Specific Aims

Three to five million people suffer from Parkinson's disease in India, a country with only around 1,100 neurologists.[1] Due to their sheer numbers and distribution, lack of awareness, and the prohibitive cost of seeing a doctor, most of these people will never see a neurologist, let alone one specializing in movement disorders. Reaching out to these people to collect data on their condition is critical for better understanding the prevalence of the disease, its context and the variation in symptoms. Current information about prevalence is based primarily on door-to-door surveys in a limited sample of people.[2] With the widespread use of mobile phones throughout India, there is an opportunity to gather data from potentially millions with the disease. India ranks third in the world in the number of smartphone users, estimated at 117 million, and has a penetration rate of more than 10% per year.[3]

The most commonly used scale in the clinical study of Parkinson's disease is the Unified Parkinson's Disease Rating Scale (UPDRS).[4] While the Movement Disorder Society's version of the UPDRS consists of a set of well-validated questions covering different categories of symptoms, these questions are written in English. To make these questions accessible to anyone in the world means representing the questions in a universal way. A rating scale consisting of pictures rather than text has the potential to be understood by billions of people, and through widespread mobile devices, has the potential to reach hundreds of millions. This would empower people in India with Parkinson's to be better informed and to engage in research. It would also empower researchers, who would be able to engage vastly greater number of participants in a given study. We propose the following three aims to realize a universal, global survey instrument as part of a growing research collaboration between the U.S. and India:

Aim 1: To make the UPDRS universally intelligible across languages, cultures, and education levels, as well as intuitive and engaging, we will create a visual analog of the UPDRS, the "Visual Parkinson's Disease Rating Scale" (VPDRS). Our intent is for the VPDRS to enable more widespread, diverse, and consistent responses from Parkinson's patients, and to promote greater collaboration between Indian and U.S. researchers. We have experience creating visual taxonomies and administering the UPDRS to patients.

Aim 2: To improve the VPDRS visuals' comprehensibility and ability to serve as proxies for spoken versions of the UPDRS questions, we will evaluate them through clinical observations of English- and non-English-speaking patients and controls in India and the U.S. This evaluation will span the second year, where the VPDRS will evolve as it is iteratively validated against the UPDRS in new patients. During this time, this collaboration will establish common protocols for presentation and evaluation of the questionnaires and a shared understanding of the types of responses gathered from patients. VPDRS data will not be used to inform medical care, as the UPDRS will still be used as the primary assessment tool. Our team includes clinical experts in Parkinson's who have enrolled patients in the U.S. and in India.

Aim 3: To administer a consistent and widely accessible implementation of the VPDRS, we will deploy it on a mobile phone application, and store the data on server technology that we have developed and will establish in India for managing large-scale data collection from mobile devices in future studies. We will be able to take advantage of the experience we have gained from our iOS mobile phone application that captures sensor data and monitors variations in Parkinson's symptoms[5] and includes UPDRS questions.

Exploratory Aim 4: To facilitate future studies between Indian and U.S. collaborators, we will strive toward a better understanding of consent and research approval in each country. Over the course of the project we will hold governance/consent discussions across institutions, with a goal of incorporating our fully electronic consent process in the VPDRS app for future epidemiological studies. To ensure that our partners and others in India are able to build on this research, we will make all of our work open source and freely available, including the visual assets, the mobile app code base, and all research materials.

Upon completion of all the Aims, we intend to conduct epidemiological studies with our collaborators to better quantify Parkinson's prevalence, incidence rates, and symptom variations throughout India (current estimates are based on limited door-to-door surveys[2]). These studies could also gather demographic and ethnographic data to explore various potential factors in the etiology of Parkinson's and inform evidence-based policy in India. Further development of the mobile app to include capabilities of other apps we are piloting would enable us to correlate these surveys to sensor data captured by the phone. Another long-term goal of this project is to one day help triage patients at a vast scale, to ensure that those most in need receive treatment, alleviating the burden on doctors and hospitals.

