2 Experimental Results

Figure 48 shows the evaluation results for the first question in the survey. The main aim of this question is to find out the comfort levels of patients while they are taking the quiz on a web site and in a virtual environment.

Form Figure 48 we can observe that almost 57% of the users felt relaxed while taking the quiz in a virtual environment. Also about 9.5% of people felt anxious while taking the quiz on a web based environment. These results prove that people feel more comfortable and relaxed in taking quiz through virtual environments than on a web based environment.

List of Survey Questions

1. In each of the following environment, how would you rate your comfort levels at the time of taking the quiz?

	Relaxed	Calm	Normal	Anxious	Worried
Virtual Environment					
Web Based Environment					

2. In each of the following environment, how would you rate the fun level while taking the quiz?

	Extreme Fun	Great fun	Neutral	Bored	Not interesting
Virtual Environment					
Web Based Environment					

3. In each of the following environment, how satisfied were you with the quiz environment and settings?

	Extremely satisfied	Satisfied	Satisfied to an extent	Unsatisfied	Extremely Unsatisfied
Virtual Environment					
Web Based Environment					

4. In each of the following environment, how would you rate your concentration level/ involvement/ focus while taking the quiz in a virtual environment?

	Very High	High	Moderate	Low	Poor
Virtual Environment					
Web Based Environment					

5. How would you rate the usability of each environment

	Very Easy	Easy	Normal	Difficult	Very Difficult
Virtual Environment					
Web Based Environment					

6. What did you like the most while playing the quiz in virtual environment?
   - Virtual avatar
   - Gesture based responses
   - Multiple sets in the environment

7. Which type of environment did you find more easy to use?
   - Web Based
   - Virtual environment

8. Which type of interface would you prefer/ suggest is the best way for taking the quiz?
   - Web Based
   - Virtual environment

9. Which environment took more time to complete the quiz?
   - Web Based
   - Virtual environment

10. What would you like to see changed about the Virtual Environment?

Figure 47: VirtualMindtrial Anonymous Survey Questions

1. In each of the following environment, how would you rate your comfort levels at the time of taking the quiz?

	Worried	Anxious	Normal	Calm	Relaxed	Rating Average	Response Count
Virtual Environment	4.8% (1)	0.0% (0)	9.5% (2)	28.6% (6)	**57.1% (12)**	4.33	21
Web Based Environment	4.8% (1)	9.5% (2)	**52.4% (11)**	28.6% (6)	4.8% (1)	3.19	21
					answered question		21
					skipped question		0

Figure 48: Evaluation Results for Question1

Figure 49 shows the evaluation results for question 2 in the survey. The main aim of this question is to find out the amount of fun users had while taking the quiz in each of the above mentioned environments. As we can see from the Figure 49, about 57% of people felt virtual environments provided extreme fun and about 42% of the people felt virtual environments provided great fun. On the other hand 33.3% of users felt bored while taking the quiz on a web based environment.

2. In each of the following environment, how would you rate the fun level while taking the quiz?

	Not Interesting	Bored	Neutral	Great fun	Extreme fun	Rating Average	Response Count
Virtual Environment	0.0% (0)	0.0% (0)	0.0% (0)	42.9% (9)	**57.1% (12)**	4.57	21
Web Based Environment	4.8% (1)	**33.3% (7)**	**33.3% (7)**	28.6% (6)	0.0% (0)	2.86	21
					answered question		21
					skipped question		0

Figure 49: Evaluation Results for Question2

Figure 50 shows the evaluation results for question 3. The aim of this question is to determine the user satisfaction in both the environments. As we see from Figure 50 about 57% of users were extremely satisfied with the virtual environments, while 55% of the users claimed that they were satisfied to an extent with web based environment. These results conclude that virtual environment provide high degree of satisfaction than web based environments.

3. In each of the following environment, how satisfied were you with the quiz environment and settings?

	Extremely Unsatisfied	Unsatisfied	Satisfied to an extent	Satisfied	Extremely satisfied	Rating Average	Response Count
Virtual Environment	0.0% (0)	0.0% (0)	0.0% (0)	42.9% (9)	**57.1% (12)**	4.57	21
Web Based Environment	0.0% (0)	20.0% (4)	**55.0% (11)**	15.0% (3)	10.0% (2)	3.15	20
					answered question		21
					skipped question		0

Figure 50: Evaluation Results for Question3

Figure 51 shows the evaluation results for question 4. The main aim of this question is to determine the concentration level of users at the time of taking the quiz. As we can observe from the results about 42% of users had very high degree of concentration and about 52% of users had high degree of concentration while taking the quiz though the virtual environment. On the other hand the concentration level remained moderate while taking quiz through the web environment. The results prove that user have high concentration and involvement when they are taking the quiz through the virtual environment.

