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A Pilot Study of a Device and Drug Therapy for ADHD

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1.1 Introduction & Background

1.1.1 Background Information

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by difficulty paying attention, impulsivity, and hyperactivity. The medical community has been largely unable to standardize an accepted definition of ADHD as indicated by the medical community's differing definitions according to Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5)¹ and the International Classification of Mental and Behavioural Disorders 10th revision (ICD-10)². ICD-10 refers to disorders in this area as hyperkinetic disorders rather than attention deficit and relies upon hyperactivity to distinguish ADHD from other disorders. The DSM-5 separates patient phenotypes into three differing presentations: predominantly inattentive-type, predominantly hyperactive-impulsive type, and combined inattentive hyperactive-impulsive. Diagnosis of ADHD is predominantly based upon patient, teacher and parent responses to standardized questionnaires containing questions based on a list of criteria for diagnosing ADHD. People with ADHD are expected to have experienced at least six symptoms of inattention (predominantly inattentive-type), or hyperactivity (predominantly hyperactive-impulsive type), or both (combined) within the six months previous to the time of the assessment.

In this study, we will use specially designed training activities performed within the environment of the popular computer game Minecraft to determine if they affect executive function, working memory, and restraint in patients diagnosed with ADHD. Various cognitive training interventions are currently under investigation for their effects on improving deficits in executive function in ADHD, and the addition of gaming elements to the cognitive training may help improve outcomes (for review, see Ref 3 P. 5–9). For example, utilization of a video game format to train biofeedback skills (reduction of heart rate through slowed breathing) in children with ADHD resulted in improved scores on the ADHD Questionnaire and the Strengths and Difficulties Questionnaire⁴. Gamification of the Conners Continuous Performance Test II, used to measure sustained attention, resulted

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in significant improvements in performance compared to the regular test in children with ADHD⁵. The addition of gaming elements to standardized working memory training tasks resulted in significantly improved motivation, training performance, and working memory of children with ADHD⁶ and the use of a gaming task also normalized task persistence in ADHD children in a visuospatial working memory task⁷. Finally, a multiple domain executive function training game resulted in improvements in the specific domains trained (inhibition, visuospatial short-term memory, and visuospatial working memory) in children with ADHD, although no benefits were seen in overall behavior ratings⁸.

1.1.2 Rationale

1.1.2.1 Rationale for use of stimulant-type medications to treat ADHD—

Amphetamines are non-catecholamine sympathomimetic amines with CNS stimulant activity. The mode of therapeutic action in ADHD is not known, but amphetamines increase extracellular dopamine and norepinephrine. These alterations in extracellular neurotransmitters are a result of amphetamine's inhibition of the Dopamine Transporter (DAT), Norepinephrine Transporter (NET), Vesicular Monoamine Transporter-2 (VMAT-2), and Monoamine Oxidase (MAO).

DAT and NET are located in the presynaptic terminal cell membrane, where they function to clear dopamine and norepinephrine, respectively, from the synaptic cleft into the presynaptic neuron. This clearance is necessary to end the response of the postsynaptic neuron and recycle the neurotransmitters in the presynaptic neuron for subsequent repackaging and release. Thus, competitive inhibition of DAT by amphetamine prolongs the presence of dopamine in the synapse, which results in a greater degree of dopamine signaling to the postsynaptic cell. In addition to competitive inhibition of DAT function, amphetamine can reverse the direction in which dopamine is transported. This effect can further increase synaptic dopamine levels beyond the level resulting from transport inhibition alone. Although NET primarily uses norepinephrine as a substrate, it is also capable of transporting dopamine and its inhibition can increase synaptic dopamine levels⁹.

While DAT and NET are located in the presynaptic cell membrane, VMAT2 and MAO are located within the presynaptic nerve terminal. VMAT2 is responsible for transporting monoamine neurotransmitters into vesicles within the nerve terminal, after which they can be released into the synaptic cleft. When VMAT2 is inhibited by amphetamine, cytosolic dopamine levels will increase. The increased cytosolic dopamine can then be acted on by the "reversed" DAT and transported into the synaptic cleft. However, while in the cytosol, dopamine is also susceptible to oxidative degradation by MAO. By inhibiting MAO function, amphetamine prevents this degradation and leaves increased cytosolic dopamine available for transport into the synaptic cleft¹⁰. In contrast, methylphenidate inhibits DAT and NET and has weaker inhibition of MAO than amphetamine¹⁰. Thus, methylphenidate increases extracellular dopamine levels by blocking its reuptake only, rather than also increasing its release as amphetamine does¹¹.

1.1.2.2 Rationale for use of Minecraft as add-on therapy to stimulant type ADHD medications—

Diagnosis rates of ADHD in children range from 5–11% compared

to 2.5% in adults^{12–14}. Diagnosis of ADHD rose 42% from 2003–2004 to 2011–2012¹³. In 2011, 3.5 million children were being treated with therapeutics as reported by their parents¹³. One of the issues with continued reliance upon therapeutics to treat ADHD is that increased availability tends to increase nonmedical use of amphetamine-type ADHD drugs by adolescents and young adults. In addition, parents prefer non-drug treatment options for ADHD¹⁵, and thus medical treatments for ADHD remain underutilized¹⁶. Finally, the beneficial effects of currently available drug and behavioral therapies do not persist after discontinuation^{17,18}, thus making alternative treatments with benefits that continue long-term highly desirable.

Some new companies make video games designed to treat ADHD, and FDA has issued a guidance for therapeutic game designers. Lexington is becoming a hotbed of videogame development^{19,20}. Pfizer and Shire Pharmaceuticals are funding research in videogames. Drug companies will head toward drug/device combinations, even though they currently seek prescription video games. Companies like CogCubed and Akili are developing videogames for approval as FDA regulated devices, but not drug device combinations. There is some evidence of efficacy of games, but the efficacy could be improved. The ultimate goal is to increase overall treatment efficacy and create the first FDA-approved device/drug combination for ADHD treatment.

To that end, this clinical trial will be conducted as an exploratory study to investigate the functional relationship between NICHQ scores, game aspects of Minecraft, and executive function. Two study groups will be included: a videogame group (ADHD drug regimen + Minecraft a minimum of 30 minutes per day, 5 times per week \times 4 weeks) and a control group (ADHD drug regimen only \times 4 weeks). By using a no Minecraft control group who will continue their usual ADHD medication regimen, we expect to be able to determine the effect on executive function from adding Minecraft to the usual standard of care for ADHD. (All subjects enrolled in the study will be free to play any video games or computer games that they want to play during the course of the study. However, the Minecraft group will be the only group of subjects playing in the private Minecraft Realm and doing the activities described there.) Furthermore, subjects in the control group will be taking varying doses of stimulant medications as well as different types of stimulant medications prior to enrolling in the study. This will allow for easier recruitment and, more importantly, allow for additional data to be collected. A dose response effect across dose parameters will be examined, and the introduced variance will be managed with factor analysis²¹. However, one potential problem in this study design is the effects of other medications used to treat ADHD (such as atypical antipsychotics or alpha-2 receptor agonists) that may have negative effects on cognitive function, and therefore confound the results. We expect that such effects will be negated by requiring that the study subjects are being treated with a stimulant medication, which would counteract the negative effects of these medications on cognitive function.

Previous studies which found effects of gaming interventions on executive function have used study durations ranging from 2–16 weeks, with 2–5 training sessions per week³. However, a less intense schedule of 5 \times 30 minute (minimum) game sessions per week for 4 weeks was chosen for this study because of concerns related to lowered compliance to study procedures. These concerns are due to the study's taking place during the school year, when

increased time demands for the study subjects could limit adherence to a more intensive intervention schedule.

Our hypothesis is that subjects in the videogame group (usual ADHD drug + Minecraft) will show improvements in NICHQ scores and executive function at the end of the 4 week game playing period compared to the control group.

Pharmaceutical therapy is the most effective monotherapy for most patients with ADHD, with the exception of the very young²². The advantages of a combining pharmaceutical therapy with behavioral therapy include lower cost, as personnel time with patients is reduced, and reduced doses of pharmaceuticals (50–75%)²³. Additionally, the benefits of behavior therapy are more likely to carry forward once treatment has stopped²³. Behavior therapy for ADHD patients includes repetitively reducing negative behaviors with consequences and increasing positive behaviors with rewards²². One possible mechanism of action associated with the effects of Minecraft on ADHD is the opportunity for reinforcement of positive behavior and punishment for negative behaviors provided by Minecraft. Minecraft is an online medium with several built-in components similar to behavior therapy exercises but enjoyable so that children are likely to want to play. High performance in several major executive functions noted to be lacking in autistic children is positively reinforced by gameplay, in that success yields completion of a specific task, acquisition of a rare in-game item, or even character survival in a given situation. Furthermore, Minecraft allows players to re-attempt failed challenges as characters respawn after death, though with certain disadvantages. This both gives players the impetus to improve in those executive functions (to prevent character death or hassle) and the ability to continue improving.

