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ARRoW-CP: Effect of an Augmented Reality Active Video Game for Gait Training in Children with Cerebral Palsy following Single-Event Multilevel Surgery - Protocol for a Randomized Controlled Trial

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Abstract

Introduction. The natural history in people with cerebral palsy (CP) is a gradual decline in ambulatory function as children grow and age. Single-event multilevel surgery (SEMLS) aims to realign the musculoskeletal system to reverse this tendency. Recent studies show that rehabilitation after surgery should include intensive exercises and functional gait training to improve walking capacities. Fun and motivation are also critical keys to successful therapy in pediatric rehabilitation. Various interventions have shown positive effects, high-interest levels, and engagement with active video games (AVG). The combination of AVG and gait training seems to be an exciting approach for the postoperative rehabilitation of children with CP. In this study, we will investigate if an overground gait training program with an AVG can improve the gait performance of children with CP.

Methods and analysis. The ARRoW-CP study is a randomized clinical controlled trial. A total of 14 children and adolescents between the age of 12–18 years with CP will be included. The minimum time between surgery and inclusion will be seven weeks, and participants will have a Functional Mobility Scale 50 meters rating superior or equal to 2. Both groups will follow a gait training program of four weeks to improve their gait performance. The intervention group will participate in the overground gait training protocol with the ARRoW-CP game. The control group will consist of gait training on a treadmill with a maximal duration of 30 minutes. Measurements will occur before the gait training, directly after, and six months later. The primary objective is anaerobic performance. Secondary objectives are aerobic performance and enjoyment.

Ethics and dissemination. Ethical approval has been obtained from the French Ethical Committee Sud-Est and the French Commission of Informatics Freedom. The study has been registered in ClinicalTrials.gov (NCT04837105). Publications in peer-reviewed journals and conferences will disseminate the findings.

Strengths and limitations of this study:

This study is the first randomized control trial to evaluate the impact of an active video game on gait performance in children with cerebral palsy after surgery

The active video game ARRoW-CP game is dedicated to children with cerebral palsy using a PROGame design framework, including a multidisciplinary team.

The addition of gait training to conventional care may improve the aerobic and anaerobic gait performance in children with CP after surgery.

The enjoyment could decrease over time because of the relative limitation of game elements and game mechanics deployed in the ARRoW-CP game.

Introduction

Cerebral palsy is commonly defined as a "group of permanent disorders of the development of movement and posture, causing activity limitation."[1] The overall prevalence of CP remains constant (2.11 per 1000 births)[2] with an estimated prevalence of 17 million people worldwide.[3] Individuals with CP present various clinical symptoms, including a non-exhaustive list of neurological, orthopedic, movement, cognitive, vision/hearing, aerodigestive disorders.

Musculoskeletal disorders are secondary impairments contributing to restricted mobility in childhood and adulthood.[4–6] Since 1985, therapeutic interventions to correct orthopedic disorders include single-event multilevel surgery (SEMLS). This surgery proposes to realign the musculoskeletal system during one operative period, practicing tendon transfer, muscle lengthening, derotation, deflexion osteotomy, and joint stabilization. In a recent systematic review presenting the state of the evidence on effective interventions for children with CP, SEMLS has been classified as effective ('probably do it W+') for improving both Gross Motor, walking speed, and walking capacity but also contracture and alignment deformities.[7] To date, systematic reviews on the effect of SEMLS reported improvement in passive range of motion, kinematics and kinematics gait parameters, overall gait index, and energy efficiency.[8,9] Results disputed the long-term effect on temporospatial gait parameters, gross motor function, and the activity and participation domain.[10]

A recent review has proposed a model of 5-step that could guide clinicians during postoperative rehabilitation.[11] The authors suggested that the fourth phase, which included more intensive exercises, functional gait training, and resistive muscle strengthening, should be optimized to improve the gross motor function and walking speed after surgery. Functional gait training has been defined as actively practicing walking to improve walking ability.[12] Intervention could be overground gait training (OGT) or treadmill gait training (TT), with or without body support.

