Mobile Medical Application for Cost-effective Strabismus Screening

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Clinical trial protocol and statistical analysis plan

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BACKGROUND:

The goal of the proposed project is the development and evaluation of a novel mobile medical application for the detection and monitoring of strabismus (eye misalignment). The image analysis technology necessary to measure strabismus using the corneal reflection technique (Photographic Hirschberg Test) has been available for many decades (Brodie 1987), however it has never been deployed using a smart phone. A smart phone platform will eliminate barriers of cost (since the hardware is maintained and updated by the smart phone industry), leading to rapid widespread application and allowing the technology to finally reach its potential level of impact for children's' eye care in the detection and management of strabismus. Strabismus causes visual confusion and double vision which ultimately results in the brain suppressing vision from the deviated eye. In children this results in under-development (amblyopia) with permanent vision loss in the deviated eye if not detected and treated at a young age (Rowe, 2012). Strabismus in children is also associated with coordination problems such as postural instability (Lions et. al. 2013) and severe social disadvantages (Lukman et. al. 2011). Strabismus develops in an estimated 3-8% of children in the U.S. (Taylor et.al. 2011; Cotter et.al. 2009; Rowe 2012). The prototype smart phone app (Referred to here as the Mobile Eye Alignment App – MEAA), uses photographic analysis of the corneal reflection (Purkinjie image) generated by the smart phone camera flash. The corneal reflection method uses the displacement of the reflection from the center of the pupil in the deviated eye to calculate the amount of eye misalignment.

This measurement technique will be deployed for the proposed project using the hardware of the Samsung Galaxy, a popular phone with an Android operating system. Preliminary results suggest the app can measure differences in eye alignment of 1.6° (2.8 prism diopters). If successfully developed, the app has potential to be utilized to advance pediatric strabismus research by facilitating and reducing the cost of collecting enormous amounts of data from the general population and underserved or remote populations for epidemiologic studies and allowing researchers to capture eye alignment data much more frequently than is currently possible. Such a tool could better delineate the natural history of strabismus and perhaps help determine its causes.

While devices are available which could make these measurements, the costs are prohibitively high (>$3,000 ea.) and will not reach the widespread availability of smart phones. Clinical goals for the app are to provide eye doctors with an objective measurement tool in the exam room, allow daily monitoring of treatment effects, and eventually to be used as a screening tool by school nurses, pediatricians, and parents. The barriers to market success of stand-alone devices is not the accuracy sensitivity or specificity of photographic analysis technique which has been reported with sensitivity from 53% to near 90% and specificity ranging from 76% to 94% for strabismus detection (Loudon et.al. 2011; Barnard et.al. 2013).

Impact of strabismus screening for the young - Early detection for strabismus in young children, especially during the critical period up to 2 years of age, is important to ensure that treatment is administered as soon as possible (Klaver et. al. 2011; Williams et.al. 2002). The success of amblyopia treatment depends on several factors, but principally on the age of onset and the age at which the treatment is initiated (Taylor et.al. 2011). Therapy for amblyopia is maximally effective if started before age 3 and can be initiated as early as 8 months, underscoring the critical need for early and widespread access to strabismus screening (Epelbaum 1993; Williams et. al. 2002). Indeed, countries with long-standing early vision screening programs have reported significantly reduced rates of amblyopia (Eibschitz-Tsimhoni et.al. 2000). Access to strabismus

screening is also important for older, school age children (age 7-17) suffering from amblyopia, for whom treatment can lead to significant improvements in visual acuity ranging from 20%-70% of patients, depending on their age bracket (Taylor 2011; Scheiman et. al. 2005).

AIM

AIM 1:

Develop and test key functionality of the strabismus app by comparing measurements with successive versions of the prototype app to known angles of eye deviation (non-strabismic volunteers will gaze at off axis targets of known eccentricity).

AIM 2:

Evaluate the strabismus app accuracy and feasibility in a clinical environment. Participants with strabismus will be tested with both the app and clinical methods and analyzed for levels of agreement and test-retest repeatability, satisfaction with the app evaluation, impact on symptoms, and perceived value.

