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Implementation of active injury management (AIM) in youth with acute concussion: A randomized controlled trial

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Abstract

Background: Nearly 2 million youth seek acute medical care following concussion in the U.S. each year. Current standard of care recommends rest for the first 48 h after a concussion. However, research suggests that prolonged rest may lengthen recovery time especially for patients with certain risk profiles. Research indicates that physical activity and behavioral management interventions (sleep, stress management) may enhance recovery. To date, there is limited empirical evidence to inform acute (<72 h) concussion recommendations for physical activity and behavioral management in adolescents.

Objective: To determine the effectiveness of physical activity and behavioral management for acute concussion in adolescents and young adults, and to evaluate the role of patient characteristics on treatment response.

Methods: This multicenter prospective randomized controlled trial will determine which combination of physical activity and behavioral management is most effective for patients 11–24 years old who present to the emergency department or concussion clinic within 72 h of injury. Participants are randomized into: 1) rest, 2) physical activity, 3) mobile health application (mHealth) behavioral management, or 4) physical activity and mHealth app conditions. Assessments at enrollment, 3–5 days, 14 days, 1 month, and 2 months include: concussion

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Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cct.2022.106965.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

symptoms, balance, vestibular-ocular and cognitive assessments, quality of life, and recovery time. Somatic symptoms and other risk factors are evaluated at enrollment. Compliance with treatment and symptoms are assessed daily using actigraph and daily self-report. The primary study outcome is symptoms at 14 days.

Conclusion: Prescribed physical activity and behavioral management may improve outcomes in youth following acute concussion.

Keywords

Clinical trial; Pediatrics; Concussion

1. Introduction

Mild traumatic brain injury (mTBI) impacts nearly 2 million youth in the United States each year [1]. Although most mTBIs resolve within 3 months, some patients may benefit from more effective acute management strategies [2]. Acutely, both physiological and psychological factors are associated with persistent symptoms. However, as time passes, the contribution of psychological factors to the preservation of symptoms increases [3–5]. It has been shown that accurate assessment of injury severity and consequent outpatient guidance may decrease recovery time and reduce the risk of secondary complications [6]. Current guidelines for the acute post-injury period recommend rest for up to 48 h followed by a gradual symptom-guided increase in activity [7,8]. As symptoms persist beyond the first few days, patients are presented with two options: expose themselves to potentially provocative stimuli by resuming normal activities or focus on their symptoms and decrease activity. The first strategy may lead to spikes in symptoms, while the second strategy may lead to deconditioning, perseveration, and persistent symptoms [9]. Evidence suggests that prolonged rest following acute mTBI in pediatric patients contributes to a greater symptom burden and slower recovery [10,11]. Additionally, patients who presented with post-concussive symptoms alone, without more severe signs of injury (e.g., loss of consciousness, confusion, and amnesia), were at higher risk for the negative outcomes from prolonged rest [12]. In theory, rest reduces metabolic demands of cognitive and physical activities on the recovering neurons. In practice, the evidence supporting rest was limited, relying on retrospective studies without controls or studies of select patients from sports medicine clinics [13,14]. The 2013 Institute of Medicine and Research Council report states “there is little evidence regarding the efficacy of rest following concussion or to inform the best timing and approach for return to activity ...” and recommends implementing “randomized controlled trials to determine the efficacy of physical or cognitive rest.” [15] For pediatric patients with chronic (> 1 month) mTBI symptoms, experts recommend encouraging physical activity and targeted rehabilitation [7,11,16]. Physical activity has been successfully prescribed in the sub-acute/chronic phase of injury [17–19]. More recent trials have demonstrated some benefit of early physical activity in the acute phase of injury [20–22]. Understanding whether early activity and behavioral management are effective treatments, particularly for adolescent and young adult patients at high-risk of negative outcomes is a critical to improving management.

This clinical trial will determine the benefit of prescribed low-intensity physical activity, behavioral management, or both, versus standard-of-care rest discharge instructions in adolescent and young adults with acute mTBI. The primary aim of this clinical trial is to determine which treatment strategy is the most beneficial (i.e., lower symptom scores, recovery, higher quality of life scores) at 14 days (primary time point) and at 1 and 2 months (secondary time points). The secondary aim of this study is to assess the best strategy for the subgroup of patients at higher risk of negative outcomes from rest.

