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Clinical Trials Re-spec: The Role of Games and Gamification in the Future of Clinical Trials

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***Abstract*— This article explores the use and potential of games and gamification in clinical trials. Case examples of games used in three contextual areas are presented: education about clinical trials to encourage consideration of trial participation; the use of games to measure objective health outcomes; and the use of gamification approaches to drive positive patient compliance behavior and reduce unnecessary withdrawals during clinical studies. It is concluded that the use of gamification to enhance compliance and retention offers great potential. Games to measure health outcomes offer particular value in niche indications, but their universal applicability needs to be especially considered if they are to be used in non-supervised settings.**

Keywords—clinical trials; serious video games; health; education; engagement; gamification

I. Introduction

Over the past two decades, clinical development programs have become increasingly complex, involved more clinical trials with higher numbers of patients, each including a greater volume and variety of assessments and clinical procedures and operating with a larger global footprint. This has been associated with spiraling costs. Developing a new drug can take around 12 years from patent application at a cost of $1.4 billion in direct costs ($2.6 billion in capitalized costs) [1].

Within this picture, the pharmaceutical industry recognizes the challenges of recruiting and retaining patients in clinical trials. Today 80% of studies fail to meet their recruitment timelines, and 30% of study sites fail to recruit a single patient. Gartner, in a study on clinical trial performance, estimated that a day of drug development costs a sponsor $37,000 in operational costs, with opportunity costs for delayed drugs ranging from $600,000 to $8 million per day [2]. While most patients enroll in clinical studies for altruistic reasons, many are not aware of the opportunity to participate in studies or have false perceptions concerning participation that prevent them from finding out more about potential study participation.

In addition to recruiting patients, keeping subjects engaged in study participation is vitally important to the success of a trial. Studies typically experience dropout rates ranging from 15 to 40%. Many withdrawals are due to loss of interest or engagement with the study, or finding study participation too burdensome, as opposed to health concerns such as side effects. Withdrawals can undermine the integrity of the trial results due to insufficient outcomes data. In 2014, the US FDA declined to approve an application for the wider use of Xarelto, a blood clot preventing medication, as the evidence from trials was not strong enough due to the quantity of missing data due to patient withdrawals [3].

For these reasons, pharmaceutical companies are considering approaches to make clinical trial participation more convenient and patient centric. One such approach, and the topic of this article, is the use of games and gamification to provide a more fun, interactive and engaging experience, to encourage patient recruitment and retention while collecting vital data and information that can be used to measure the effects of drug treatment. This paper considers three areas of application, reviewing approaches that have been used or piloted in clinical trials: patient education about clinical trials, using games to measure health outcomes, and using gamification concepts to increase patient engagement.

II. Video Games for Patient Education

A survey of almost 6,000 cancer patients conducted in 2000 found that 85% were either unaware or unsure that participating in a clinical trial was an option [4]. Of those aware of clinical trial opportunities, common reasons for not participating included: the belief that clinical trial treatment would be less effective than standard care, concerns about being treated like a guinea pig, and not having enough information.

Games provide a fun and engaging approach to learning and have been used to provide information about clinical trial participation with an aim to helping users understand common reasons for and against participation, dispelling myths about clinical research, understanding the purpose of clinical trials and what is involved in participation, and knowing the benefits and drawbacks of participating. A study including 55 patients showed that using interactive media improves comprehension of research study procedures and risks [5]. Providing information that is consumed effectively enables objective decision making by patients should they be invited to participate in a research study, and this better qualification may also lead to improved patient engagement throughout the trial. Two examples of game solutions for clinical trial education

which have been used locally by the owning research institutions are described below.

A. *The Paper Kingdom*

One example, The Paper Kingdom, is a unique educational role playing video game developed by New England Research Institutes, MA, USA, funded by the US National Heart, Lung, and Blood Institute, and produced by Wisdom Tools [6]. The aim of the game is to alleviate fears that children and their parents may have about participating in a clinical trial. It helps to educate why clinical research is important, and addresses common concerns with participation.

The game, aimed at 8 to 14 year olds, commences with the player being transported into a book entitled "The Paper Kingdom". The player needs to rescue their brother from this fantasy world, who has escaped into the book so that he does not need to take his medicine. The player follows their brother into the book to embark on an adventure to rescue him and learn about his fears and to teach him about clinical trials. The game player must navigate a virtual world and collect weapons and armor to defeat dragons and rescue the citizens of the kingdom, including their lost brother (Fig. 1). Each dragon encountered represents a fear or myth about clinical research which the user defeats to discover a realistic perspective through their mission. Quests in the game teach about such topics as confidentiality, ability to say no, what is and is not part of a study, peer or parental pressure, and why clinical research is important.