OBJECTIVES:

1) Using simulated strabismus, we will systematically evaluate changes to the prototype app. The app will be tested in various lighting conditions and in participants with various iris colorations, using this information to refine and eventually select the best algorithm.

2) Compare the app measurement with the following common clinical tests of eye alignment: the cover-test with prism neutralization, modified Thorington, or Von Graefe method to determine accuracy, test-retest variability, and robustness of the prototype (optimized in objective 1) to accurately measure strabismus.

3) Determine the best methods for tele-strabismus consultation and rapid delivery of prism treatment, develop a user interface, and determine the perceived value.

HYPOTHESES:

For strabismus ranging from 1 to 30 prism diopters (target range), the optimized version of the app will provide measurements which are not significantly different from the ground truth (simulated strabismus) or clinical tests of eye alignment.

STUDY DESIGN:

Prospective research and development study

ELIGIBILITY CRITERIA

Inclusion criteria:

Ground truth:

- Normal or corrected to normal vision or with strabismus.

Clinical study:

- Strabismus
- Ability to keep looking at the target for 30-60 seconds
- Able to report location of the target
- Uncorrected visual acuity of 20/30 or better

Exclusion criteria:

- Inability to keep looking at the target for 30-60 seconds
- Inability to report location of the target

STUDY OUTCOMES

Primary outcome:

The primary outcome is a comparison between the app and the ground truth and between the app and clinical tests.

Secondary outcome:

1) Accuracy of the app quantified by calculating the mean difference between the app and simulated or measured strabismus.

2) Test-retest repeatability

3) Robustness measure: calculation of the percentage of capture failures (capture failures/ total number of attempted image captures)

4) Analysis of the effect of different factors (i.e. age, iris color, refractive error) on the accuracy.

5) Success rate of tele-strabismus consult and perceived value (captured in a perceived value survey).

STUDY PROCEDURES

Using a conventional smartphone with a high resolution rear camera and flash (for example, Samsung Galaxy S4 and above; Samsung, Seoul, South Korea, and iPhone 5 and above; Apple, Cupertino, CA), the EyeTurn app automatically detects the difference in corneal reflection position relative to the eye center (based on fitting a curve to the limbus boundary) to calculate ocular misalignment, and provide an objective measure of eye deviation from the captured image

of the patient's eyes (Fig 1). The captured images are processed entirely within the smartphone using custom image processing algorithms, and the eye deviation measurements are displayed on the screen usually within a couple of seconds. We use iris center (center of the eye, or the center defined by the limbus curve) instead of pupil center as the reference for computing the corneal reflection decentration, as it has been reported to be a more robust reference for measuring ocular alignment, especially when computing binocular differences (Barry JC, Backes A 1997). Also, for darker iris colors, the limbus boundary is better-delineated than the pupil boundary in visible spectrum images captured by a typical smartphone camera. The corneal reflection decentration distance is converted to prism diopters (D) using an HR in the range of previously reported values (Jagini, 2014).