2. Methods

2.1. Overall study design

This is an unmasked phase II factorial randomized controlled trial (RCT) of prescribed low-intensity physical activity, behavioral management, or both, versus standard-of-care (resting for 24–48 h followed by a symptom guided return to normal activities) in adolescents and young adults with acute (defined a < 72 h per NINDS) mTBI presenting to the pediatric emergency department (ED) or concussion specialty clinic (See Fig. 1. for overview) [23]. The study team recruits participants from two sites: Children's Wisconsin (Medical College of Wisconsin), Milwaukee, WI, and Children's Hospital of Pittsburgh (University of Pittsburgh Medical Center), Pittsburgh, PA. The Medical College of Wisconsin serves as the central Institutional Review Board and data coordinating center for this trial. This trial is recorded on clinicaltrials.gov. Patients presenting to either site's ED or concussion clinic within 72 h of mTBI will be recruited for participation (see inclusion and exclusion criteria below). Subjects who consent to participate will be assessed to confirm the clinical diagnosis of mTBI and collect data on symptoms and neurocognitive, vestibular/ocular, and balance functioning. Subjects are then randomized into one of four treatment groups: 1) REST (up to 48 h of rest), 2) ACTIVITY (low-intensity physical activity; i.e., 10,000 steps/day); 3) mHEALTH (application for behavioral management; i.e., SuperBetter©); or 4) both ACTIVITY & mHEALTH. Subjects are discharged home with group-specific video and paper instructions. Subjects complete a phone survey at 3–5 days, an in-person (home or clinic) clinical assessment at 14 days, and phone follow-up at 1 and 2 months. (See appendix) During the first 14 days all subjects are also assessed using a commercial actigraph to track activity and with a symptom tracking app to record cognitive activity, symptoms, and document compliance with discharge instructions. Enrollment began on June 3rd, 2019.

2.1.1. Study population—Approximately 388 subjects will be recruited to retain 308 or ~ 80% of all subjects. Inclusion criteria for this study include: participants age 11–24 years old diagnosed with mTBI within the past 72 h verified using the Acute Concussion Evaluation-ED version available as part of the CDC's Heads Up Clinicians toolkit [2]. Exclusion criteria for this study include: Do not speak/read English, have any conditions that could limit ability to complete assessments or provide informed written consent and/or assent, history of brain surgery, moderate-severe traumatic brain injury, previous mTBI within the last 6 months, substance abuse, history of major psychiatric disorder other than generalized anxiety disorder or major depression, developmental delay or any other

neurological disorder; need for hospital admission; previous enrollment in the study; lack of access to a smartphone; or if the treating clinician is not comfortable with randomization.

A planned secondary analysis will evaluate treatment effects in a subgroup of patients at high-risk for persistent symptoms and prolonged recovery. The high-risk subgroup is defined as subjects with a symptoms-only clinical presentation (e.g., subjects diagnosed with mTBI based on post-concussive symptoms only with the absence of early signs of altered mental status (i.e., LOC > 30 s, peritraumatic amnesia, or disorientation/confusion) or subjects with high levels of somatization defined as levels at or above the 90th percentile on the Somatization subscale of Brief Symptom Inventory-18) [24].

3. Study phases and treatments

3.1. Recruitment and consent

Research assistants and nurses from the pediatric ED sites and concussion clinics will recruit subjects. The treating clinician and/or research assistant will identify subjects based on presenting chief complaint of mTBI or events that can lead to mTBI to (e.g., fall, motor vehicle crash). Informed assent/consent will be obtained from patient participants and their legally authorized representatives. Families will be offered compensation for subsequent completion of clinical follow-up assessments at 14 days (+/− 4 days) and return of the study actigraph, as well as the 1- and 2-month phone surveys. (funds up to $135 prorated based on completion of study tasks).

3.2. Standardized instructions and interventions

Subjects in all groups will be instructed not to return to high-risk activities (e.g., climbing, biking) or sport-specific activities (practice, competition) until they are formally cleared in follow-up by their primary care physician or other healthcare provider. All subjects will receive standardized discharge instructions modified from the Progressive Activities of Controlled Exertion (PACE) [25] and Reduce Educate Accommodate Pace (REAP) [26] return-to-learn programs, which specify signs and symptoms of mTBI, reasons to return to the ED, basic post-concussion self-care (i.e., sleep, diet, hydration), and return-to-learning guidance, including a letter to the school and strategies to reintegrate students to the classroom. All subjects will be given a commercial actigraph (Fitbit) to monitor physical activity and download a study-specific smartphone/tablet application (AIM app) to record cognitive activity (e.g., time spent sleep, school attendance, homework), symptoms, and document compliance with activity recommendations. The Fitbits being used are the Fitbit Flex and Fitbit Inspire 2. The AIM app and Fitbit were validated in our preliminary studies [27]. We will also monitor compliance with remote and in-person assessments. After randomization, subjects will be given standardized printed comic-based discharge instructions and presented standardized video discharge instructions which provide recommendations for the next 2 weeks specific to their assigned treatment condition (See Table 1).