Application of executive functions in gameplay is exemplified in the following:

1. Executive Functions Exemplified in Construction - A great deal of time and focus are required to acquire the necessary resources and build a desired project, particularly in Survival mode (a mode of gameplay which requires players to harvest resources while harassed by cartoon monsters); a great amount of time and self-direction are required to build an ideal structure in Creative mode as well (a mode of gameplay in which players have free, unlimited access to all resources, unlimited mobility, and no danger of character death). The construction of complex structures requires inhibition as players must work exclusively on one project to complete it in a timely fashion, working memory as players must mentally construct the project in their minds in order to place building blocks on the proper squares of the game grid, planning as players choose how much of the resources they wish to acquire and design their structures, and self-monitoring as players balance their time and the amount of risk associated with the acquisition of resources.
2. Executive Function Exemplified in Mobility - Manual dexterity is required for proper placement of blocks, navigation of obstacles, and combat with cartoon monsters. All of these can be difficult, and the failure to execute these maneuvers

correctly results in character death (and loss of experience and items) and/or in the frustration of traveling back to the location, often over difficult terrain.

3. Executive Function Exemplified in Fluidity - Maintaining and changing mental set and emotional regulation is applicable to overcoming challenges presented in survival mode in particular, though challenges also arise in the building process in any mode, and players often have to modify their strategies in order to succeed.
4. Executive Function Exemplified in General Gameplay - Focus and concentration skills are practiced as players must monitor their health and surroundings in the game to stay alive. Due to the fact that Minecraft is borderless, subjects can become lost if attention is not paid to their surroundings. While other games may also require monitoring of health, there is an element of required organizational skills that may be missing in other video games popular with this demographic. While subjects will likely have an exhaustive inventory of general supplies after having played for awhile, survival may mean the ability to find needed supplies quickly and acquisition of specialized resources is still a lengthy and sometimes difficult process (when play is conducted in Survival mode).

In contrast to the behavioral training components of Minecraft, the training of executive function is expected to yield more generalizable benefits across multiple environments, because executive function processes underlie all cognitive processes while training to modify behaviors can only affect the specific behaviors targeted²⁴. Moreover, training of working memory has previously been shown to increase cortical D1 receptor density²⁵. As dopaminergic function is compromised in ADHD²⁶, these alterations could provide additional benefits in improving the function of patients with ADHD. In order to direct the practice of these executive functions, during this trial players will be required to work from an activity list with additional reinforcement for practicing behavior therapy type activities. A self-assessment component of the trial will encourage subjects to develop self-cognition, or metacognition.

In addition to its effects on behavior and executive function, Minecraft could beneficially affect neurological functions underlying cognitive control. A previous study assessing the effects of a therapeutic video game designed to train multitasking ability in elderly subjects found that improvements in multitasking were associated with increases in midline frontal theta power and long-range theta coherence between the frontal and posterior brain regions as determined by two electroencephalography methods used to assess cognitive control. These improvements persisted for six months following the completion of training and reached a level comparable to that of younger adults²⁷.

Furthermore, utilizing cognitive training activities in a gaming format is suggested to increase motivation and one's ability to learn⁸. This effect is thought to be mediated by games producing increased striatal dopamine levels^{28,29} that enhance long-term potentiation of neural connections in the striatum^{30,31}.

1.1.3 Potential Risks and Benefits

1.1.3.1 Known Potential Risks of Video Games, Specifically Minecraft—The immediate risks of this study appear to be few. Although there is little research on the effect of Minecraft in humans, there is considerable research on the effects of other video games. Like pharmaceuticals, the effect seen seems to be often related to the amount and style of video games to which humans are exposed. One person shooter games with violence are associated with anxiety³². The negative outcomes of video play include obesity³³, aggressiveness³⁴, and addiction³⁵. The risk of obesity is complicated by some studies that suggest high school students who exceeded the recommended screen time (TV and computers) were also more likely to consume fast food and sugary drinks and less likely to consume fruits and vegetables³⁶. Additional potential risk might include eye strain³⁷, repetitive motion injuries³⁸, seizures³⁹, and vertigo/motion sickness⁴⁰.

Diagnosis rates of ADHD in children range from 5–11% compared to 2.5% in adults^{12–14}. Diagnosis of ADHD rose 42% from 2003–2004 to 2011–2012¹³. In 2011, 3.5 million children were being treated with therapeutics as reported by their parents¹³. Unfortunately, increased availability of stimulants tends to increase nonmedical use of amphetamine-type ADHD drugs by adolescents and young adults. An estimated 97% of adolescents play video games⁴¹. On average, American children play video games at least one hour per day⁴². Additional nonpharmaceutical therapies are needed for ADHD because stimulant diversion is associated with increased availability of amphetamines. The prevalence of ADHD along with the total amount of time American children spend playing video games would provide a rationale for the study of both.

The video game chosen, Minecraft, is considered to be nonviolent. One of the only violent aspects is cartoon skeletons that have the ability to shoot arrows. Thus, care has been taken to select a nonviolent game. Secondly, time spent playing Minecraft was limited to 30 minutes/day, far less than the normal amount of time most American children spend playing video games. Risks have also been minimized with purchase of private Minecraft Realms for the participants. Children playing Minecraft during the trial will only interact with investigators and other subjects while playing and their play will be monitored periodically by investigators to ensure appropriate play by all.

1.1.3.2 Known Potential Risks of Video Games with CNS Stimulant Treatment

—Little is known about potential risks of videogame play with a background of CNS stimulant treatment. Sudden death has been reported in association with CNS stimulant treatment alone at usual doses in children and adolescents with structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that may predispose increased vulnerability to the sympathomimetic effects of a stimulant drug.

Administration of stimulants may exacerbate symptoms of behavior disturbance and thought disorder in patients with pre-existing psychotic disorder. Particular care should be taken in using stimulants to treat ADHD patients with comorbid bipolar disorder because of concern for possible induction of mixed/manic episode in such patients.

Treatment emergent psychotic or manic symptoms, e.g., hallucinations, delusional thinking, or mania in children and adolescents without prior history of psychotic illness or mania can be caused by stimulants at usual doses.

Other adverse effects of amphetamines include growth suppression, loss of appetite, weight loss, stomach ache, insomnia, headache, rebound symptoms, and irritability/jitteriness⁴³.

1.1.3.3 Known Potential Benefits of Video Games—Action video games are associated with increased multiple tracking tasks (improved attention)⁴⁴, increased basic cognitive skills such as tracking objects moving at greater speeds, better ability to detect changes to objects stored in visual short-term memory, to change tasks more rapidly, and mentally rotate objects more efficiently⁴⁵.

1.2 Objectives and Purpose

1.2.1 Primary Objective

To derive a functional⁴⁶ relationship between NICHQ scores, game aspects of Minecraft, and executive function.

1.2.2 Secondary Objectives

Using EDA and factor analysis, we will examine specific clinical symptoms of ADHD, including deficits in inhibition, working memory, planning, self-monitoring, verbal regulation, motor control, maintaining and changing mental set and emotional regulation as revealed by the NICHQ questionnaire and other assessments, that are affected by putative therapeutic features of the game Minecraft to determine which features to enhance to increase effectiveness of the intervention.

1.3 Study Design and Endpoints

1.3.1 Description of the Study Design

This clinical trial will be conducted as an exploratory, randomized parallel open label pilot study to investigate the functional relationship between NICHQ scores, game aspects of Minecraft, and executive function in ADHD patients receiving stimulant type medications as standard of care.

The study has two arms and is conducted at a single center using multiple physicians. The study agent/intervention is the video game Minecraft. Subjects will be randomized by sex and age to the video game group or the combination group. The two study groups include a study group (ADHD drug regimen + Minecraft played for a minimum of 30 minutes per day, 5 times per week for 4 weeks) and a control group (ADHD drug regimen only followed for 4 weeks). There are no schedule changes, stratifications, or dose escalations.

1.3.2 Study Endpoints

1.3.2.1 Primary Endpoint—The primary endpoint of this pilot study will be change in ADHD symptoms as measured by the NICHQ questionnaire after 4 weeks of therapeutic gaming. No statistical hypothesis is being tested. Post hoc exploratory data analysis (EDA)

techniques will be applied to compare drugs used and their doses along with game features to the NICHQ results.