(A) SIGNIFICANCE

Parkinson's in India:
The majority of the large population in India suffering from Parkinson's disease will never see a neurologist, due to the relative shortage of neurologists[1], lack of patient awareness, and the prohibitive cost of seeing a doctor. This is devastating for two reasons. First, if these patients are not properly diagnosed, the probability of their being properly treated is low, and the primary treatment, levadopa, could help many of these people to manage otherwise progressively crippling symptoms. Second, the data that could be garnered from these millions of people would help us better estimate the prevalence and incidence rates, which are known to vary significantly across India, from as low as 14 to 41 per 100,000 to one of the highest proportions in the world: 328 per 100,000 in Parsi communities,[6] and is believed to be twice as high in rural as in urban areas.[7] Without a clear understanding of the distribution of the disease and the severity of its symptoms, it is impossible to know how and where to best intervene. What is needed is a means of gathering data from vast populations to better understand the distribution of Parkinson's and the variation in its symptoms, ultimately to aid in its diagnosis, determination of symptom severity, and prediction of disease progression in individuals. *Toward these ends, we propose to create a novel system for enabling widespread collection of Parkinson's-related information.*

The MDS-UPDRS Parkinson's rating scale: A primary difficulty in gathering survey data from across India is the country's great diversity of cultures and languages, which makes it difficult to present a commonly intelligible set of questions. The most commonly used scale in the clinical study of Parkinson's disease throughout the world is the Movement Disorder Society's Unified Parkinson's Disease Rating Scale (MDS-UPDRS).[4] This scale consists of well validated, text-based questions covering different categories of symptoms. The original questions are written in English, and some groups have attempted to translate some of these questions into other languages, such as Hindi.[8,9] Translations are inherently imperfect, and the UPDRS has not been translated into most of the languages on the planet. And even if the UPDRS were translated into every language, there are vast numbers of people who cannot read well, let alone read a Parkinson's questionnaire, and having someone who reads well administer these questions verbally to those who don't read well is an unreasonable expectation across a large population. The ideal would be a universally intelligible set of questions, presented without text or audio, such as pictorial representations of the content of the questions. *We propose in Aim 1 to introduce just such a set of visual analogs to text-based survey questions -- the Visual Parkinson's Disease Rating Scale, or VPDRS. In Aim 2, we propose to ground this visual rating scale in the text-based UPDRS.*

Mobile phones to collect data: To get a representative sample of Parkinson's patients in India requires incredible outreach using conventional methods. For example attempts to gather data via door-to-door surveys is an extremely limited approach.[2] Mobile phones are becoming widely available in India, which is third in the world in the number of smartphone users, estimated at 117 million, after the U.S. and China, and has a penetration rate of more than 10% per year.[3] There is a huge range of devices from very basic, which support just calling and SMS (telephony services) to basic multimedia options, to middle-end and high-end smartphones. The scenario in rural India also varies from telephony devices to feature phones with modest multimedia capabilities with GPRS/data (for connecting with remote servers and the Internet), and basic smart phones are becoming more prevalent as well; people generally go for low-cost devices which have multimedia capabilities (for loading songs, films, etc.). The primary technologies include Java-enabled basic multimedia phones, Android, and Mobile Linux (from China), as well as CDMA phones. Android devices are the most obvious devices to target for epidemiological studies, given their low cost, technical capabilities, and increasing use, particularly in rural India. Their prices are going down, and currently range from Rs. 3000 ($50) to Rs. 6000 ($100). There are cheaper Chinese devices but they have their own proprietary platforms and are hard to develop applications for. *We propose in Aim 3 to implement our VPDRS questionnaire as an Android app for widespread accessibility across India, and indeed, the world. This will make it possible for us to later conduct the largest epidemiological study of Parkinson's disease.*

(B) INNOVATION

Aim 1 is innovative since it will introduce the world's *first universal visual representation of a neurological rating scale*. The VPDRS will construct visual icons and animations that correspond to the text questions in the UPDRS. Whereas attempts are currently underway to painstakingly translate the UPDRS into different languages[9], this Aim would introduce a universally intelligible representation of the questions that will span languages, cultures, and education levels. Another innovative aspect of this Aim is that we intend to transform the dry text of these questionnaires into a more visually engaging experience, necessary for keeping participants involved in a given study. This is critical since one of the goals of this proposal is to prepare for epidemiological studies where participants everywhere, not just those entering a hospital, would need to be enticed to use, and continue using, a mobile phone app implementation of the VPDRS.