Treatment conditions are as follows:

1. In the REST group, participants will be instructed to rest per current consensus recommendations. The REST group will be recommended to return to school/work and light physical and cognitive activity as soon as tolerated—but no sooner than 48 h post-injury. Notifications from the Fitbit app will be turned off, and the step goal will be set at 500, to minimize positive feedback and reminders from achievement of activity goals.

2. The ACTIVITY group will be instructed to use their Fitbit to measure their steps and activity. The ACTIVITY group will be encouraged to engage in light-to-moderate physical activity regardless of presence of symptoms. Subjects will be encouraged to engage in low-risk activities (e.g., walking). Subjects will be instructed to avoid activities that may increase risk of re-injury (e.g., biking, climbing, sports). Fitbit notifications will be turned on and the step goal will be set at 10,000. For the first week of participation subjects have a goal of reaching 10,000 steps for 3 days for that week. For the second week of participation subjects have a goal of reaching 10,000 steps for 5 days that week.

3. The mHEALTH group will be instructed to download the SuperBetter© application in addition to following the REST group recommendations. SuperBetter is an app designed to improve psychological resilience, promote social and emotional learning, and reduce anxiety and depression. It is designed to motivate individuals with game mechanics (e.g. points, levels, ‘power-ups’) to promote “mental, physical, social, and emotional resilience.” The application has been demonstrated to improve depression and anxiety in one recent clinical trial, and post-concussive syndrome in pediatric patients in the outpatient setting [28,29]. The SuperBetter© app presents goals (e.g. hug a friend, breath, chug a glass of water) from patients to complete and rewards them with points. These goals/ milestones will give the patient an opportunity to celebrate the achievement of improvement from mTBI with the goal of generating a positive contextual frame for recovery. In addition to the pre-programmed general “resilience” goals, research assistants will help the subjects to set personal mental, social, and emotional rehabilitation goals and milestones for acute recovery from mTBI using available in pre-populated lists (“power-packs”) of resilience goals. Research assistants will not set any physical activity goals for subjects.

4. The ACTIVITY & mHEALTH group will receive both interventions. Interventions will be integrated by having research assistants add physical activity Superbetter© goals to the subject’s SuperBetter© app (e.g., take a 30-min walk, march in place for 5 min, increase my step count by 2000 today, achieve 10,000 steps today).

3.3. Schedule clinical follow-up appointment and remote survey

Follow-up appointments will be scheduled at the time of ED/concussion clinic visit or during the 3 to 5 day assessment. Follow-up appointments or remote assessments for

reevaluation were conducted by the research assistants within 14 days (+/− 4 days) after their ED/concussion clinic visit, which corresponds to the typical clinical follow-up time-period. The follow-up will confirm recall and adherence to the prescribed discharge instructions and use of Fitbit and AIM app. During the follow-up, the research assistants will administer a brief survey.

3.4. Clinical follow-up assessment

At the clinical follow up 14 days (+/− 4 days) after enrollment, subjects will complete assessments either remotely or in person under the supervision of the research assistant. Subjects will receive compensation upon completion of the clinical follow-up assessment and return of the study Fitbit.

3.5. Follow-up assessments

Research assistants will contact subjects at 30 (±7 days) and 60 (±7 days) days post-injury to administer a brief survey. The research assistant will also ask subjects to recall if/when symptoms and impairments resolved and if/when they resumed full activity. Subjects will receive compensation for completing each follow-up assessment at 1 and 2 months.

4. Clinical trial outcomes

We will assess symptom, quality of life, and recovery outcomes based on treatment group assignment for all subjects and high-risk subjects. We have selected assessments and outcome measures are based in part on the NINDS Sports Concussion CDE recommendations [30] (see Table 2). We will compare symptoms between subjects with prescribed activity (ACTIVITY and ACTIVITY & mHEALTH (SUPERBETTER)) versus subjects with prescribed rest (REST and mHEALTH (SUPERBETTER)) to assess safety.