Fig. 1. The Paper Kingdom, reproduced with permission of New England Research Institutes, Inc., Watertown, MA, USA.

A study in 250 children aged 8 to 14 years old comparing knowledge learnt between a paper information sheet and The Paper Kingdom game, showed that while users of the video game increased their knowledge, the control group was superior and it is unclear whether this format can be used more effectively than more traditional approaches [7].

This is an engaging approach targeted at children. Clinical trials in children are increasingly important as the way medicines are absorbed, distributed, metabolized and eliminated can be markedly different between adults and children.

B. *Clinical Trial Simulator*

A second example produced by the UK National Institute for Health Research's Clinical Research Network uses a retro-style low-resolution graphics similar to the Nintendo Super Mario Bros. game released in 1985. For this reason it may have particular appeal to an older demographic that grew up with these games, although its ease of use and educational level will be suitable for all.

In this game, the player enrolls on a study of a test drug that is intended to make people fly. As opposed to a fantasy, this game steps through and explains all the processes involved in a clinical trial through sequential gameplay segments, at each stage providing additional information about what might happen in a real clinical trial. As the player continues through the game, they go through an initial screening visit, take their first treatment and allow the doctor to test how the treatment is working for them. During this process, the game provides information to help the player understand technical clinical trial terminology such as blind trial, standard of care and control group. At the end of the game the player is asked if they would consider being part of a research study in the future. In 2013, it was estimated that 90% of the few hundred players that had accessed the game had responded positively to this question [8].

These examples show that Interactive game-based technologies can provide an engaging environment to deliver information and provide education, and potentially remove some of the fear and uncertainty concerning participating in clinical trials. This may provide the opportunity to create better informed trial participants with associated reduced dropouts, and may lead to increased participation in clinical trials.

III. Games to Measure Health Outcomes

A. *Cognitive Function Testing*

While some drugs are developed to have an intended effect on cognitive function – for example in Alzheimer's disease – it is important to understand the effects of all medications on cognitive function as this can affect the labelling of new medicines. For example, warnings may be required relating to driving or operating heavy machinery. Cognitive effects in clinical trials are traditionally measured in laboratory conditions using a battery of tests delivered on a computer. The CDR system [9] is a good example, and uses a simple response interface comprising a unit housing "Yes" and "No" buttons. Tests on this system typically include measurement of:

- Reaction times including simple reaction time (the speed of reaction to a single stimulus – for example, pressing the "Yes" button when prompted) and choice reaction time (where different actions are requested to different stimuli , requiring more processing before reacting – for example, pressing the "Yes" or the "No" button depending on the stimulus).
- Working memory such as immediate word or picture recognition – being presented with a list of words or pictures, and identifying if subsequent items were members of the original list.

- Episodic secondary memory such as delayed word or picture recognition (identifying words or pictures presented earlier in the test battery, after completing other tests).
- Spatial working memory, for example highlighting four squares in a 3x3 grid and presenting the user with a random sequence of individual highlighted windows and requesting the user to identify whether each was one of the original four.
- Executive function using for example a digit vigilance test where a target number needs to be identified from a sequence of numbers rapidly displayed.

In each test, speed and accuracy are typically measured.

More recently, similar concepts have been introduced into gaming scenarios where similar aspects of reaction time, memory and problem solving can be measured within the context of gameplay as opposed to within a battery of discrete tests.

Project:Evo is a game application developed by Akili Interactive Labs that can be used to measure and improve interference processing, a key component of executive function. The premise of the game, which operates on mobile phones and tablets, is to provide an environment where a player's ability to process out distractions during the focused conduct of a specific action can be assessed and measured. It is intended to be an engaging alternative to conventional cognitive test batteries. During the short gameplay sessions, players navigate a floating platform at speed around a course, using concentration and reactions to avoid collisions with the sides. At the same time, they need to deal with distractions appropriately – tapping certain types and ignoring others, without crashing the float. Elements of speed, control and sensitivity adapt continuously during gameplay, and based on how well players are performing and processing the interference of distracting objects, the level of interference increases driving the user to process more and more interference as they are able to.

The Project:EVO game platform is currently being tested in a variety of clinical studies in multiple patient populations around the globe, including ADHD, autism, depression, and traumatic brain injury. Pfizer, for example, has recently funded a study to determine if the game can be used as a biomarker to enable the selection and longitudinal assessment of Alzheimer's patients in clinical trials [10]. Shire is also funding investigations on the use of the game in ADHD clinical trials.