Aim 2 consists of an evaluation study of the VPDRS. There are three innovative aspects to this Aim: (1) It will measure how closely the scores obtained using the visual analogs of the UPDRS questions correlate with the conventional text versions, *in an iterative manner*. That is, the evaluation study will be conducted in many stages, where the visuals will be improved at each stage for a new group of participants, while also presenting the revised questionnaires to the same participants. (2) For a given question, the effectiveness in conveying the question will be assessed for static icons as compared against moving stimuli (animations). (3) This will be the first study that directly compares UPDRS responses by Indian and U.S. participants.

Aim 3 takes the innovative approach of implementing both visual and textual rating scales in a mobile phone application, for consistent presentation and for later widespread use in epidemiological studies and monitoring of patients' health. A mobile phone implementation makes it possible to reach hundreds of millions of people compared with the extremely small number of patients who are administered the UPDRS by neurologists in the patient's primary language.

Exploratory Aim 4 will attempt to bring fully electronic consent to Indian research studies, which would herald a new era of conducting health research using mobile devices in that country.

(C) APPROACH

Aim 1: *To create a visual representation of the UPDRS questionnaire, the VPDRS*, we will attempt to simplify the UPDRS questionnaire by visually depicting the condition described in each question at differing degrees of severity. The MDS-UPDRS has four parts[4]:

> Part I (non-motor experiences of daily living), Part II (motor experiences of daily living, Part III (motor examination) and Part IV (motor complications). Part I has two components: IA concerns a number of behaviors that are assessed by the investigator with all pertinent information from patients and caregivers, and IB is completed by the patient with or without the aid of the caregiver, but independently of the investigator. These sections can, however, be reviewed by the rater to ensure that all questions are answered clearly and the rater can help explain any perceived ambiguities. Part II is designed to be a self-administered questionnaire like Part IB, but can be reviewed by the investigator to ensure completeness and clarity… Part III has instructions for the rater to give or demonstrate to the patient; it is completed by the rater. Part IV has instructions for the rater and also instructions to be read to the patient. This part integrates patient-derived information with the rater's clinical observations and judgments and is completed by the rater.

In this project, the VPDRS will encompass all self-administered questions of the MDS-UPDRS (Parts 1B and 2) and we will also make an attempt to include and evaluate clinically administered questions from Part 1A. We will construct two types of visuals for each question: a static graphic and a simple animation. We will create the static graphics as vector-based images and the simple animations as sequences of these images, and convert them to the format most suitable for presentation by the Android app.

The static graphic is intended to represent the condition described in the question using an iconic or cartoonish visual. For some of the questions, it will suffice to portray the condition outright, such as with problems with sleep, daytime sleepiness, eating, dressing, hygiene, etc. For behavioral or cognitive conditions that do not have a clearly outward expression, such as pain, light headedness, etc., we will employ the most universally intelligible semiotics in Indian and U.S. children's comic books and comic strips. And for questions related to motor activities, we will incorporate indicators of motion in the graphic. The principle advantage of the static graphic is that it places the lowest demands on the mobile device and should be viewable on even the lowest end Android devices.

The simple animation will consist of a two- or three-step sequence of pictures corresponding to the static graphics above. Animation can overcome potentially ambiguous semiotic cues. For example, movement can be directly represented as a moving sequence of images rather than with imaginary lines, arrows, blurring, or repeated images. Animations could also allow for the full screen to be used, by sequentially displaying the condition at different levels of severity rather than having to display all levels simultaneously, as is the case with the static graphic. We do not include video clips with real people and objects for four reasons: (1) video production of patients raises concerns we don't face with cartoons, (2) inclusion in an app would place the greatest demands on the mobile device, (3) videos richly represent their subject matter, which can result in distracting details that are avoided for clarity in cartoons (which can also more easily emphasize or exaggerate salient features), and (4) because of their realism, videos portray people and environments in ways that can be too culturally specific, another issue that is less relevant with cartoons.