The primary study outcomes will be symptoms on the Post-Concussion Symptom Scale (PCSS) at 14 days. We chose the 22-item PCSS as it is commonly used and would ensure consistency in longitudinal comparisons [31]. We have validated PCSS administration via phone in previous studies [32]. The PCSS comprises 22 self-reported symptoms (e.g., dizziness headache) rated on a scale from 0 (none) to 6 (severe). PCSS score of ≤7 will be defined as symptom recovery. All subjects will be assessed via phone at 3–5 days and in person at 14 days. The secondary outcomes will be to determine the influence of interventions on comprehensive aspects of physiologic recovery and patient-centered outcomes including symptoms (PCSS) at 3 days; neurocognitive, balance, and vestibular/ocular motor impairment, and recovery at 14 days; pediatric quality of life measures; time to symptom resolution; and return to normal activity via phone survey at 1 and 2 months.[30]Recovery will be assessed at 14 days and is defined as being medically cleared for full return to activities based on being symptom and impairment free at rest and no symptoms following exertion. Neurocognitive function will be assessed using Immediate Post-Concussion Assessment and Cognitive Test (ImPACT) computerized test which tests visual working memory, verbal recognition memory, reaction time, visual processing speed, numerical sequencing ability, and learning. The PI has validated ImPACT in the ED in several previous studies [10,32]. We will assess balance using the modified Balance Error

Scoring System (mBESS), a cost-effective way to objectively assess balance. The test consists of three stance conditions (double leg, single leg, tandem) performed on firm flooring. In all stances, errors are recorded as the quantitative measurement of postural stability which has be previously validated [33]. We will assess vestibular/ocular motor impairment using the Vestibular/Ocular Motor Screen (VOMS) The VOMS is a validated structured assessment of symptom provocation during 1) smooth pursuits, 2) horizontal and vertical saccades, 3) convergence, 4) horizontal and vertical vestibular ocular reflex and 5) visual motion sensitivity.. Convergence is assessed via symptom report and near point of convergence [34]. We will assess health-related quality of life using the PedsQL, a validated tool that has been used in healthy children and adolescents and those with acute and chronic health conditions including post-concussion [35,36].

5. Sample size estimates

The sample size requirements for this study are based on completing the planned subgroup analysis and reflect a power analysis to detect differences in the primary outcome measure for a subgroup of high-risk patients at 14 days. It is estimated that approximately 60% of the total patients will be high-risk. We will use a repeated measures ANOVA study with the Hotelling-Lawley Trace test to test for a day-by-treatment interaction. PCSS will be assessed at enrollment (day 0), days 3–5, 14, 30 and 60 post-injury. Based on previous studies, we predicted measures of PCSS will have a standard deviation of 10 [37]. Based on clinical experience, we predict that the correlation among repeated measures in the same individual will decrease slowly over time. Hence, we assumed a linear exponent autoregressive correlation structure with correlation of 0.7 and a decay-rate of 0.5. Given a sample size of $N = 308$ participants ($n = 77$ per group), we will have 80% power to detect a 23% absolute increase in the rate of recovery between each of the intervention groups compared to the control using a two-sided test for proportions ($\alpha = 0.0167$) assuming the probability of recovery is 20%. For the high-risk sub analysis, assuming the high-risk patients comprise 60% of the total sample, we will need to enroll $N = 184$ participants ($n = 48$ per group) to achieve a desired power of approximately 79% and a type I error rate of 5%. Based on past experience, we expect 20% loss to follow up. We will adjust the sample size to account for the attrition, for a total enrollment goal of 388 participants, or 97 participants per treatment arm.

6. Randomization and masking

Randomization of groups will be accomplished using permuted blocks with random block sizes using SAS version 9.4 to generate a randomization list uploaded to an electronic database, Research Electronic Data Capture (REDCap). Research assistants will retrieve the allocation only after entering all baseline information and the patient is determined to be completely eligible. Allocation is only provided for each participant being considered; therefore, allocation of subsequent participants is concealed. Patients and providers cannot be masked in a trial comparing different behavioral treatments. As most outcomes are patient-reported through questionnaires, the outcome assessments will also be unmasked. To ensure that providers adhere to treatment allocation, the interventions are presented in

standardized videos and patient discharge instructions, and research assistants will observe and record any additional discharge instruction information verbally provided to subjects.