1.3.2.2 Secondary Endpoint—Using EDA and factor analysis, we will examine specific clinical symptoms of ADHD, including deficits in inhibition, working memory, planning, self-monitoring, verbal regulation, motor control, maintaining and changing mental set and emotional regulation as revealed by the NICHQ questionnaire and other assessments, that are affected by putative therapeutic features of the game Minecraft to determine which features to enhance to increase effectiveness of the intervention.

1.3.2.3 Exploratory Endpoints—Not Applicable.

1.4 Study Enrollment and Withdrawal

1.4.1 Participant Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Primary diagnosis of ADHD in accordance with DSM-5.
2. On a current regimen of a stimulant type ADHD medication, such as Vyvanse.
3. Sex: males and females.
4. Age: between 10 and 15 years of age.
5. Stated willingness to comply with all study procedures and availability for the duration of the study, including adherence to medication and play regimen.
6. Are capable, as determined by the investigator, to perform the following:
 - a. complete the study log.
 - b. are able to comply with the required study visits.
7. Have given written informed assent along with parents/legal guardians to participate in this study in accordance to local regulations before any trial related activities (other than initial screening) are carried out.
8. Are Minecraft players and have access to a full version of PC/Mac (Java) Minecraft, Xbox Minecraft, or pocket Minecraft version (Android, Kindle) that supports play on Realms.
9. Subjects' parents and subjects both currently have Google accounts and electronic devices to access Google accounts online.
10. Must have an NICHQ Vanderbilt Assessment scored by parents and teacher(s) within the last month, or get an assessment scored by parents and teacher(s) within one week of enrollment and before beginning to play the video game if the subject is in the video game arm).
11. At least one parent and the subject must be proficient in spoken and written English.

1.4.2 Participant Exclusion Criteria

Any of the following would render a person ineligible to participate in the study:

1. Current or past history of substance abuse.
2. Patients who for whatever reason are deemed by the investigator inadequate for participation in this trial (e.g., patients with incapacitating mental illness).
3. Have previously completed or withdrawn from this study after having signed the informed consent/assent document.
4. Lack of proficiency in spoken and written English

1.4.3 Strategies for Recruitment and Retention

As the study is a pediatric study, the pediatric population is the only one being studied. ADHD disproportionately affects children and therefore, children are the subjects being recruited. Recruitment will include females and minority groups as appropriate. The ADHD population is predominantly male, so our study population will reflect the patient population. The medical investigators contacted for this trial have indicated they predominantly treat Medicaid patients, thus lower economic status patients should also be adequately represented.

Compensation (\$100/subject) will be provided to children and parents in a 60/40 split to compensate for their playing time, travel time, and expenses to the site. Children will be given \$60 gift cards for participation and one parent/legal guardian will be paid \$40 via check.

As the study duration is only 4 weeks, study retention is not likely to be a problem. Additionally, study personnel will contact subjects periodically if subjects do not appear to be logging on and playing Minecraft or if data is not being shared with researchers. Subjects will be asked to unshare their data with us after the trial has been completed.

UK CCTS will be the only clinical site. Thirty-two patients (32) will be screened in order to enroll 16 subjects (8 female 8 male), to ensure 12 complete the study. The study will enroll 16 participants (8 female, 8 male) with a previous medically confirmed diagnosis of ADHD at the CCTS in order to have at least 12 complete the study. All of the 16 subjects enrolled will currently be on a stimulant type ADHD drug regimen with active prescriptions.

An i2b2 survey conducted in July 2016 identified 257 potential subjects which are currently on a standard of care including a stimulant type ADHD drug. It is expected that all investigators will go through their medical files and will review existing patient records to screen these patients for inclusion and exclusion criteria. Similarly, additional study candidates will be referred by other physicians or will respond to advertisements or web announcements made by CCTS if recruitment falls short of goals.

1.4.4 Participant Withdrawal or Termination

1.4.4.1 Reasons for Withdrawal or Termination—Participants are free to withdraw from participation in the study at any time upon request. An investigator may terminate participation in the study if:

- Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.

1.4.4.2 Handling of Participant Withdrawals or Termination—In case any participant drops-out from the study at any given point during the study period, every effort will be made to contact the subject by phone, mail, and email to investigate the reason for the subject stopping participation in the trial. Should a subject decide to withdraw, all efforts will be made to complete and report the observations as thoroughly as possible and collect study products (NICHQ assessments, Minecraft Realms, self-assessments). Additional subjects initially screened but not enrolled may be added if the investigators feel this is warranted.

1.4.5 Premature Termination or Suspension of Study

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification documenting the reason for study suspension or termination will be provided by the suspending or terminating party to the Investigator, funding agency, and regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

The study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the sponsor and IRB.

1.5 Study Agent

1.5.1 Study Agents(s) and Control Description

1.5.1.1 Acquisition—The study agent in this study is the video game Minecraft. The subjects will already be Minecraft players and will already have Gmail accounts. The subjects will receive instructions for Minecraft play via their Google Mail accounts. Study

subjects will already be on a regimen of prescription drugs as standard of care from their physicians.

1.5.1.2 Formulation, Appearance, Packaging and Labeling—The Minecraft game is available for download on the Internet and has no packaging, labeling or appearance.

Minecraft Study participants in this protocol will already be on a regimen of various FDA approved stimulant-type ADHD medication therapies in various doses. Those drugs are standard of care agents and it is not practical to discuss the formulation, appearance, packaging or labeling of all the different types of possible pharmaceuticals.

1.5.1.3 Product Storage and Stability—Minecraft can be stored on a hard drive or removable media (such as a USB memory stick). Downloaded Realm worlds will be saved with a user's single player worlds. Downloaded worlds are accessible offline and are available for upload to another Realm or world on your Realm.

1.5.1.4 Preparation—Subjects will be asked to play the desktop computer version of Minecraft.

1.5.1.5 Dosing and Administration—Subjects will be asked to play Minecraft for a minimum of 30 minutes per day five times per week.

1.5.1.6 Route of Administration—Not applicable.

1.5.1.7 Starting Dose and Dose Escalation Schedule—Subjects will be asked to play Minecraft for a minimum of 30 minutes per day five times per week. There will be no escalation.

Subjects will maintain their prescribed doses of ADHD medication that were determined by their physician prior to enrollment in the study.

1.5.1.8 Dose Adjustments/Modifications/Delays—Not applicable.

1.5.1.9 Duration of Therapy—The videogame trial is scheduled to last for four weeks. Subjects will maintain current standard of care during and after the trial.

1.5.1.10 Tracking of Dose—Subjects will log their own video game play on their existing online accounts.

Parents will track children's medication compliance on their existing online accounts. They will be asked to share the data periodically with investigators.

1.5.1.11 Device Specific Considerations—Not applicable.

1.6 Study Procedures and Schedule

1.6.1 Study Procedures/Evaluations

1.6.1.1 Study Specific Procedures—Medical history will be obtained by interview by CCTS. Most recruited individuals will be the patients of the initial medical investigators and the investigators will also have their patients' histories. Investigators will be added if recruitment falls short of goals.

Questions to be asked of subjects include:

1. Do you have any current medical problems or issues other than ADHD?
2. What illnesses have you been diagnosed with in the past? Age at diagnosis?
3. What surgeries have you had in the last five years?
4. How often do you normally play computer and video games? What hardware platforms do you use (desktop, pad, phone, console?) How long is an average session of playing on each? What video games have you previously played on each? What are the dates you played these games (i.e., approximately when did you start, and if you no longer play, when did you stop?)

Medicinal history will be obtained by interview. CCTS personnel will use this information to ascertain whether subjects are eligible for enrollment as all participants are required to be currently taking a stimulant type ADHD medication.

Questions will include:

1. What prescription medications are you taking for ADHD? What are the doses and schedule?
2. What prescription medications are you taking for other indications? What are the doses and schedule?
3. What OTC medications, or herbal supplements are you currently taking? What are the doses? How often do you take them?

Physical examination will include height and weight at both exams.

Discussion Points:

1. No results will be shared with trial subjects.
2. Assessment of study agent adherence
3. Administration of questionnaires or other instruments for subject-reported outcomes, such as the NICHQ, self-assessment questions, parent reported study compliance for medications, video gaming log, and completed activity list.

1.6.1.2 Standard of care study procedures—A Psychiatrist will serve as the medical director and a site PI. The PI as well as the other physicians (Medical Investigators) are responsible for standard of care and NICHQ assessments from parents and teachers.

Standard of care for children 6–11 years of age is FDA-approved medications for ADHD and/or evidence based parent and or teacher-administered behavior therapy as treatment, preferably both²². Stimulant based medication is strongly recommended. Adolescents, aged 12–18, should be administered FDA-approved ADHD medication with the patient’s accent. Behavior therapy may also be added to the prescription regimen. The dose of the medication should be titrated to achieve the maximum benefit of the drug with the fewest side effects.