In another example, Cogcubed have developed a game outside the traditional video game environment by using Sifteo intelligent cubes. The cubes, 1.5 inch blocks, connect wirelessly to a computer and contain a color LCD display that is able to represent game elements. A tri-axial accelerometer within each cube detects movement, shaking, rotating and flipping – movements which control game actions. The cubes also contain near-field object-sensing technology which enables the game technology to identify when cubes have been placed against each other. One of the game applications develop by Cogcubed, Groundskeeper, uses a set of four Sifteo cubes to present a game that can be used as an assessment tool for executive functioning deficits such as ADHD. The game, which can last 30 minutes moving through 16 progressive levels, presents a variety of randomly changing images on three of the cubes with the fourth cube being the game control piece held by the user. The images presented on the three play cubes alternate between an empty golf course, a variety of animals and the groundskeeper himself. The image on the control piece can be alternated by shaking. When gopher images appear on the play cubes, the user needs to select the hammer on the control piece and place that cube against the one containing the gopher. As with other games that measure aspects of cognition, simple and choice reaction times can be measured in addition to the accuracy of gameplay. The game is able to assess performance with increasing distractions as the game progresses through its levels. By measuring aspects of attention and distractibility, Groundskeeper has been used to predict the likelihood of having symptoms associated with disorders like ADHD in children and adolescents by comparing patterns of responses produced by players in the game to clinical benchmarks. The game may also provide objective measurement of treatment related effects in clinical trials of treatments for these conditions.

B. *Measuring Movement and Mobility*

The advent of motion-based games has brought with it the opportunity to use the same technology to assess motion and mobility in patients, in addition to their use in rehabilitation. One example, the ACTIVE-Seated (Abilities Captured through Interactive Video-based Evaluation) application uses the Microsoft Kinect gaming interface to gather positional information about an individual's upper extremity movement to determine functional reaching volume, velocity of movement, and rate of fatigue while playing an engaging video game.

Fig. 2. The ACTIVE-Seated application, reproduced with permission of Nationwide Children's Hospital, Columbus, Ohio, USA.

The game, in which the player must search for gems within a cave, requires the player to use their arm movements to squash spiders and collect gems when navigating a passageway. The further a user reaches in each direction, the more gems they are able to collect. The game measures maximal reach overhead, side-to-side, and forward to quantify reachable space while the player remains seated at a table and facing a video screen (Fig. 2). Early published studies have indicated the promise of the game in making reliable and valid measurement of the furthest arm excursion in subjects with

muscular dystrophy. Individuals with muscular dystrophy undergo progressive loss of muscle strength and function across their lifespan, and the seated game has enabled the development of an objective outcome measure in patients unable to walk. Current upper extremity evaluation tools fail to fully capture changes in upper extremity strength and function across the disease spectrum as they tend to focus solely on distal ability [11]. Additionally, the competitive element of the game format encourages repeatable, maximum effort each time the game is played, and therefore provides a valuable objective assessment for longitudinal tracking.

IV. Gamification to Increase Patient Engagement

Gamification aims to increase engagement in a task, or knowledge about a subject, by appealing to our basic curiosity, our response to challenges, and our sense of fun. Gamification involves the use of video game elements to improve user experience and user engagement in non-games services and applications [12]. It applies game-design ideas to non-game applications to make them more fun and engaging. Most commonly, gamification has been seen in consumer marketing as a means to increase engagement and drive behavior by encouraging increased service use, for example through loyalty schemes such as store loyalty programs and frequent flyer miles. Commercial vendors now offer gamification as a service layer that can be integrated with other applications and can associate reward and reputation with points, badges, levels and leader boards (for example Badgeville, BigDoor, Bunchball and Funifier).

Some gamified approaches have involved leveraging the collective power of an engaged online community. One such example is Foldit (University of Washington, WA), an online game in which users attempt to fold amino acid strings to create the configuration of selected protein molecules. This competitive puzzle combines the engagement of a fulfilling problem-solving game with further gamification and motivational elements including rewards (points and status), social praise (chats and forums), the ability to work individually or as a team, and the connection between the game and scientific outcomes [13].

Gamification is able to drive behavior because it leverages the motivational drivers of human behavior through reinforcements and emotions [14]. Through these motivational mechanisms it is possible to elicit outcomes that become habits, ultimately requiring less concerted effort by the user as the desired behavior is repeatedly reinforced [15].