7. Data analysis plan

All analysis testing the effectiveness of the interventions will follow intention-to-treat based on treatment group. The primary outcome measure will be the PCSS total severity score at 14 days. The PCSS will be measured at baseline, 3–5, 14, 30, and 60 days post-injury. We will use repeated measures models to compare the symptom changes across time among the four groups with fixed effects for time and group*time and baseline symptoms in the outcome vector (constrained baseline longitudinal model). We will account for the correlation among measurements from the same individual over time using compound symmetry, autoregressive, and unstructured covariance patterns and will use Akaike's Information Criteria and Bayesian Information Criteria (AIC/BIC) to determine the optimal correlation structure. We will use contrasts at the 14 day measure to test the hypotheses that patients prescribed low-intensity physical activity, mHealth app, or both will report improved symptoms compared to patients prescribed rest. Results will be presented as differences in means and 95% confidence intervals. Secondary outcomes are recovery and quality of life. We will use Chi-square tests and logistic regression to compare the probability of recovery among the four groups. Results will be presented as odds ratios and 95% confidence intervals. The four groups will be compared on the secondary outcomes using the same approach described for the primary outcome.

Additional secondary outcomes include neurocognition, balance, and vestibular/ocular motor impairment at 14 days and return to normal activity at 1 and 2 months. Numeric measures such as verbal memory, visual memory, and processing speed will be treated as continuous variables and analyzed using analysis of covariance controlling for the baseline measure. We will first test for treatment effects across the four groups using the overall F-test for the group variable. Treatment comparisons will be made between the control group and each of the other 3 groups (low-intensity physical activity, mHealth, both) and presented as adjusted mean differences and 95% confidence intervals. We will compare the proportion of participants that report returning to normal activity at 1 month and return to normal activity at 2 months using Chi-square tests and pairwise comparisons to the control group if the overall Chi-square is significant.

The subgroup analysis for participants who are high-risk for prolonged recovery is the same as described above because the outcomes are the same. We will stratify the analysis by high-risk versus not high-risk for prolonged recovery.

A Data Safety Monitoring Board will look at the data at regularly planned intervals to monitor patient safety. A ten-point or more increase in PCSS that persists for two consecutive days will result in a call from the research coordinator to the subject to assess clinical status. An adverse event for monitoring will be defined as an increase of the PCSS by 10 points over two consecutive days within the first 14 days compared to baseline, or any severe adverse event of grade III or higher. Interim safety evaluations will be conducted at

the end of year one and year two with an overall one-sided 5% significance level will be used.

8. Discussion

Research suggests that mTBI causes a neurometabolic cascade triggering an energy crisis in the brain [38]. This leads to the functional impairments seen in mTBI. While most mTBIs have a recovery time of 1–3 months, there are patients who experience these symptoms longer than the average recovery time frame [39]. Considering mTBI recovery, there is a common trajectory that most patients follow [40]. However, recovery and symptoms can be influenced by biological factors such as gender [41,42], age [43,44], previous injuries [45], cultural background [46,47], as well as psychological factors like pre-injury psychiatric conditions [48] including somatization [3–5].

The most common course of treatment for acute mTBI symptoms is prescribed rest (e.g., restrictions on physical and cognitive activity) [49]. In theory, rest helps restore energy stores in the brain and address the metabolic mismatch seen after concussion [50]. While some rest is currently recommended after acute mTBI, there is data that suggest prolonged rest in harmful. A push for an evidence-based approach to treating mTBI is being advocated for in the field, including a call for randomized controlled trials to determine the efficacy of physical and cognitive rest [15].

Rest is an intuitive and widely embraced therapy for many medical conditions. However, a review of research on bed rest, long considered essential for recovery of many medical conditions, showed bed rest to be ineffective or harmful in all 15 different conditions studied [51]. Additionally, the only randomized clinical study of bed rest for adults with mTBI showed no significant benefit in prolonged rest [52]. In our prior randomized trial comparing prolonged rest (5 days) to standard-of-care rest (24–48 h), symptom outcomes were worse for those who were prescribed prolonged rest (with no differences in neurocognitive outcomes) [10]. Other studies have been published reporting that prolonged rest also led to worse post-concussive symptoms [53]. DiFazio et al. suggested the “psychological consequences of removal from validating life activities, combined with physical deconditioning, contribute to the development and persistence of post-concussive symptoms after mTBI in some youth.” [54] As current practice guidelines recommend rest followed by a symptom-guided return to activity, patients who are susceptible to high and variable symptom reporting may experience self-imposed prolonged rest while perseverating on their symptoms [40].