1.6.2 Laboratory Procedures/Evaluations

1.6.2.1 Clinical Laboratory Evaluations—Not applicable.

1.6.2.2 Other Assays of Procedures—Not applicable.

1.6.2.3 Specimen Preparation, Handling, and Storage—Not applicable.

1.6.2.4 Specimen Shipments—Not applicable.

1.6.3 Study Schedule (Fig. 1, Table 1)

1.6.3.1 Screening—This is a rolling enrollment trial. Enrollment is expected to be open for a maximum of 62 days. Final visit will occur within 7 days of completing 42 days of video therapy.

Prescreening Visit (Day 0 to 60)

- Obtain informed consent/assent of potential participant verified by signature on written informed consent for screening form.
- Review medical history to determine eligibility based on inclusion/exclusion criteria.
- Review medications history to determine eligibility based on inclusion/exclusion criteria.
- Review history of computer and video game play (which games, start date, end date, minutes per day)
- Perform medical examinations needed to determine eligibility based on inclusion/exclusion criteria.
- Provide participants with instructions, such as, we will evaluate your tests and contact you within 4 weeks to tell you whether you have been chosen to participate in the study. Do not do anything regarding this trial until we contact you. If you are chosen you should follow the instructions in the subject instructions (hand potential subjects’ and parents a copy of these instructions). Review important parts of the trial protocol in the instructions including the difference in the trial groups, the IT requirements, and the data to which the investigators will expect to be given access.

1.6.3.2 Enrollment/Baseline—Enrollment (Day 1–44)

- Ascertain that potential participants have NICHQ scores (no older than 1 month old) from parents, collected on visit 1, and teachers, submitted by medical investigators, before subjects can be enrolled in trial. After eligibility has been determined, attempt to enroll eligible subjects, with priority given to 10–12 years old, but open up to 15 year olds if 16 subjects are not available in the 10–12 year-old range, with randomization based upon age and sex. If for any reason the final NICHQ assessments from teachers are not available, the study will simply treat them as missing data. However, the initial assessment must be available for enrollment. Enrollment will be conducted by electronic means (telephone and/or email).
- Contact eligible participants via phone to reconfirm current eligibility and enrollment, provide groups assignment, and review study instructions, including continuing with ADHD medication. If potential participants can not be reached after 3 phone call or 2 emails, they will be excluded from the study and another participant enrolled. Ask subjects to verbally confirm what their activities will be during the trial to confirm their understanding. Gather Google emails addresses from parents and children, if available. Determine which version of Minecraft the subjects randomized to the Minecraft group will play (i.e. do subject wish to play via a PC or a gaming console or mobile device) Details to discuss with participants: See phone script. Remind subjects that study instructions will also be shared with them via Google Drive.
- Schedule final study visits for participants who are enrolled in the study.

1.6.3.3 Follow-up—Not applicable.

1.6.3.4 Final Study Visit—Final Study Visit (Visit 2, Day 29–86, including + 7 day window to have final visit after last completer of 28 days of video therapy)

- Record adverse events as reported by participant or observed by investigator. Subjects will be told to report AEs to their physician.
- Record weight and results of post- NICHQ questionnaire. The post study NICHQ data will allow us to assess the primary endpoint, change in NICHQ scores. The secondary endpoints can be assess through the electronic data made available to the investigative team periodically by the subjects and their parents throughout the study.
- Record participant's adherence to regimen.
- Provide final instructions: Continue your standard of care routine from your physician.
- Inform patients and parents that data will not be available to them. Since this is an exploratory study neither efficiency nor safety is being assessed. Thus, it is unlikely to present any meaningful information to the subjects. It will likely consist of only patterns and be used to guide further research.

1.6.3.5 Early Termination Visit—If an early termination visit occurs, all final study visit procedures should be performed.

1.6.3.6 Unscheduled Visit—Since this trial is only 4 weeks long, it is doubtful that any unexpected visits will occur. If an unscheduled visit should occur data concerning AEs will be documented.

1.6.4 Concomitant Medications, Treatments, and Procedures

All concomitant prescription medications taken during study participation will be recorded on the case report forms (CRFs). For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the CRF are concomitant prescription medications, over-the-counter medications and nonprescription medications.

1.6.4.1 Precautionary Medications, Treatments, and Procedures—Not applicable.

1.6.4.2 Prohibited Medications, Treatments, and Procedures—Not applicable.

1.6.4.3 Prophylactic Medications, Treatments, and Procedures—Not applicable.

1.6.4.4 Rescue Medications, Treatments, and Procedures—Not applicable.

1.6.4.5 Participant Access to Study Agent at Study Closure—Although Minecraft is commercially available to play for free the Minecraft Realms used in this study will be closed and not available for additional play by participants.

1.7 Assessment of Safety

1.7.1 Specification of Safety Parameters

1.7.1.1 Definition of Adverse Events (AE)—Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

1.7.1.2 Definition of Serious Adverse Events (SAE)—An AE or suspected adverse reaction is considered “serious” if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that

do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

1.7.1.3 Definition of Unanticipated Problems (UP)—OHRP considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research (“possibly related” means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

This study will use the OHRP definition of UP.

1.7.2 Classification of an Adverse Event

1.7.2.1 Severity of Event—All AEs will be assessed by the clinician using a protocol defined grading system. For this trial, AEs related/not related will be those associated with playing the video game. Stimulant related AE’s, which are standard of care, will be reported to Medwatch at physician’s discretion. For AEs not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- Mild – Events require minimal or no treatment and do not interfere with the participant’s daily activities.
- Moderate – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- Severe – Events interrupt a participant’s usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

1.7.2.2 Relationship to Study Agent—All AEs will have their relationship to study agent or study participation assessed with a level of specificity appropriate to the study design.

The clinician’s assessment of an AE’s relationship to study agent is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. All AEs must have their relationship to study agent assessed. In a clinical trial, the study product must always be suspect. To help assess, the following guidelines are used.

- Related – The AE is known to occur with the study agent, there is a reasonable possibility that the study agent caused the AE, or there is a temporal relationship between the study agent and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study agent and the AE.
- Not Related – There is not a reasonable possibility that the administration of the study agent caused the event, there is no temporal relationship between the study agent and event onset, or an alternate etiology has been established.

1.7.2.3 Expectedness—Expected adverse reactions are AEs that are common and known to occur for the study agent being studied and should be collected in a standard, systematic format using a grading scale based on functional assessment or magnitude of reaction. An AE or suspected adverse reaction is considered “unexpected” if it is not listed in the IB or is not listed at the specificity or severity that has been observed; or, if an IB is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the protocol, as amended.

Medical Investigators (i.e., the subject’s physician) will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for Minecraft.

1.7.3 Time Period and Frequency for Event Assessment and Follow-up

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate CRF. Information to be collected includes event description, time of onset, clinician’s assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant’s condition deteriorates at any time during the study, it will be recorded as an AE. UPs will be recorded in the data collection system throughout the study.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At the study visit, the investigator will inquire about the occurrence of AE/SAEs since the initial visit. Events will be followed for outcome information until resolution or stabilization.

1.7.4 Reporting Procedures

1.7.4.1 Adverse Event Reporting

Responsible Parties: Sponsor/Investigator/ Safety Officer- Robert Lodder

Other Investigators - Medical Investigators (site PIs), Adriane Grumbein, and Kyra Hunting

The Sponsor-Investigator/Safety Officer will inform the IRB of any events of which he becomes aware of.

1.7.4.2 Serious Adverse Event Reporting—Safety reports will be made of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 14 calendar days after the sponsor determines that the information qualifies for reporting.

The PI will report any suspected adverse reaction that is both serious and unexpected. The sponsor must report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the therapeutic agent and the adverse event, such as:

1. A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome);
2. One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture);
3. An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical.

Life-threatening suspected adverse reaction as soon as possible but in no case later than 7 days after sponsor determines that the information.

SAE Forms will be completed by study clinicians within the timelines shown in Figure 2.

All deaths and immediately life-threatening events, whether related or unrelated, will be recorded on the SAE Form and submitted to the study sponsor within 24 hours of site awareness.

Other SAEs regardless of relationship, will be submitted to the study sponsor within 24 hours of site awareness.

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by the study sponsor and should be provided as soon as possible.

The study sponsor will be responsible for notifying IRB of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information.

1.7.4.3 Unanticipated Problem Reporting—Incidents or events that meet the OHRP criteria for UPs require the creation and completion of an UP report form. It is the site investigator's responsibility to report UPs to their IRB. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are SAEs will be reported to the IRB within 7 days of the investigator and to the sponsor within 24 hours of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the study sponsor within 14 days of the investigator becoming aware of the problem.