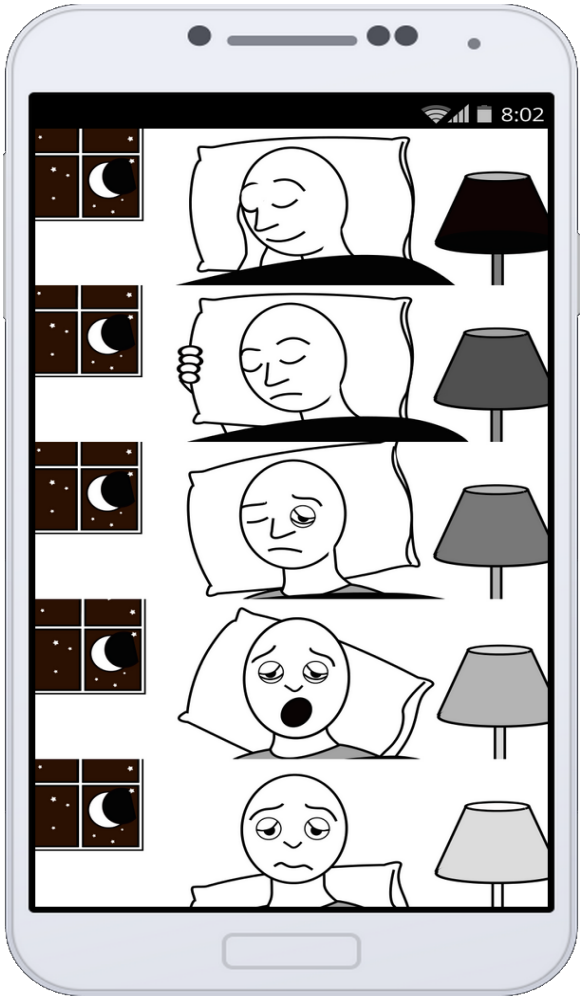


Fig.1. First pass at a VPDRS static graphic

Figure 1 corresponds to the first self-administered MDS-UPDRS question:

1.7 SLEEP PROBLEMS.

Over the past week, have you had trouble going to sleep at night or staying asleep through the night? Consider how rested you felt after waking up in the morning.

0: Normal: No problems.
1: Slight: Sleep problems are present but usually do not cause trouble getting a full night of sleep.
2: Mild: Sleep problems usually cause some difficulties getting a full night of sleep.
3: Moderate: Sleep problems cause a lot of difficulties getting a full night of sleep,
but I still usually sleep for more than half the night.
4: Severe: I usually do not sleep for most of the night."

Aim 2: *To evaluate the VPDRS*, we will have coordinators in two locations in India (government hospitals in New Delhi and in Hyderabad), and one coordinator in the U.S. administer both the UPDRS and VPDRS to Parkinson's patients and healthy controls. Our Indian coordinators on this proposal are Dr. Madhuri Behari, Professor of Neurology at the All India Institute of Medical Sciences in New Delhi, and Dr. Rupam Borgohain of the Department of Neurology at the Nizam's Institute of Medical Sciences in Hyderabad. Each of these coordinators see 30-40 patients each week, and many of these patients return every few months, so there is an opportunity not only to administer the UPDRS and VPDRS to thousands of patients over the course of the study, but also to conduct a longitudinal assessment of the evolving visual stimuli on some of the participants. Dr. Saloni Sharma, working with Dr. Karl Kieburtz at the Center for Human Experimental Therapeutics, University of Rochester Medical Center, NY, will serve as our U.S. coordinator for the evaluation study.