Prolonged rest can lead to physiological harm through deconditioning that may induce changes in cerebrovascular control which in turn can affect post-concussive symptoms [55]. This can lead to disturbances within the autonomic nervous system as demonstrated by changes in heart rate variability, cardiovagal responses and baroreflex sensitivity to changes in position [56–59]. Combining brain injury with rest may have negative synergistic effects on autonomic function.

Psychologically, rest as a treatment may cause harm through the nocebo effect [60–62]. Nocebo refers to the negative signs and symptoms patients can develop in response to an inactive therapy. Approximately 25% of patients given a placebo will describe negative "side-effects" likely due to misattribution minor, often transient, experiences as symptoms. The neurochemical basis for both placebo and nocebo effects has recently been validated and elucidated through novel experiments with fMRI and other techniques [61,63]. There is growing concern that TBI may be particularly susceptible to placebo/nocebo effects, impacting the ability to detect treatment effects in randomized controlled trials [64].

While prolonged rest has negative impacts on recovery, there is growing evidence to show that returning to low-intensity physical activity can be beneficial for various conditions. There is evidence that prescribing goal-directed exercise is a successful strategy for patients with prolonged post-concussive symptoms [19,65,66]. Grool et al. found in a secondary analysis that returning to physical activity was correlated with an increased likelihood of recovery after 1-month post-injury [20]. In a recent randomized controlled trial of patients recruited from a concussion clinic within 10 days of injury, Leddy et al. found that aerobic exercise safely reduced recovery time and the risk for persistent post-concussive symptoms in adolescents [67]. Similarly, Ledoux et al. found in a recent randomized controlled trial of adolescents seen in the ED, there was no difference in symptoms at 2 week between those recommended early activity compared to those instructed to rest 72 h after concussion [21]. The benefits of physical activity can be seen in animal trials that show the potential benefits that early exercise can improve recovery for a variety of conditions including mTBI [68–70]. Specifically, Mychasiuk et al. found that in simulated mTBI in rodents, cognitive and behavioral recovery was improved in those who exercised 1–3 days after injury [71]. Within these trials, rodents were given cognitive and physical enrichment to improve their recovery trajectory. In humans however, enrichment is more complex and consists of opportunities to engage in various physical activities and social interactions. Enrichment has been heavily documented to help in the rehabilitation of those who have sustained a chronic brain injury [72]. We hypothesize that treatments that promote prolonged rest and avoidance of cognitive and physical activities may contribute to a longer recovery period by reducing opportunities for recuperative enrichment.

There are rare medical conditions in which "complete rest" is the universal recommended treatment. Even in the case of serious neurologic conditions or medical procedures, active rehabilitation is the standard of care. Furthermore, there is growing evidence to suggest that some activity may, in fact, be beneficial after acute mTBI [20]. Framing the injury as a challenge that can be overcome proactively with behavioral management may also have significant influence on outcomes.

We hypothesize that an active injury management approach with physical activity, mHealth app or both, will be superior to rest. Additionally, we hypothesize that prescribed activity and use of the mHealth app will have synergistic effects. If we do not see benefits of active treatment in the whole population of acute concussed subjects, our planned sub-analysis of a high-risk population found to be at greater harm from rest will allow us to detect benefits in high-risk subpopulations [12]. As an alternative hypothesis, rest could be superior to our interventions for all patients or for high-risk subpopulations. This finding would still have

significant value, as there is limited RCT evidence to support the current consensus-based standard of care. However, this trial faces challenges that are shared with other randomized clinical trials active during the COVID-19 pandemic. Given how critical recruitment and retention will be in the study, we have developed recruitment strategies informed by our previous research experience. We have developed compensation that should motivate patients to complete the study procedures by exchanging study-issued Fitbits for additional funds added to a gift card at the 14-day visit and providing additional compensation for phone contact. We will ensure that subjects are given ample follow-up options including in-home follow-up. During the COVID-19 pandemic, we developed remote assessment alternatives to maximize patient retention and maintain social distancing. While the planned analyses are intention-to-treat, if we find no benefit to the intervention, it could be secondary to noncompliance. To ensure this is not the case, we will conduct a per-protocol analysis based on Fitbit data and mHealth app use to evaluate whether there is a dose-response relationship between adherence and outcomes.

In conclusion, the design, interventions, and outcome measure of the AIM randomized controlled trial are designed to determine the optimal treatment recommendations for pediatric patients presenting with acute mTBI.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability

No data was used for the research described in the article.