All UPs should be reported to appropriate institutional officials (as required by UK per Serious or Continuing Noncompliance or Unanticipated Problems Involving Risks:IRB Reporting to Federal Agencies using the UK IRB reporting form within the timeline in accordance with the SOP for Unanticipated/Anticipated Problem/Adverse Event Reporting (UK) of the IRB's receipt of the report of the problem from the investigator.

1.7.4.4 Events of Special Interest—Not applicable.

1.7.4.5 Reporting of Pregnancy—Report as a non-treatment related AE to the IRB. Physicians will ultimately make the decision as to whether to continue the drugs they have prescribed. If subjects are removed from their ADHD pharmaceutical regimen then participants will be discontinued from study. Subjects that remain on the ADHD pharmaceutical regimen will continue in the study.

1.7.5 Study Halting Rules

Administration of study agent will be halted when three severe AEs determined to be "probably related" are reported to the Study Coordinator. The Study Coordinator will notify the study sponsor and investigators immediately when the third severe event is reported and enrollment screens will stop accepting new study participants. The study sponsor will inform the IRB within 24 hours of this occurrence and will provide the IRB with AE listing reports.

The Investigative team, medical investigators, and CCTS will convene an ad hoc meeting by teleconference or in writing as soon as possible.

1.7.6 Safety Oversight

As overall risk of this study is extremely low due to use of subjects' normal standard of care FDA approved pharmaceutical and a non-rated, fairly innocuous video game (No language concerns, limited violence (i.e. cartoon skeletons shooting arrows and scary cave noises), as well as portals to the Nether). Therefore, a data safety management board will not be used. Safety oversight will be under the direction of the Monitor, with prior expertise in clinical monitoring. The Monitor will inspect the CCTS site at least once to assess data in the study. The Study Monitor will provide its input to the study sponsor.

1.8 Clinical Monitoring

Our designated monitor will conduct the monitoring. The monitor has experience monitoring other human trials. Monitoring will include an on-site initiation visit and close down visit. Additional remote monitoring will be conducted to verify data by our auditor. Data verification will be comprehensive (100%) of the primary endpoint. Secondary endpoint verification of data will be more random with at least 10% of data verified. The monitor will also distribute monitoring reports to the Sponsor/Investigator and our research coordinator at CCTS.

Independent audits will not be conducted to ensure monitoring practices are performed consistently across all participating sites.

CCTS will perform internal quality management of study conduct, data collection, documentation and completion. An individualized quality management plan will be developed to describe the site's quality management.

1.9 Statistical Considerations

1.9.1 Statistical and Analytical Plans

This is a pilot study to investigate video game use as an add-on to stimulant type ADHD medications.

1.9.2 Statistical Hypotheses

None. This is an exploratory data analysis to look for relationships between game design factors and NICHQ scores and executive functions.

1.9.3 Analysis Datasets

Safety Population - All subjects who play at least one day on the trial Minecraft realm will be included in the safety analyses. All adverse events reported in this study will be listed and tabulated using descriptive statistics, frequencies, and proportions.

Intent-to-Treat (ITT) Analysis Dataset will include all randomized subjects.

Per-Protocol (PP) Analysis Dataset: All subjects with a pre- and post-trial NICHQ questionnaire scores and completed at least 80% of each of the components of the study.

1.9.4 Description of Statistical Methods

1.9.4.1 General Approach—This is a pilot study with a parallel design in which one group plays Minecraft and the other group does not. Both groups will already be receiving the ADHD standard of care stimulant drugs. No preliminary data are available and there are no expectations regarding the results. This pilot study will enable us to propose further studies with testable statistical hypotheses.

Exploratory data analysis (EDA) techniques will be used for analysis. EDA is an approach to analyzing data sets to summarize their main characteristics, often with visual methods. A statistical model may or may not be used, because the purpose of EDA is primarily to see what the data can tell us beyond a formal modeling or hypothesis testing task. Typical EDA modeling techniques include: box plot, histogram, Multi-vari chart, run chart, pareto chart, scatter plot, stem-and-leaf plot, parallel coordinates, odds ratio, multidimensional scaling, targeted projection pursuit, principal component analysis (PCA), multilinear PCA, projection methods such as grand tour, guided tour, and manual tour, interactive versions of the plots, single linkage cluster analysis, and other forms of hierarchical clustering methods. Quantitative techniques that may be applied include median polish, trimean, and ordination to distinguish related patterns. Post hoc tests of significance may be performed. In addition, exploratory data analysis enables checks of assumptions (e.g., normality) underlying statistical procedures.

1.9.4.2 Analysis of the Primary Efficacy Endpoint(s)—For the primary endpoint, due to the small sample size and the fact that this is a pilot study, exploratory data analysis will be used. Data to be collected includes pre-play and post-play NICHQ questionnaire scores, drugs and doses, and executive functions played out in Minecraft. We will be looking for correlation trends and goodness of fit of linear and nonlinear models as well as the presence of covariates and factors in the predictive model for NICHQ scores.

All attempts will be made to prevent any missing values. Data imputation may be done as part of EDA. For the analysis of the primary endpoint (NICHQ values), the Last Observation Carried Forward (LOCF) concept will be used for subjects who discontinue prematurely from the study. These results will be compared with those obtained by the use of data splines. If for any reason the final NICHQ assessments from teachers are not available, the study will simply treat them as missing data and continue with only the assessments from the parents.

Data points that appear to be erroneous or inexplicable based on clinical judgment will be investigated and considered outliers. If a data point is identified as an outlier, two analyses will be performed, one with the outlier data point and one without the outlier. All data points will be reported in the listings, including any data point that may have been identified as an outlier. No data points will be excluded from the listings.

1.9.4.3 Analysis of the Secondary Endpoint(s)—Secondary Endpoint exploratory data analysis will include subject reflection data, number of Minecraft assigned activities completed, subject-reported compliance rate of game play and pharmaceutical use, Minecraft Realm history, sex, age, and drugs and dose levels as the factors of interest. For missing data, models will be built with and without data imputation and the results compared.

1.9.4.4 Safety Analyses—All subjects who play at least one day in the trial Minecraft realm will be included in the safety analyses. All adverse events reported in this study will be listed and tabulated using descriptive statistics, frequencies, and proportions.

Safety data will be analyzed for all subjects in the safety population. The safety population is defined as all subjects who have signed the study Informed Assent Document and have played at least one day in the Minecraft Realm. The safety variables that will be analyzed, at the minimum, include all reported adverse events.

All adverse events (AEs) as defined by the Common Terminology Criteria for Adverse Events⁴⁷ (CTCAE) will be analyzed for safety and tolerability. All study emergent adverse events (TEAEs) will be coded using the latest version of the MedDRA dictionary.

The number and proportion of subjects who report any TEAE will be tabulated by study group. All reported TEAEs will be summarized using descriptive statistics (n, mean, median, range, SD, or number and percentage of subjects) per study group. Study- emergent adverse events are defined as those events occurring or worsening upon or after receiving the first exposure to the randomized study agent (Minecraft). Adverse events will be listed by study group and subject. For any inferential statistics, appropriate statistical tests [Chi-square or Fisher's exact tests for categorical variables and Analysis of Variance (ANOVA) or Analysis of Covariance (ANCOVA) with the baseline value as the covariate for continuous variables] will be used. These models along with their parameters will be detailed in the SAP.

The Intent-to-Treat (ITT) population, safety population, and efficacy evaluable population will be defined and described in detail as part of the Statistical Analysis Plan (SAP). The SAP will be developed and finalized before the database is locked. This is a pilot study of a videogame and it is not clear what kind of safety information will be collected if any during the course of the trial. Information gathered during the interim analysis may help in the design of the SAP.

1.9.4.5 Adherence and Retention Analyses—Minecraft Realms provides user statistics to allow some subject adherence analysis. Additionally, users will be required to provide some user completion data of Minecraft associated activities. All subjects will keep a log of video gaming play (all games, including Minecraft). The log will include dates, times, and specific video games played, which will be analyzed for adherence and possible confounders.

1.9.4.6 Baseline Descriptive Statistics—Baseline demographic data will include age, sex, and race. Baseline intervention data will include NICHQ pre-study questionnaire scores, gaming history, and medical and drug history.

1.9.4.7 Planned Interim Analyses—An interim analysis will be conducted by the PI two weeks after the study begins to ensure the software is working properly and that all relevant data are being collected in the CRF. Conducting an interim analysis will allow investigators to determine any issues associated with subjects' use of technology and/or missing data and resolve these issues before database lock. There is no risk in conducting an interim analysis because the study is not blinded.

1.9.4.8 Additional Sub-Group Analyses—Both the primary and secondary endpoints will be analyzed based on age, sex, and race.