The evaluation study will undergo multiple stages. At each stage, the current set of visual stimuli in the VPDRS and the conventional UPDRS are presented to participants one question at a time. In the UPDRS, a participant responds to each question in the form of a numerical rating, or score, from zero to four indicating normal to severely impaired behavior. For the VPDRS, the participant responds to each question by selecting one of five images, corresponding to the 5-point scale. If the VPDRS score is similar to the corresponding UPDRS score for a given question, and this holds across the participants in the study, then we consider the VPDRS's visual representation to be a potential proxy for the textual UPDRS question. If, on the other hand, the correlation between participants' UPDRS and VPDRS scores for a given question is low, then we will update the visual stimulus and reassess it at the next stage of evaluation. Updating the visual will only occur after conferring with the coordinators, Parkinson's experts, and graphic designer colleagues. We will also explore the possibility of crowdsourcing interpretations of the visuals[10]. We will determine which type of presentation, static graphic or simple animation, works best for each question.

Aim 3: *To implement the VPDRS as a mobile phone app*, we will draw from our experience developing other health-related apps, using Node[11] to develop a new Android app. Our collaborator Solomon Abiola (see LoS) helped to develop an initial prototype (see Figure 2) based on one he tested for monitoring contagion event likelihoods, using real-time sensors and questionnaires with geolocation. As an epidemiological tool, it was successfully used with support from the NSF[12] for an Ebola study in Nigeria. He designed it to be adapted for various global health applications, and given the similar infrastructural limitations of India and Nigeria, we intend to adapt this app for use in assessing Parkinson's disease symptom severity through the UPDRS and VPDRS. The adapted version will be able to store the data locally on the phone and upload to a server (see below) when a data network is available.

Solomon will provide a licensed version of Node free for our research through a shared repository and collaborate as needed with ZMQ to improve the backend of the application to support our Bridge server (see below). The current prototype will support local saving and credentialing, in addition to the UPDRS questions. Additional work will be done by ZMQ: (1) to incorporate images with the UDPRS, (2) VPDRS and (3) add support for the application to upload data to the Bridge server. ZMQ will build upon the existing Node codebase by altering the code around the questionnaires to incorporate images. Upon successful prototyping, the database where the data are saved will be switched to the Bridge server. Following the successful implementation of an image enhanced version of the UPDRS application, a video layer will be added to the Node platform to support VPDRS animations.

Bridge server clone: Data collected using the app will be stored on a clone of the Bridge[13] server-side technology developed by Sage Bionetworks to be built in India. Bridge is designed to support the design and execution of adaptive clinical trials delivered through smartphone platforms. Participants in a study interact with the Bridge server through an app which is custom designed for each particular study. The Bridge server provides a way to configure a study with a set of survey questions to ask study participants and way to schedule times for the various survey and app data collection tasks to run. Storing this configuration on the server allows researchers to dynamically adjust the study as data are collected without distributing new builds of the app to participants. The Bridge server provides services for study participants to create an account, authenticate, and manage informed consent to participate in a research study. The app will periodically save survey and sensor measurements to the server; client-side SDKs help manage transmission of his/her data over intermittent mobile network connections. Study data are stored separately from readily identifiable user account data so that study participants can be de-identified and the data shared, while protecting their anonymity.