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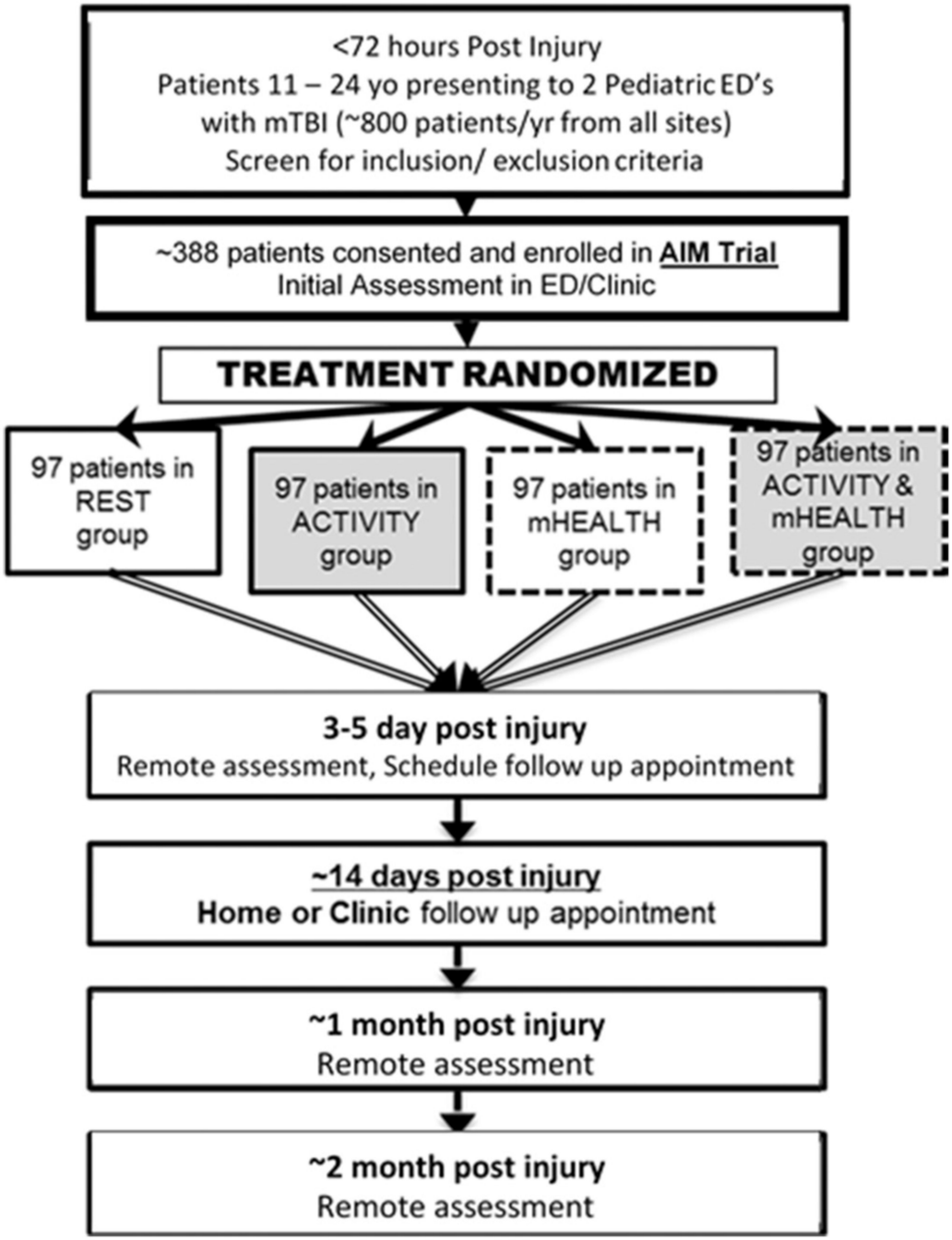

Fig. 1. ACTIVE INJURY MANAGEMENT (AIM) CLINICAL TRIAL-
Overview of the Randomized Controlled Trial.

Table 1

ACTIVE INJURY MANAGEMENT TRIAL:

Overview of Treatment Groups.

Group assignment	Activity recommendation	mHealth intervention
1) REST	Rest for up to 48 h then symptom guided return to physical activity	None
2) ACTIVITY	Low intensity physical activity * regardless of symptoms	None
3) mHEALTH	Rest for up to 48 h then symptom guided return to physical activity	Use of the “SuperBetter©” resilience app
4) BOTH	Low intensity physical activity * regardless of symptoms	Use of the “SuperBetter©” resilience app

* Advised to increase physical activity with the explicit goal of reaching an average of 10,000 steps per day. Regardless of current symptoms; 3 times the first week, and 5 times the second week post injury.