1.9.4.9 Multiple Comparison/Multiplicity—Not applicable.

1.9.4.10 Tabulation of Individual Response Data—Individual participant data will be listed by measure and time point.

1.9.4.11 Exploratory Analyses—Exploratory analysis will be performed on the NICHQ scores, including:

Self-reflective scores, video gaming logs, drug use, and Minecraft Realm play by subjects digitally saved during the trial will be analyzed post hoc. Exploratory data analysis (EDA) is an approach to analyzing data sets to summarize their main characteristics, often with visual methods. A statistical model may or may not be used, because the purpose of EDA is primarily to see what the data can tell us beyond a formal modeling or hypothesis testing task. EDA will be conducted to identify outliers, trends and patterns in data that merit further study.

Types of exploratory procedure will include: box plot, histogram, multi-vari chart, run chart, pareto chart, scatter plot, stem-and-leaf plot, parallel coordinates, odds ratio, multidimensional scaling, targeted projection pursuit, principal component analysis, principal curve analysis, multilinear PCA, projection methods such as grand tour, guided tour and manual tour, interactive versions of these plots, single linkage cluster analysis, or other hierarchical clustering methods. Typical quantitative techniques that may be used include median polish, trimean, and ordination.

1.9.5 Sample Size

The study will enroll 16 subjects (8 female, 8 male) at the UK Center for Clinical and Translational Science (CCTS) with a previous medically confirmed diagnosis of ADHD in order to have at least 12 complete the study. As this study is primarily exploratory, no sample size calculations were performed. Having 6 subjects per group allows a standard deviation to be calculated as well as a mean for each group, and also minimizes the number of subjects exposed to the intervention in this preliminary pilot study.

If a participant is lost to follow-up at any point during the trial the subject outcome will be assessed in the intent to treat analysis under the principle of the last observation carried forward (LOCF).

Statistical software used will include R and Matlab.

1.9.6 Measures to Minimize Bias

1.9.6.1 Enrollment/Randomization/Masking Procedures—The population of subjects with ADHD is predominantly male. The enrollment of sexes between the two study arms will be equalized as much as possible. The enrollment of different races and ages will also be equalized between the two arms as much as possible within the constraints of the small sample size. Participants who discontinue early will not be replaced.

The exploratory pilot study is open label and blinding procedures will not be employed.

1.9.6.2 Evaluation of Success of Blinding—Not applicable.

1.9.6.3 Breaking the Study Blind/Participant Code—Not applicable.

1.10 Source Documents and Access to Source Documents

Appropriate medical and research records will be kept for this trial for a minimum of 6 years. FDA and IRB personnel will be given access to source data as needed.

Source Documents and Data

Participant files included in trial: CRFs, study compliance logs (gaming and medication), self reflection questions, pre- and post-study completed NICHQ questionnaires, and memoranda.

Software as a Service Vendor (SaaS) Models⁴⁸—This project will use the multi-tenant infrastructure cloud provided by Google. The inclusion criteria will limit subjects to those who are already using Google services. The security and privacy controls are basically the same for everyone, with a few variations such as two factor authentication which can be enabled or disabled by the subjects. (The therapeutic video game (TVG) project can only be accessed with two-factor authentication on, but individual subjects have the option of using two-factor authentication or leaving it turned off for their own data). 21 CFR part 11 compliance is gained by a business associate agreement with Google, by designing our security controls to interface with those specified by the agreement with Google, and by following our SOP's (built around 21 CFR part 11 compliance). Google also employs version control making the trial documents, even those completed by subjects, completely traceable. Version control, a standard feature of Google Drive, allows researchers to monitor the date, ownership, and exact change made to any source document, including assessments. Minecraft Realm administrator privileges also allow the research team to access the individual playing time metrics to analyze for discrepancies between actual time played versus the self reported playing time.

Platform as a Service (PaaS) vs. SaaS⁴⁹—NIST defines PaaS as the capability provided to the user to deploy onto the cloud infrastructure programs created by the user or acquired by the user. Acquired applications are created using programming languages, libraries, services, and tools supported by the provider. The purpose of PaaS is to provide a programming platform to create a software application solution without the overhead of hosting and maintaining the underlying technology stack.

NIST defines SaaS as the capability provided to the user to run the provider's applications executing on a cloud infrastructure (Fig. 3). The applications are accessible from various client devices through either a thin client interface, such as a web browser, or a program interface. The user does not manage or control the underlying cloud infrastructure including network, servers, operating systems, storage, or even individual application capabilities, with the possible exception of limited user specific application configuration settings.

Using both SaaS and PaaS enables the encryption of subject-provided data from a SaaS system in a PaaS system (the Therapeutic Video Games or TVG Google PaaS) (Fig. 4–5).

Data stored will be encrypted using the OpenPGP standard as defined by RFC4880. Data transmitted on networks will be encrypted by Transport Layer Security or Secure Sockets Layer.

The list of subjects and ID numbers will be encrypted with a different key than the key used to encrypt all of the other data.

Cloud services the subjects and their parents already use include Minecraft and Google by the inclusion and exclusion criteria. These are all SaaS. The data aggregator to collect the subjects information from Minecraft in Google must have access to Google (PaaS) in order to create the backup at UK (Fig. 5)

CCTS personnel, PI, the trial Monitor, and the trial Auditor will have access to CRFs. CRF data will be recorded electronically because most of the data (which include the Minecraft Realm evolution over 4 weeks as recorded for backup purposes in save-sets, as well as subject reflections on gameplay for Minecraft, and logging of other video game play are in large data sets and only available in electronic form. Other CRF data include medical problems/issues, past illnesses as well as age at diagnosis, surgeries, amount of time subjects spend playing video games, gaming platform, typical length of playing session, video games previously played, age at which subject started playing, list/doses of current prescription, etc, and herbal supplements being taken, and height/weight.

The de-identified CRF data listed above will be copied to a compact disk for archiving. The de-identified data will also be available in the UK repository. The data will be de- identified during the download process by removing fields tagged as identifiers as part of the download process.

The CCTS study coordinator, will input the baseline NICHQ teacher scores into the eCRF from paper records if a teacher test record exists in participants' files that is no more than 1

month old, once subjects' parents/legal guardians have given consent for the information to be accessed.

Study and drug compliance records subjects make on their own Google Drives (Google is an inclusion criterion), as well as study reflection questions, will be shared by the subjects with the PI online via Google, ensuring protection for data with personal identifying information (PII) or personal health information (PHI). The PI will automatically collect the shared data, which will be de-identified while still on Google and downloaded for backup to a password-protected single-user computer behind a firewall. Periodically and at the end of the study, the data will be downloaded to a password-protected compact disk.

1.11 Quality Assurance and Quality Control

QC procedures will be implemented beginning with the data entry system and data QC checks for the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution. If for any reason the final NICHQ assessments from teachers are not available, the study will simply treat them as missing data. However, the initial assessment must be available for enrollment.

The monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, and GCP.

The investigational site will provide direct access to all trial related materials, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

1.12 Ethics/Protection of Human Subjects

1.12.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

1.12.2 Institutional Review Board

The protocol, informed consent/assent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent and assent forms must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

1.12.3 Informed Consent Process

1.12.3.1 Consent/Assent and Other Informational Documents Provided to Participants—Consent forms describing in detail the study agent, study procedures, and risks are given to the participant and written documentation of informed consent is required

prior to starting intervention/administering study product. The following consent materials are submitted with this protocol: Informed Consent, Assent, web advertisement, activity list, video gaming log, drug compliance log, example self-assessment question list.

There are two ways in which subjects may enter this trial. In the first way, subjects will be referred by their physician. In this case, the physician will obtain informed consent and assent. The second way is through advertisements. When a subject responds to an advertisement, the subject will have first contact with the research coordinator in the CCTS, and will be taken through the informed consent and assent process by the clinical research coordinator in the CCTS. The medical investigator or clinical research coordinator will explain the research study to the participant and answer any questions that may arise. The participant of legal age will sign the informed consent document prior to any procedures being done specifically for the study. A participant of less than legal age must sign an assent form, while that person's parent or guardian must sign the consent document. The participants (i.e., the subject or the subject's parent) may withdraw consent or assent at any time throughout the course of the trial.

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

1.12.3.2 Consent Procedures and Documentation—Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent and Assent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent and assent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent / assent document

prior to any procedures being done specifically for the study. The participants may withdraw consent or assent at any time throughout the course of the trial. A copy of the informed consent / assent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

1.12.4 Participant and Data Confidentiality

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the UK Data Repository and on password protected CD. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical personnel and CCTS research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the UK Data Repository.