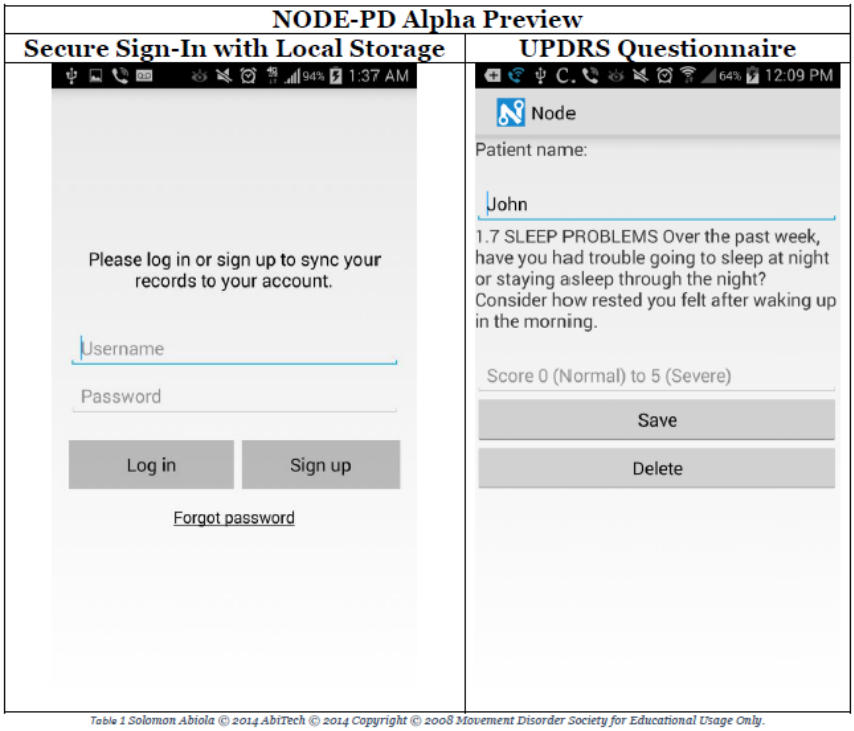


Table 1 Solomon Abiola © 2014 AbiTech © 2014 Copyright © 2008 Movement Disorder Society for Educational Usage Only.

Fig.2. Prototype for the mobile phone app

This screen shows a pre-release version of Node, which will support the VPDRS/UPDRS modules. Here we present a means by which a person administering a questionnaire can securely log into and manipulate patient information locally and through cloud services and lastly an example clinician-administered UPDRS question.

Exploratory Aim 4: We will introduce the Indian collaborators to Sage Bionetwork's e-consent process through demonstrations of Sage's iOS Parkinson app and teleconference discussions with Sage's governance team (see below). Our iOS Parkinson app includes an electronic consent process Sage developed that assists participants in their understanding of what they are getting into by taking part in the study. Our e-consent process is the first fully electronic consent process used in a Parkinson's disease study conducted on a mobile device, and would be useful to incorporate in the VPDRS app for future epidemiological studies.

Preliminary studies:

Mobile phone apps in India: Our software engineering partner, ZMQ Software Systems, has significant experience developing graphics, animated content, and small videos for Android devices in rural projects throughout India. As a Technology for Development Company, ZMQ has developed various mHealth technology solutions in India and Africa, especially for low-resource settings. Some recent projects include:

1. **MIRA Channel** - Women Mobile Lifeline Channel for improving maternal and child health in rural India (http://www.MiraChannel.org)
2. **Freedom Polio Project** - Largest mhealth project for managing polio and routine immunization of over 1.5 million children below the age of 15. (http://www.freedompolio.org)
3. **Freedom Tuberculosis**: DOTS Management system and patients monitoring through mobile technology (http://www.freedomtb.org)
4. **INFORM** - A mobile platform for screening children for autism, cerebral palsy, to identify and provision unmet needs, and to train caregivers using animated videos

Also, ZMQ has developed over 40 games for improving healthy behaviors and delivered over 2,000 hours of health training content over mobile phones.