Table 2

ACTIVE INJURY MANAGEMENT

Clinical Trial Measures.

Name of Measure	Description of Measure	When Tested	Methods (Time)	Primary Metric
mTBI Diagnosis and Medical History: **Acute Concussion Evaluation Emergency Department (ACE-ED) V 1.4** [73]	Standardized diagnostic assessment of acute mTBI	Day 0 (ED/Clinic)	Self Report (5 min)	◦ Medical history ◦ Key mTBI features ◦ Symptoms ◦ Risk factors for prolonged recovery
Symptom Assessment: **Post-Concussive Symptom Scale (PCSS)** [31]	Measure of post-concussion symptoms: ● Cognitive, fatigue, physical, sleep ● 22 items ● 6-point scale (0 = none to 5 = severe)	Day 0 (ED/Clinic) Day 3–5 (phone Day 10–14 (F/U) 1 mo (phone) 2 mos (phone)	Self-report (5 min)	◦ Total PCSS score ◦ Mean scores on subscales
Neurocognitive Assessment:**Immediate Post-Concussion Assessment and Cognitive Test$_{(ImPACT)}$** [74]	Computerized neurocognitive test ● Validated in pediatric populations ● Assesses Verbal and Visual memory, motor processing speed, and reaction time Measure of Vestibular/ oculomotor impairment	Day 0 (ED/Clinic) Day 10–14 (F/U)	Self-report (25 min)	◦ Mean scores on Verbal memory, Visual memory, Processing speed, and reaction time
Vestibular Oculomotor Assessment:**Vestibular/ Ocular Motor Screen (VOMS)** [34].	● 7 assessments ● Rate change in symptoms after assessment ● 10 point scale (0 = none to 10 = severe)	Day 0 (ED/Clinic) Day 10–14 (F/U)	Research Assistant (5 min)	◦ Pre-post symptom provocation for headache, dizziness, nausea, fogginess ◦ Near point convergence >5 cm
Balance Assessment: **Modified Balance Error Scoring System (mBESS)** [33]	Measure of Balance ● 3 stances (Double leg, single leg, tandem) ● number of postural errors in timed trial	Day 0 (ED/Clinic) Day 10–14 (F/U) Day 0 (ED/Clinic)	Research Assistant (5 min)	◦ Total Balance errors ◦ Balance errors for each stance
Physical Activity Assessment:**International Activity Questionnaire (IPAQ) Short form** [75]	Measure of Physical Activity ● recall of physical activity over last 7 days ● 7 items ● Amount of time in each physical activity	Day 10–14 (F/U) 1 mo (phone) 2 mos (phone)) Day 3–5 (phone)	Self-report (5 min)	◦ Preinjury and Post injury activity level ◦ Low, medium, high activity levels ◦ Average MET-min/week
Mood Assessment: **Brief Symptom Inventory-18 (BSI-18)** [24]	Measure of Mood ● depression, anxiety, and somatization ● 18 items ● 5-point scale (0 = none to 4 = severe)	1 month (phone) 1 mo (phone) 2 mos (phone)	Self-report (4 min)	◦ Mean score on Depression, Anxiety and Somatization dimension ◦ Overall Global Severity index
Somatization Assessment:**Somatization Subscale of Child Behavior Checklist (SS-CBCL$_{)}$** [76]	Measure of somatization ● 9 items ● 3-point scale (0 = Not true to 2 = very true)	Day 3–5 (phone)	Self-report (5 min)	Clinical somatization levels at or above 95th percentile on SS-CBCL
Quality of life Assessment:**Pediatric Quality of Life Inventory (PedsQL)** [36]	Measure of Quality of Life ● Assess functional outcome ● 23 items ● 4-point scale (0 = never to 4 = Always)	Day 0 (ED/Clinic) Day 10–14 (F/U) 1 mo (phone) 2 mos (phone)	Self-report (5 min)	◦ Total QOL score ◦ Mean physical, emotional, social and school QOL scores
Screen time Assessment; **Generalized Internet Problematic Use Scale 2 (Screens)** [77]	Measure of screen time and internet use Assess screen media use items ● Amount of time in screen use ● Assess internet use ● 5 items	Day 10–14	Self-report (5 min)	◦ Mean scores hours of screen media use and internet use

Name of Measure	Description of Measure	When Tested	Methods (Time)	Primary Metric
	● 8-point scale (1 = Definitely disagree to 8 = Definitely agree)			