1.12.4.1 Research Use of Stored Human Samples, Specimens, or Data—The investigator will assure that subject's anonymity will be maintained. On CRFs or other documents submitted for analysis, subjects will not be identified by their names, but by an identification code. The investigator will keep a separate log of subjects' codes and names.

The data from this study may be used for additional analysis, but it will be coded or blinded data. Data collected for this study will be analyzed and stored by Investigator. After the study is completed, the de-identified, archived data will be transmitted to and stored at the Investigator/Sponsor's lab, under the supervision of PI, for use by other researchers including those outside of the study. Permission to transmit de-identified raw data to the designated UK data repository will be included in the informed consent.

1.12.5 Future Use of Stored Specimens

Not applicable.

1.13 Data Handling and Record Keeping

1.13.1 Data Collection and Management Responsibilities

All data will be entered on CRFs at each examination, reviewed and verified. To ensure accurate, complete, and reliable data, Investigator/Sponsor will do the following:

- Provide instructional material to study sites, as appropriate
- Sponsor a start-up training session to instruct the investigators and study coordinators. This session will give instruction on the protocol, how to complete the CRFs, and study procedures.
- Periodic visits will be made to the study site
- Be available for consultation and stay in contact with study site personnel by mail, telephone, and/or fax
- Review and evaluate CRF data using standard computer algorithms to detect errors in data collection
- Conduct a quality review of the data base

To ensure the safety of participants in the study, and to ensure accurate complete, and reliable data, the investigator will keep records including clinical notes, and subject medical records in the subject fields as original source documents for the study. If requested the investigator will provide the sponsor, applicable regulatory agencies, and applicable IRB with direct access to original source documents.

Copies of the electronic CRF (eCRF) will be provided for use as source documents and maintained for recording data for each participant enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's official electronic study record.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) will be entered into a file on Google Drive, a data capture system. Clinical data will be entered directly from the source documents, if necessary.

This project will also use the multi-tenant infrastructure cloud provided by Google. The inclusion criteria will limit subjects to those who are already using Google services. Data, such as drug and study compliance logs and subject evaluation questions, will be uploaded to a secured Google Drive web page which uses Secure Sockets Layer for transmission and shared with Dr. Robert Lodder by the subject. The security and privacy controls are basically the same for everyone, with a few variations like two factor authentication. (The TVG project can only be accessed with two factor authentication on, but individual subjects have the option of using two factor authentication or leaving it turned off for their own data). 21 CFR part 11 compliance is gained by a business associate agreement with Google, by designing our security controls to interface with those specified by the agreement with Google, and by following our SOP's (built around 21 CFR part 11 compliance).

1.13.2 Study Records Retention

In order to comply with HIPAA requirements, IRBs generally require investigators to retain research records for six years after completion of the study⁵⁰. However, most FDA regulations require records be kept at least 2 years post-marketing approval, which could be as long as 10–15 years in this particular case. Therefore, records will be kept minimally 6 years but possibly up to 15 years by the Sponsor/Investigator. Records, which are expected to be only electronic, will be maintained in a secure fashion with limited access, including additional controls to ensure password protection, authenticity, integrity, confidentiality of electronic records.

1.13.3 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol or GCP requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

- Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- Quality Assurance and Quality Control, section 5.1.1
- Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site to use continuous vigilance to identify and report deviations within 7 working days of identification of the protocol deviation, or within 7 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents, reported to PI. Protocol deviations must be sent to the local IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements.

1.13.4 Publication and Data Sharing Policy

This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE policy, and the Section 801 of the Food and Drug Administration Amendments Act of 2007, requires that all clinical trials be registered in a public trials registry such

as [ClinicalTrials.gov](https://www.clinicaltrials.gov), which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. For interventional clinical trials performed under NIH IC grants and cooperative agreements, it is the grantee's responsibility to register the trial in an acceptable registry, so the research results may be considered for publication in ICMJE member journals. The ICMJE does not review specific studies to determine whether registration is necessary; instead, the committee recommends that researchers who have questions about the need to register err on the side of registration or consult the editorial office of the journal in which they wish to publish.

1.14 Study Administration

1.14.1 Study Leadership

The Steering Committee will govern the conduct of the study. The Steering Committee will be composed of the Study PI, Co-Investigators, and Medical Investigators. The Steering Committee will meet in person as needed.

1.15 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. The study leadership as well as the University of Kentucky has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest. However, there are currently no conflicts of interest to disclose at this time among study leadership members.

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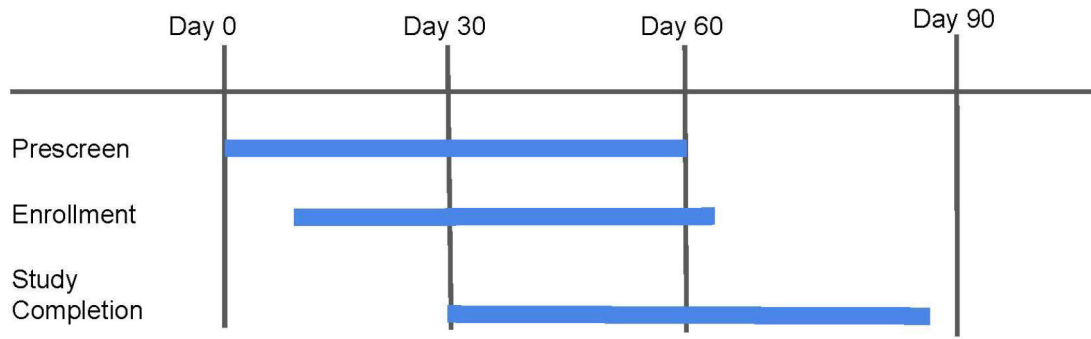


Figure 1 -
Therapeutic Video Games Pilot Study Timeline

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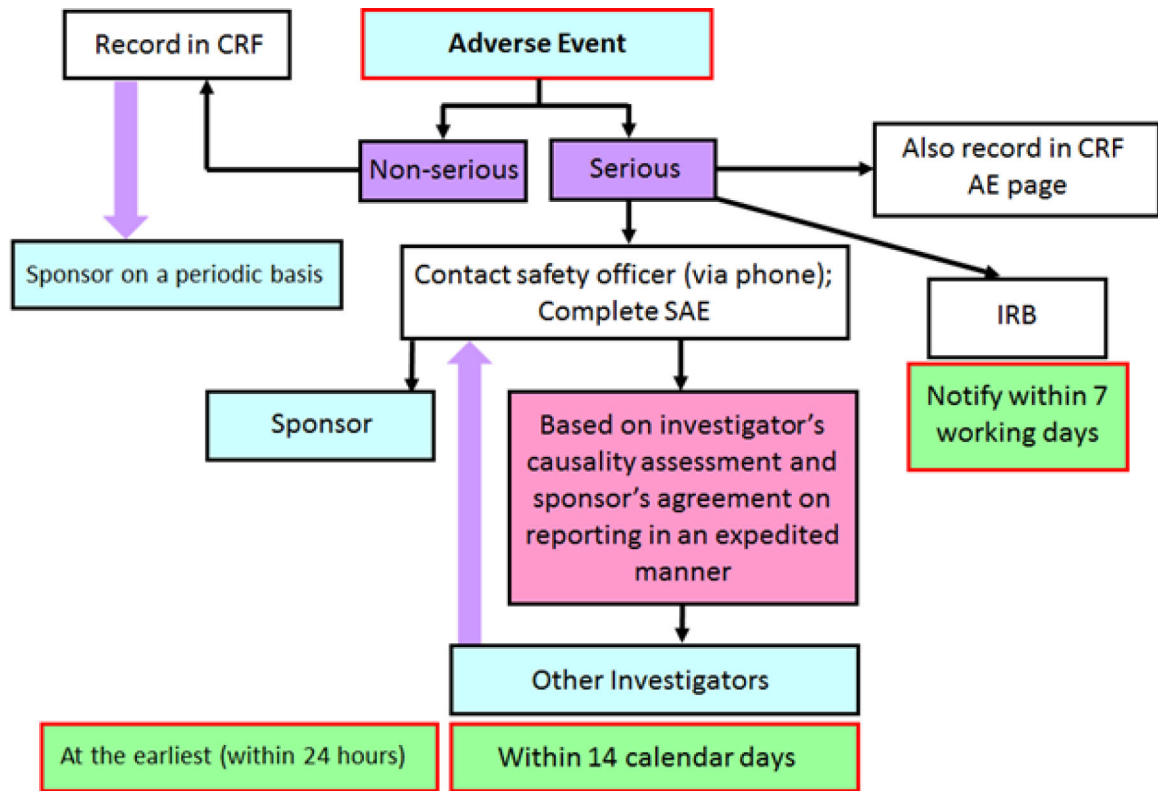