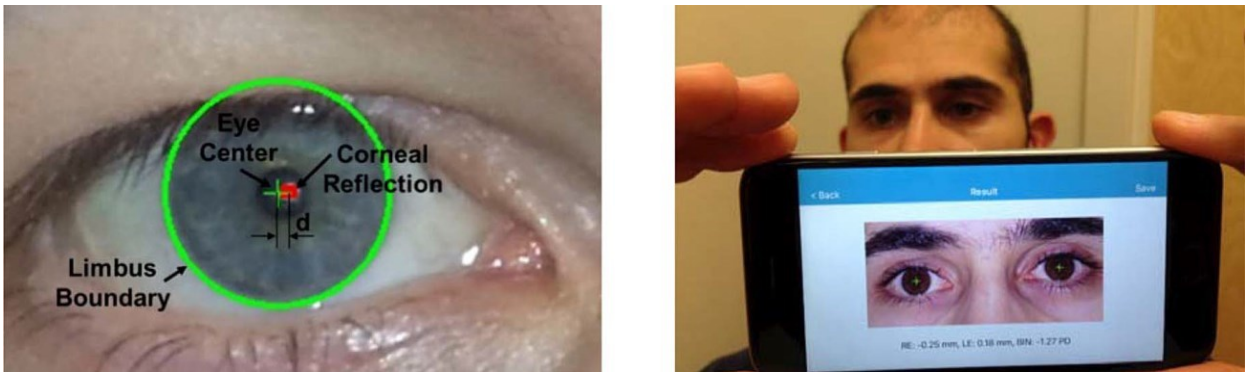

Figure:1 The EyeTurn app for measurement of eye deviations. (Left) Features detected by the app via automatic image processing: limbus boundary denoted by a green circle, its center denoted by a green cross, and the corneal reflection due to the flash denoted by a red dot. The distance between the eye center and corneal reflection, shown as 'd', is compared between the two eyes to detect eye deviation. (Right) To measure the eye alignment using a single picture, the phone is held 30 cm from the eyes of the subject and a picture is taken as the subject fixates binocularly. This mode of operation is well suited for measuring or screening for manifest eye deviation. Permission to publish photograph was obtained via a signed consent to publish document.

The app offers various operating modes through which the eye deviation can either be measured monocularly or binocularly. Additionally, the app also allows dissociated measurement, for example to measure intermittent strabismus condition or phoria, where the deviation between the eyes is not manifest. In clinic, measurement under dissociated conditions is done by performing either cover–uncover or alternate- cover tests with prisms (CTPN). One key feature of the app is the ability to measure eye deviations under dissociated conditions without the need for prism neutralization. In this operational mode, the examiner presses a button to record a video, while the patient fixates on a target binocularly. The patient's binocular fusion is broken in the traditional manner by either cover–uncover (of one eye) or alternate cover (involving both eyes). The examiner ultimately uncovers one eye, and the app records this entire event as a video sequence (Fig. 2). The user is prompted with audio tones to assist in the timing of the cover– uncover. The video frame just after uncovering an eye can be selected for processing the maximum dissociated eye deviation. Due to the high framerate of video capture (30 Hz), we can measure the deviation before a recovery vergence eye movement can be initiated. Figure 2b shows an example of the eye movement trace obtained when performing the alternate cover test, with a smartphone recording the video of this event.