Hamari et al. [16] identify the components of gamification as “motivational affordances” (such as points awarded) leading to psychological outcomes (such as satisfaction), which in turn lead to the targeted behavioral outcomes. Motivational affordances aimed at driving behavior change in gamification approaches typically involve aspects of reward, feedback, reputation and loss aversion. In the context of a clinical trial, the behavioral outcomes sought include completion of the study, compliance with the study requirements (such as timely completion of symptom diaries) and following study procedures (such as attending clinic visits and adhering to medication regimens). In their review of studies on gamification, Hamari et al. identified the award of points and badges and the publication of leaderboards as the most commonly employed techniques [16].

In clinical trials, gamification is being explored as an approach to providing more engaging patient-facing applications, but more specifically as part of stand-alone applications that can connect with the patient to drive positive behavior and encourage continued participation and compliance with study requirements. Many studies provide smartphone apps to patients for collection of symptom diary data between clinic visits. There is a growing move to use this same approach to provide greater engagement with the patient between clinic visits and to encourage greater continued interest, retention and compliant behavior.

Gamification approaches include allocating virtual rewards based on positive actions and behaviors exhibited by the patient – for example, reading a study information message or completing a diary entry on time. Virtual rewards may take the form of points, badges or levels that the patient is able to achieve, and this drives their competitive behavior to achieve more by continuing with the activities that generate rewards.

One example, TrialsConnect (www.trialsconnect.com) uses a fun reward game to encourage patient engagement by enabling a flower to grow and bloom every time they read an article, take medication, finish a visit or enter symptom diary data. Starting with a sleeping seed, the accumulation of rewards sees the seed open its eyes, begin to shoot, develop a leaf and a flower head, and ultimately grow a collection of petals in a fully developed flower. Only by completing tasks as required can the flower fully develop in this way. Such patient engagement apps also routinely contain reference information sources of value to the patient during their trial participation, such as information about the study and the dates and times of forthcoming clinic appointments.

As ethical restrictions generally prohibit the payment of patients in clinical trials (healthy volunteers can often receive payment as they are unlikely to receive benefit from treatment, but patients generally only receive reimbursement for expenses such as travel to and from the clinic) it has not been possible to translate extrinsic motivators such as virtual points awarded into material rewards for the patient. However, donations to charity have been connected to points earned by individual patients in recent clinical trials. Because the most common reason given for participation in a clinical trial is helping others with the condition, donations to a treatment-related charity is considered an additional motivator for patients to participate with a gamified engagement strategy. In addition, confidentiality regulations would prohibit the publishing of patient names on leaderboards, if used, although it would be possible to show a patient their position relative to other unnamed participants.

CyberDoctor LLC, Mountain View, CA, USA, has produced a story-driven game within a smartphone app that enables players to pick a character and make choices for them, understand the impact of those choices on health outcomes, and translate these into personal healthcare decisions. Used in routine care, the approach shows how a gamified solution can provide an engaging way to improve medication adherence without providing medication reminders. In a study of 100 non-compliant diabetic patients the PatientPartner approach

was shown to increase medication adherence from 58% to 95%, which resulted in an associated improvement in health outcomes [17]. In a clinical trial setting, this solution could help to ensure that all patients achieve high levels of compliance with the drug or therapy being tested.

V. Discussion

A. Patient Education

Interactive game-based learning may be a particularly effective approach for the millennials and generation Z. Van Eck describes the current "Net Generation" as disengaged with traditional instruction [18]. He expands that "they require multiple streams of information, prefer inductive reasoning, want frequent and quick interactions with content, and have exceptional visual literacy skills – characteristics that are all matched well with digital game-based learning." This suggests that for information transfer and education about clinical research and specific clinical trials, a gaming environment may be particularly effective for children, adolescents and younger adults as it connects well with a learning style they find optimal. This is not to say that games may not provide effective learning in older subjects. The Clinical Trial Simulator was designed in retro-style that may particularly appeal to those who were playing such games in the mid-1980s.

Van Eck further suggests that "learning that occurs in meaningful and relevant contexts is more effective than learning that occurs outside these contexts" [18]. The Clinical Trial Simulator is a game that uses the virtual experience of participating in a clinical trial to provide learning about participation in a true study. This tangible connection between the game context and the learning objective is likely to provide successful learning outcomes. However, the context of a clinical trial may not be a compelling subject for a highly engaging game. The Paper Kingdom, conversely, uses a fantasy adventure game environment with higher resolution graphics to provide a more engaging game scenario. The detachment of the learning topic from the context of the game – the dragons represent fears or objections about clinical research which when slayed provide a balanced view which is presented as a message that the player can read – may, however, mean that a user may be able to detach the completion of the adventure from reading and absorbing the educational messages. It is possible that messages could be skipped over in an eagerness to complete the adventure, as the message detail itself is not needed to complete the quest. While both games appear to meet the objective of providing learning, it is unclear which approach would be most effective, and whether either approach would be effective and suitable in older users. While the amount of learning was no better than that achieved from a paper information sheet for Paper Kingdom [7], it is not known whether more patients might elect to learn using the game as opposed to receipt of an information sheet if given the choice. Alternative approaches such as eLearning may be equally effective in providing an engaging and interactive environment to provide learning across a wide demographic.