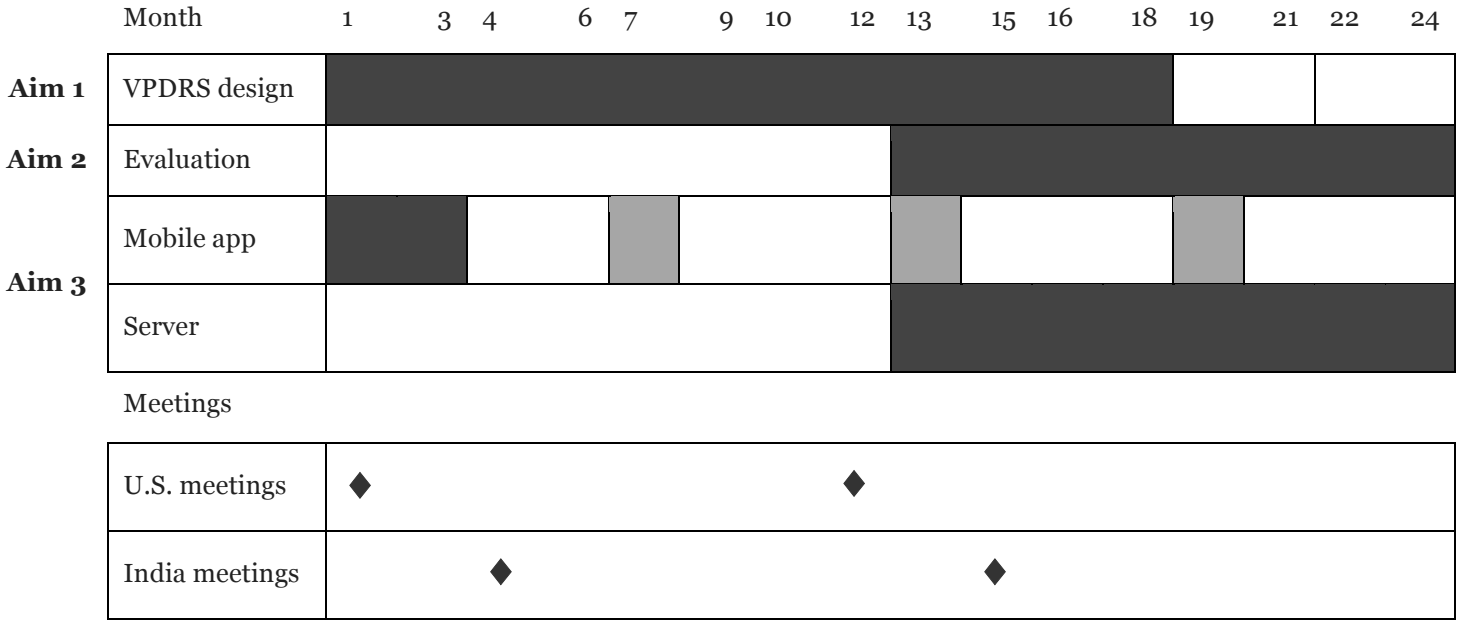
Android Parkinson app: Our collaborators Dr. Ray Dorsey and Dr. Max Little have developed and tested an Android app for people with Parkinson's that does not include UPDRS survey questions, but includes activities (finger tapping, reaction time, gait, balance, phonation) that record sensor data to infer severity of Parkinson's symptoms. In their pilot study, 20 participants performed an average of 2.7 tests per day (68.9% adherence) for the study duration (average of 34.4 days). The mean error predicting UPDRS (range 11-34) was 1.26 UPDRS points (SD 0.16).

iOS Parkinson app: Sage Bionetworks and partners are currently alpha-testing an iOS app that includes the activities in the Android Parkinson app, passive sensor feeds, and select UPDRS survey questions. If the sensor data collected during these activities enable accurate UPDRS assessment, a mobile app could potentially be used in place of Parts 3 and 4 of the MDS-UPDRS questionnaire. While we would like to incorporate the VPDRS in this iOS app, Android has far greater reach in India, and makes better sense for use in a widespread epidemiological study in India.

Contingencies: *Aim 1:* If certain questions simply fail to translate into widely interpretable visual representations, then we will omit these questions in the version of the VPDRS we use in our later epidemiological studies, and submit these questions as open challenges to the graphics community. *Aim 2:* If the evaluation study in one location is unable to enroll participants, we should still be able to enroll sufficient numbers, given that we will conduct evaluations in at least three hospitals. *Aim 3:* In the unlikely scenario that the app implementation is unable to be completed within the funding period, we can still satisfy Aims 1 and 2 by presenting and evaluating the VPDRS on a computer screen or as printouts.