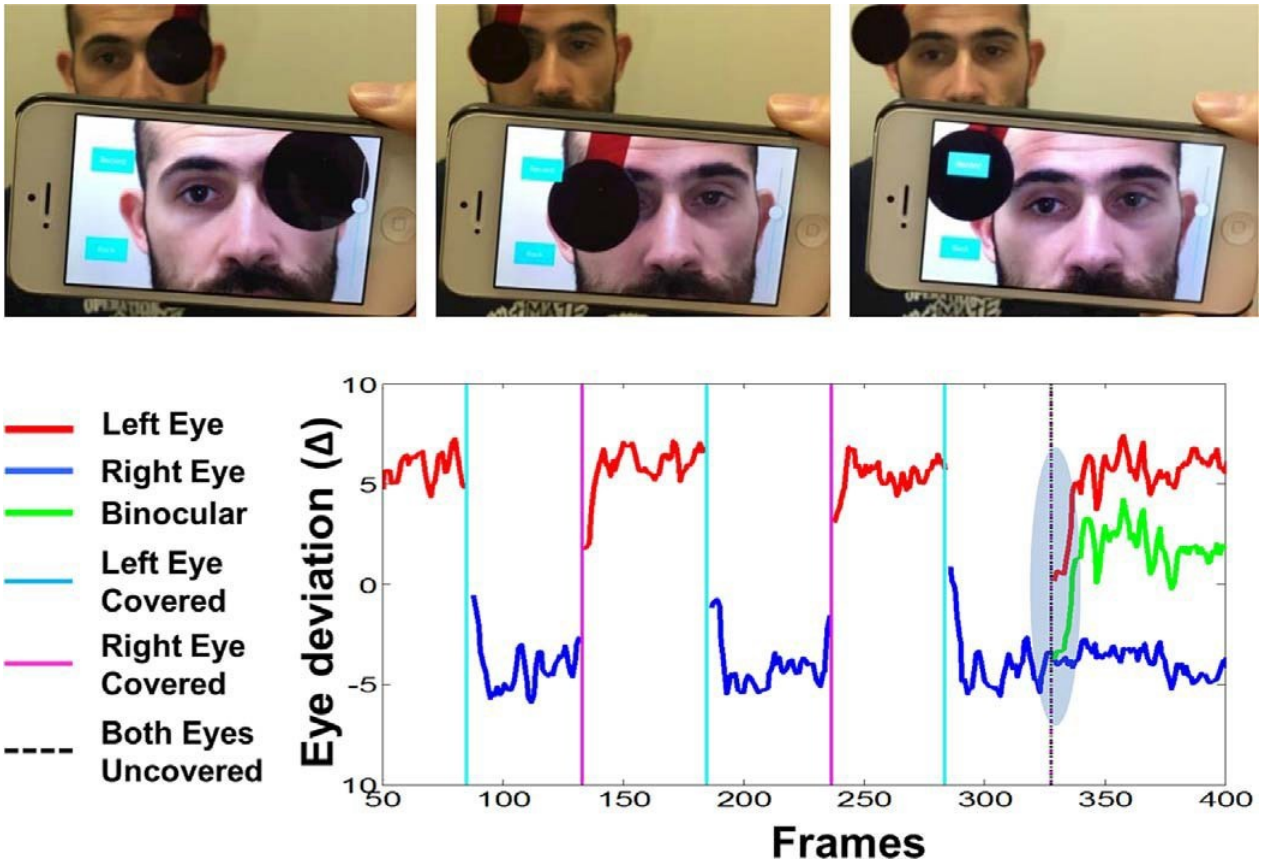

Figure 2. Cover testing mode for dissociated measurements using the app. (Top row) Alternating cover–uncover test using the video-based cover test mode. This novel operational mode can be used for dissociated measurements. The examiner alternately covers the eyes (first two images on top row). The frame with both eyes uncovered (third image on the top row) is selected for automatic processing by the app for measurement of the eye deviation. (Bottom row) Eye movement trace after offline processing of the video of the alternate cover test shows the movements of the eyes after the cover is removed. Negative values show temporal deviation (outward), whereas positive values show nasal deviation (inward). There is a brief duration after removing the cover during which the deviation can be measured (highlighted by the oval gray zone). It should be noted that the eye movement trace in this figure was generated by processing the video recorded by the smartphone on a desktop computer using the same image processing software used in the app, but may be included as part of the app in the future. Permission to publish photograph was obtained via a signed consent to publish document.

Ground truth study:

The subjects will sequentially fixate on the targets of known eccentricity placed on the rear surface of the smartphone along the horizontal direction with their head stabilized in a chin forehead rest (Fig. 3). The app does not need to be used in this manner in actual practice; however, for the purpose of establishing the true deviation values for the fixation targets, such a controlled setup was necessary. The test setup covered an angular range of $\pm$13 degree (approximately $\pm$23D with respect to a central fixation corresponding to camera lens).

Figure 3. Experimental setup to measure the accuracy of the app in Study 1. Subjects without strabismus fixated on 13 targets on the rear side of a smartphone placed at a distance of 30 cm with their head resting on a chin–head rest. Twelve of the 13 fixation targets were a black cross on a white background. The center target was the smartphone camera. With the known distances, true eye deviation magnitudes with respect to the central fixation point were computed (angular range covered by the fixation targets was 6138 or 623D) and compared to measurements with the app.

Clinical study:

In a second study, dissociated phoria measurements with the app will be compared to the Modified Thorington (MT) test. Subjects will rest their head in a chin–head rest and the phone will be mounted 40 cm from the eyes. A 20/30 size letter attached below the phone camera lens served as a fixation point and controlled accommodation. The eyes will be alternately covered and then uncovered by an examiner with an occluder while the subject maintained the fixation. The app generated auditory tones to guide the examiner when to change the cover from one eye to the other. A higher-pitched tone was a cue to stop alternate cover and to uncover both eyes. The app recorded for 2 seconds after the final higher-pitched tone, resulting in 30 recorded frames. The app displayed the recorded frames and the user swiped through the frames to find and select the first frame after uncovering the eyes, which then was processed by the app to output the measurement value. Each subject was tested three times with the app in quick succession. Phoria also was measured using an MT near card (at 40 cm).

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