B. Health Outcomes

Clinical Trials are often employed across a broad range of ages and diverse cultural groups. The ability of games to apply across a broad demographic is therefore important for their use in clinical trials. The Entertainment Software Association report that there is no longer a stereotypical game player, but that people of all ages play video games. In 2014, they reported that 59% of Americans play video games, the average age of game players was 31 years with 29% and 39% of players under 18 years and above 35 years old respectively, and 48% of game players were female [19]. Not all authors share such an inclusive view. In his book "Video Gamers", Garry Crawford suggests that such surveys may present an inflated view designed to meet an industry agenda [20], and Martin et al. report only 20% of the Spanish population play games [21]. In clinical trials, it is important that instruments used to collect data describing treatment-related effects can be applied consistently across the population studied, and often across a program of trials on a single treatment. For this reason, universal acceptability and utility is important. Many clinical trial programs apply to a wide age range of patients and involve participants from many different countries, languages and cultures. This may limit the utility of some video games to measure treatment effects, in particular games designed for non-supervised use at home.

However, game environments provide unique opportunities to capture objective data describing aspects of treatment-related effects that are difficult using traditional approaches. The use of motion-based gaming approaches offers huge potential in measuring aspects of movement and mobility that may be important in certain disease indications, for example the ACTIVE-Seated game in measurement of arm movement in wheelchair-bound muscular dystrophy patients. The use of motion-based games in providing an engaging approach to rehabilitation exercise has already been reported, for example use of the Wii console in stroke rehabilitation (see [22] and [23], for example). Such approaches, while encouraging specific exercises to improve movement and long-term outcomes through a game scenario, can in the same way measure the degree of movement observed and enable its tracking over time – a property valuable in controlled trials investigating treatment-related effects.

Games equally provide compelling environments to measure aspects of cognition. The presentation though a computerized media enables the accurate measurement of vital performance parameters such as reaction speeds, memory, accuracy and concentration. Videogames may provide unique opportunities to measure aspects of cognition that are less easily measured by traditional test batteries. The two games reviewed in this article, Project:Evo and Groundskeeper, use the richness of a game environment to enable interference performance with increasing levels of distraction to be measured – valuable in certain conditions such as ADHD, autism, depression and traumatic brain injury. Cognitive function tests rely on population data to provide context for disease-specific and age-specific deteriorations, and home-accessed web-based games uniquely enable large banks of normative data to be collected rapidly using crowdsourcing approaches. Lumosity (Lumos Labs Inc., San Francisco, USA, www.lumosity.com), for example, have developed a normative

dataset online from over 45 million users and over 1 billion game plays for their web-based brain performance test.

C. Patient Engagement

Perhaps the widest opportunity for games in clinical trials is in the execution of patient retention solutions. Retention and compliance is a concern for the majority of clinical studies, independent of the nature of the patient population studied. Gamification provides an engaging approach to drive behavior and increase motivation, and early experience suggests that gamified engagement apps may provide an effective means to increase patient compliance and reduce unnecessary study withdrawal – thus leading to a greater quantity of evaluable outcomes data.

VI. Summary

While the use of serious video games and gamification in clinical trials is in its infancy, their use in related aspects of health and wellness, and current examples of games developed specifically for clinical trials, is encouraging and worthy of continued research and development.

In particular, the wealth of developments in the use of serious games in healthcare, in particular in brain wellness and cognition, and in providing more engaging approaches to deliver rehabilitation, offer particular opportunity to use the same approaches to facilitate measurement of objective health outcomes measures that may provide a means of assessing the effects of drug treatment. Game developers may consider the development of numeric measures of change in addition to the delivery of game-based activities and tests. Self-review of such outcomes measures may provide additional patient motivation. While more research will be required to ensure that game-based outcomes measures are valid and have clinical relevance, their potential to enhancing the experience of participating in a clinical trial, and as a means of collecting novel endpoint data is evidenced by the examples reviewed in this paper.

While highly regulated, the pharmaceutical industry remains actively interested in applying innovative approaches that improve the operation of clinical trials and the thorough understanding of treatment effects. Video games and gamification remain an industry interest area where more exploration, development and examples of successful application are needed to drive their potential adoption.

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