Plans for coordination of research and activities: In addition to monthly teleconference meetings, we are planning on having four in-person meetings over the course of the two-year grant period, two in India and two in the U.S. The meetings in India will be workshops with training sessions in the use of the latest version of the VPDRS mobile phone app, held in months 4 and 15. A representative from ZMQ will demonstrate the app's use to the Indian coordinators and collaborators, and to three people attending from the U.S. At these workshops, the India study coordinators will also demonstrate the protocol they follow for administering the MDS-UPDRS and VPDRS. Sage Bionetworks in Seattle, WA will host two 3-day meetings (months 1 and 12) to confer with the Indian study coordinators on the construction of the VPDRS visuals, on the analysis methods for evaluating the VPDRS, and on e-consent and international governance issues.

Fig.3. Timeline



Milestones: A full set of initial VPDRS visuals will be constructed by 6 months, with iterative improvements through month 18. While the VPDRS will be administered to patients continually, visuals will be updated monthly, and the app will be updated about every 4 months after an initial version is completed by month 4.

Bibliography

[1] Khadilkar, SV. 2012. Neurology: the scenario in India. J Assoc Physicians India. 60:42-4. PMID:22715545 [http://www.japi.org/january_2012/07_neurology_the_scenario.pdf]

[2] Muangpaisan, W, Hori, H, Brayne, C. 2009. Systematic review of the prevalence and incidence of Parkinson's disease in Asia. J Epidemiol. 19(6):281-93. PMID:19801887 [http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3924097/]

[3] techcircle.in. May 29, 2014. Rai, A. India had third largest smartphone base with 117M users in 2013; to grow 45% in 2014: Mary Meeker Report. [http://techcircle.vccircle.com/2014/05/29/india-had-third-largest-smartphone-base-with-117m-users-in-2013-to-grow-45-in-2014-mary-meeker-report/]

[4] Ramaker, C, Marinus, J, Stiggelbout, AM, van Hilten, BJ. 2002. Systematic evaluation of rating scales for impairment and disability in Parkinson's disease. *Movement Disorders* 17(5):867–876. doi:10.1002/mds.10248. PMID 12360535.

[5] Arora, S, Little, MA, Venkataraman, V, Donohue, S, Biglan, K, Dorsey, ER. 2013. High-accuracy discrimination of Parkinson's disease participants from healthy controls using smartphones. Movement Disorders, 28(10):e12

[6] Bharucha, NE, Bharucha, EP, Bharucha, AE, Bhise, AV, Schoenberg, BS. 1988. Prevalence of Parkinson's disease in the Parsi community of Bombay, India. Arch. Neurol. 45(12):1321-3. PMID:3264148 [http://archneur.jamanetwork.com/article.aspx?articleid=588311]

[7] Gourie-Devi, M, Gururaj, G, Satishchandra, P, Subbakrishna, DK. Neuroepidemiology. Prevalence of neurological disorders in Bangalore, India: a community-based study with a comparison between urban and rural areas. 2004. 23(6):261-8. PMID:15297791 [http://www.karger.com/Article/FullText/80090]

[8] http://www.parkinson-study-group.org/parkinson-research/psg-international-collaborations

[9] http://www.movementdisorders.org/MDS/About/Committees--Other-Groups/MDS-Task-Forces/Task-Force-on-Development-of-MDS-UPDRS/MDS-UPDRS-Application.htm

[10] McMaster, S. 2012. New Approaches to Image-based Research and Visual Literacy: A Pilot Project Report. Published in New Horizons in Visual Literacy: Selected Readings of the International Visual Literacy Association. [https://www.academia.edu/Documents/in/Image_based_Research]

[11] Abiola, S. 2013. Node: A Real Time Smartphone Big Data Application for Health Care Epidemiology. Princeton University Senior Theses. [http://arks.princeton.edu/ark:/88435/dsp01sx61dm401]

[12] http://www.nsf.gov/awardsearch/showAward?AWD_ID=1516340

[13] https://sagebionetworks.jira.com/wiki/display/BRIDGE/Bridge+REST+API