4. In each of the following environment, how would you rate your concentration level/ involvement/ focus while taking the quiz in a virtual environment?

	Poor	Low	Moderate	High	Very High	Rating Average	Response Count
Virtual Environment	0.0% (0)	4.8% (1)	0.0% (0)	**52.4% (11)**	42.9% (9)	4.33	21
Web Based Environment	0.0% (0)	33.3% (7)	**47.6% (10)**	4.8% (1)	14.3% (3)	3.00	21
					answered question		21
					skipped question		0

Figure 51: Evaluation Results for Question 4

Figure 52 shows the evaluation results for question 5. This question aims in measuring the usability experience of users in both the environments. As we can see about 61% of the users felt virtual environment was very easy to use. On the other hand about 52% of users felt web based environment was pretty normal to use.

5. How would you rate the usability of each environment

	Very Difficult	Difficult	Normal	Easy	Very Easy	Rating Average	Response Count
Virtual Environment	0.0% (0)	0.0% (0)	9.5% (2)	28.6% (6)	**61.9% (13)**	4.52	21
Web Based Environment	4.8% (1)	0.0% (0)	**52.4% (11)**	28.6% (6)	14.3% (3)	3.48	21
					answered question		21
					skipped question		0

Figure 52: Evaluation Results for Question 5

Figure 53 shows the evaluation results for question 6. This question aims at comparing different features of the virtual environment. As we can see from the Figure 53, about 90% of people like the gesture based response features, 65 % of the people liked the virtual avatars and, 55% of the people liked the multiple sets in the environment.

6. What did you like the most while playing the quiz in virtual environment?

	Response Percent	Response Count
Virtual avatar	65.0%	13
Gesture based responses	90.0%	18
Multiple sets in the environment	55.0%	11
answered question		20
skipped question		1

Figure 53: Evaluation Results for Question 6

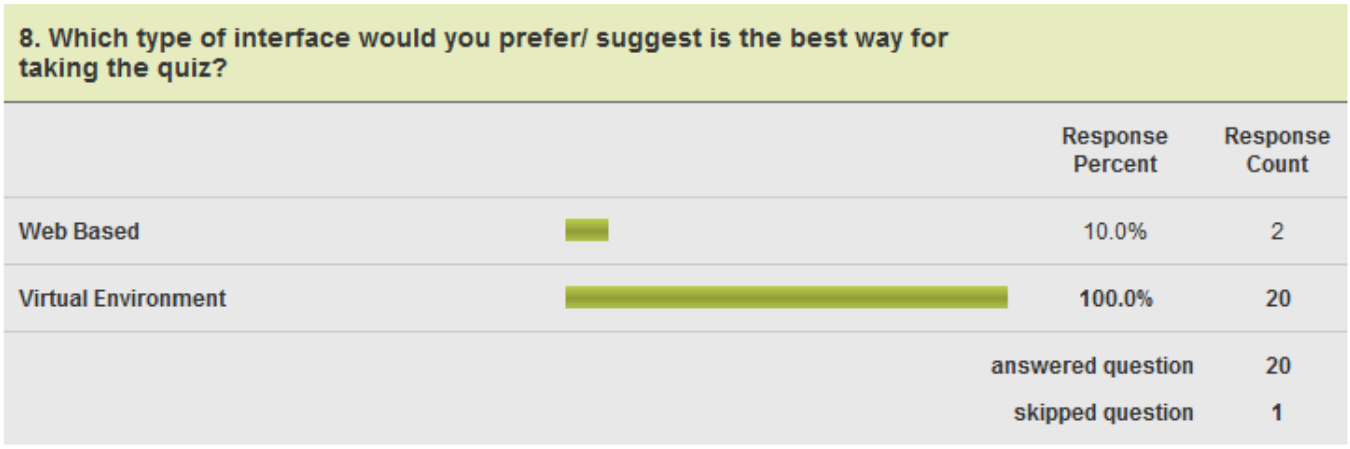
Figure 54 shows the evaluation results for question 7. This question aims at finding out which environment was easy to use. About 90% of the users felt virtual environment easy to use.

7. Which type of environment did you find more easy to use?

	Response Percent	Response Count
Web Based	30.0%	6
Virtual Environment	90.0%	18
answered question		20
skipped question		1

Figure 54: Evaluation Results for Question 7

Figure 55 shows the evaluation results for question 8. This question aims in finding out which environment would be the best way for taking the quiz according to the users. The results show that every user felt that virtual environment was the best way to take the quiz. Since multiple options could be selected about 10% of the users also felt that web based environment was also the best way for taking the quiz.