Figure 2 -
Therapeutic Video Games Pilot Study Timeline

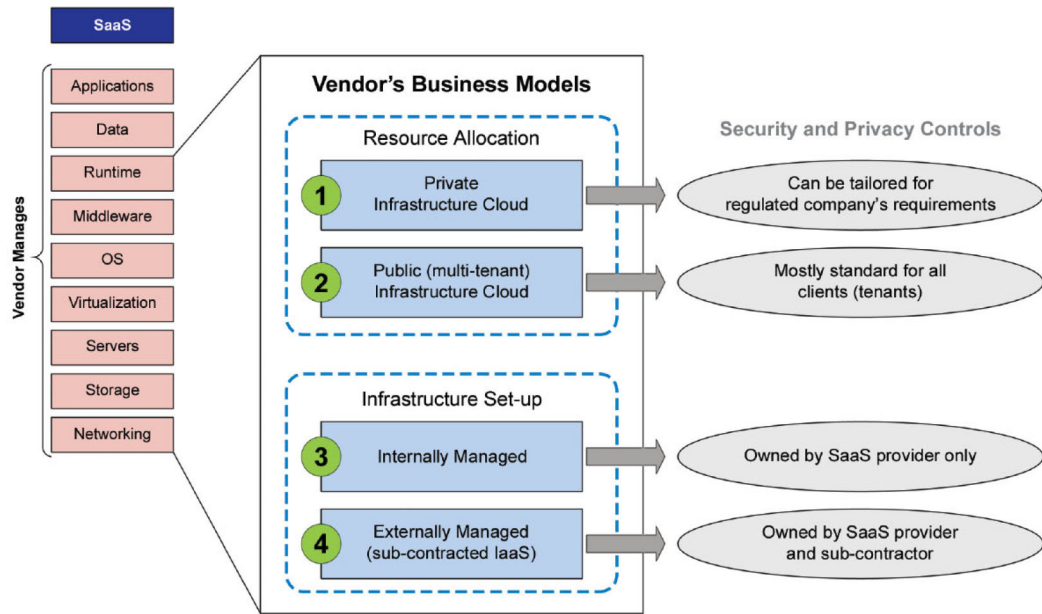


Figure 3 -
Software as a Service (SaaS) Vendor Model

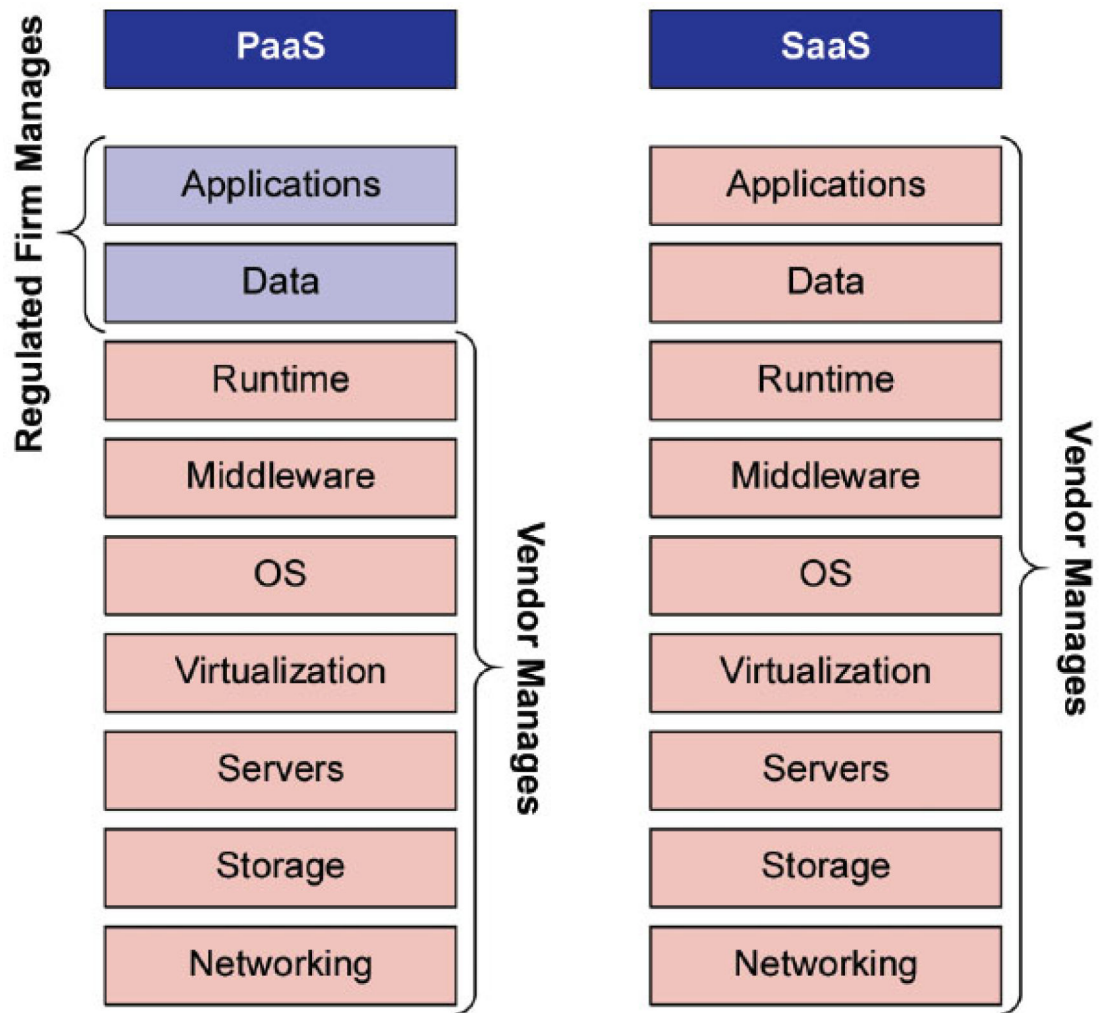


Figure 4 -
Platform as a Service (Paas) Vs. Software as a Service (Saas) Vendor Model

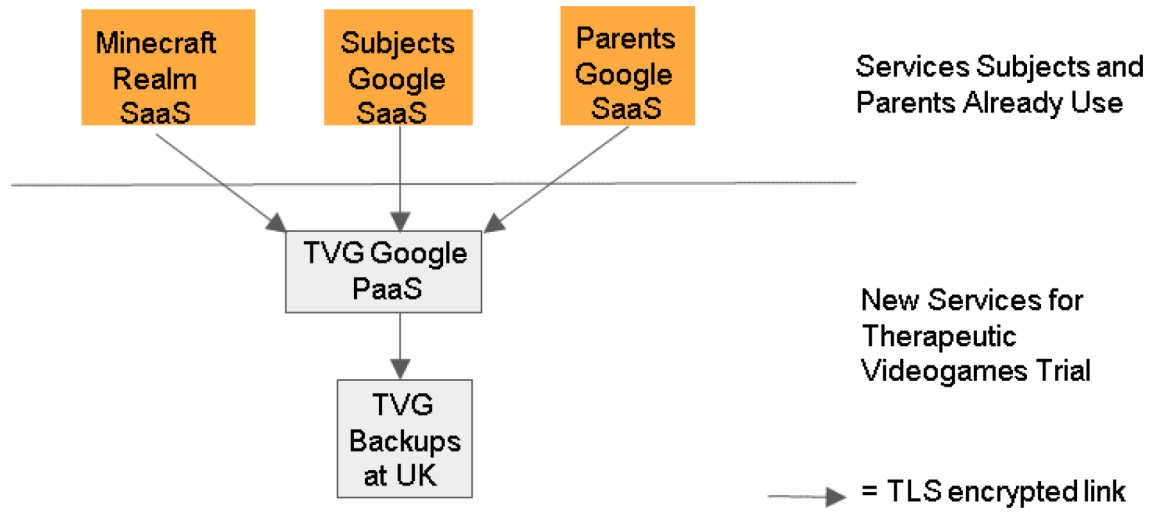


Figure 5 - Service Models for Therapeutic Video Games Pilot Study

Table 1 -

Schedule of Events in Therapeutic Video Games Pilot Study

Event	Visit 1 Screening	Enrollment	Final Visit
Registration	x		
Schedule Visit (Terminal)		x	
Informed Consent/Assent	x		
Medical History	x		
Demographics	x		
Previous & Concomitant Medication interview	x	x	x
Review Inclusion/Exclusion criteria	x	x	
Dispense questionnaire tests (ADHD assessment)	x		x
Education materials-collect questionnaires	x		x
Randomize participants		x	
CRF enter and Transmit	x	x	x

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