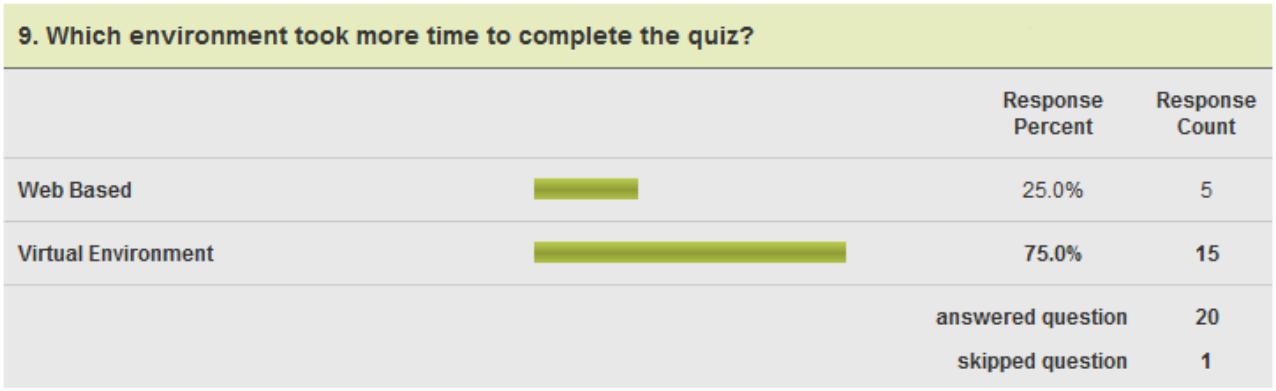
8. Which type of interface would you prefer/ suggest is the best way for taking the quiz?

	Response Percent	Response Count
Web Based	10.0%	2
Virtual Environment	100.0%	20
answered question		20
skipped question		1

Figure 55: Evaluation Results for Question 8

Figure 56 shows the evaluation results for question 9. As we can see about 75% of the users feel that virtual environments took more time to complete the quiz, while only 25% people felt that web based environment took more time to complete the quiz.

The results show that virtual environment takes much time than web based environments. We could prove by looking at the experimental results for question 4 shown in Figure 51 that this delay is due to high involvement of the users.



9. Which environment took more time to complete the quiz?			
		Response Percent	Response Count
Web Based		25.0%	5
Virtual Environment		75.0%	15
		answered question	20
		skipped question	1

Figure 56: Evaluation Results for Question 9

Question 10 in the survey is an open ended question. Its aim is to take feedback from the users, i.e. what users feel should be improved or added to the virtual environment. Only nine out of the total 21 user have answered this question. Based on the feedback given by the users, most of them want to improve the virtual environment by adding more gestures and audio to make the virtual environment event more interactive and interesting.

Based on the experimental results, we can clearly state that virtual environment provide a better user experience than web based environments in terms of fun, usability, user satisfaction, performance, and comfort level provided to the users.

CHAPTER 7

CONCLUSION AND FUTURE WORK

7.1 Summary

In this thesis, an intelligent approach to questionnaire flow called VirtualMindTrial is proposed. The proposed system could be used as an efficient screening tool for generating a list of questionnaire from a set of textual clinical trial inclusion/exclusion clinical trial eligibility criteria. The visual prototype developed as a part of the VirtualMindTrial system demonstrates that virtual world environments can be used to improve the screening process for clinical trials. The experimental results prove that the virtual screening can offer an immersive experience to the patients and can help them complete the screening process with a high comfort level and fun compared to the traditional screen process. The results also prove that this system could be used as an efficient screening tool for generating questionnaire in a short period of time for multiple users and multiple studies.

7.2 Future Work

The VirtualMindTrial system leave a lot for scope for the future, some of the features that might be extended are

1. Extending the database model to support inclusion/exclusion clinical trial eligibility criteria from other disorders.
2. Using ontologies for better classification of stored data. This classification would help in inferring new knowledge from the existing data.
3. Perform parallel screening of two or more patients using virtual environments.

4. Using more complex motion recognition techniques such as facial expression recognition to determine the patient's mood and behavior which help in improving the users experience in virtual worlds.

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VITA

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Publications:

1. Yugyung Lee, Nikhilesh Katakam, Deendayal Dinakarpandian, & Dennis Owens, VirtualMindTrial: Virtual Clinical Trials for Mental Healthcare, 44th Hawaii International Conference on Systems Science (HICSS-44 2011).
2. Yugyung Lee, Nikhilesh Katakam, Deendayal Dinakarpandian, & Dennis Owens, MindTrial: And Intelligent System for Clinical Trials, American Medical Informatics Association (AMIA), 2010 Annual Symposium.

Posters:

1. Yugyung Lee, Nikhilesh Katakam, Deendayal Dinakarpandian, Dennis Owens, Sachin Mathur, Saranya Krishnamoorthy, & John Wubbenhorst, An Intelligent Online system for Enhanced Recruitment of Patients for Clinical Research, Missouri Regional Life Sciences Summit, 2010, Kansas City, MO.