Previously, Grecco et al. demonstrated the efficacy of the treadmill gait training program, including functional mobility and gross motor function in children with CP after SEMLS.[13] Recently, a systematic review showed that gait training was a safe and effective intervention to improve walking capacity in children with CP outside postoperative context.[12] In particular, the minimal clinically important difference (MCID) for an increase in walking speed (0.1 m/s) was achieved after intervention in 12 studies/14 (studies level between II and III). The authors discussed two points: OGT could have a more significant effect on locomotor abilities than TT because OGT is more representative of natural walking,[14] and feedback could enhance patient outcomes.[15] These points were important to consider after SEMLS because the bone and muscle gestures modified the overall gait pattern of children. Novak et al. highlighted the importance of context-focused therapy and goal-directed training for children with CP.[7,16] Functional gait training should consider those recommendations and involve motor learning strategies: task-specific, variable practice, high intensity, augmented feedback during therapy sessions, and motivation of the patient.[17–19]

New technologies have been introduced in rehabilitation practice in recent years, both for upper and lower limbs therapy. These systems include extensive technology ranging from fully immersive virtual reality (VR) to augmented reality (AR). The head-mounted displays (HMD) (e.g., Oculus Quest; HTC VIVE, Microsoft HoloLens), Cave Automatic Virtual Environment (video displaying on the walls and floor)20 and game console (e.g., Nintendo Switch, PlayStation) are some of these systems.

To 'actively practice the task of walking,' systems combining treadmill training and exergame delivered through a screen in a semi-immersive environment have been tested with good results.[21–23] However, motor learning principles are not always fully integrated into VR/AR systems because of the lack of knowledge about which feedback modality and which intensity level should be provided in the rehabilitation context.[24]

To our knowledge, even if OGT was recommended for functional gait training, no AR system with active video games exists to provide high-intensity, with progressive difficulty, and variable modalities, including feedback. To this end, we have developed the active video game ARRoW-CP combining OGT based on the previous results[12] and literature[25] and motor learning theory.[17–19,26] In this active video game, continuous feedback and terminal feedback, both with different audio and visual modalities, are combined. The ARRoW-CP game, architecture, framework development, and feedback characteristics are available in **Supplementary File 1**.

The current study, denoted as the ARRoW-CP study, will investigate whether a gait training protocol through an active video game in AR can increase the physical fitness levels of children with CP following surgery. We hypothesize that the active video game ARRoW-CP is as effective as treadmill training and more enjoyable for children.

Methods and analysis

Study Design

This study is a randomized control trial with OGT using the active video game ARRoW-CP in AR (OGT-AR) and Treadmill Training control groups (TT). All children and adolescents participate in a four-week gait training intervention to improve their walking function in one of these two groups. During this period, children continue their usual physical therapy program (5 weekly 45-minutes sessions). This postoperative protocol has been standardized following a 5-step framework.[11] These usual rehabilitation sessions include muscle stretching exercises, muscle strengthening exercises (active resistance exercises), functional exercises (sit-to-stand, transfer, balance, walk, stairs).

Description of the two gait training interventions

The therapists participate in the training sessions before the start of the study. During these sessions, a member of the project team presents them the process and objectives of this study and the gait training protocol proposed for the two groups. They have trained with the Microsoft Hololens and the ARRoW-CP game via a tutorial application.

ARRoW-CP: Overground Gait Training in AR

The intervention group receives the OGT-AR protocol through the active video game ARRoW-CP using the Microsoft Hololens headset **(Figure 1)**. ARRoW-CP sessions are monitored by physiotherapists, assistant-physiotherapist, or research assistants.

The intervention consists of 4 weeks of OGT-AR (3 sessions per week), including a series of walking sprints. This protocol is adapted from Zwinkels et al.[25]. Every training session consists of a prescribed intensity, volume, and time (**Table I**).

Before the first session of each week, the target velocity is calculated during a Muscle Power Sprint Test (MPST).[44] This test is made through the ARRoW-CP game and is presented as a "calibration" to the participant. During this test, the player does not receive feedback. The highest velocity of 6 sprints defines the target speed (see *Intervention – Outcomes* section below for more details about MPST). This test is repeated every week to adapt the game's difficulty to the child's progress.

Treadmill Gait Training

The control group protocol consists of 4 weeks of GT on a treadmill (3 sessions per week), with a maximal duration of 30 minutes. This protocol is adapted from Grecco et al.[13]

Before the first session, the target velocity is estimated during a treadmill speed test: participants walk on a treadmill with increasing speed (initially 0.5 km/h and increased 0.5 km/h each minute). Each minute, the therapist asks about the shortness of breath, and the subjective responses are classified using the 1-10 Borg Rating of Perceived Exertion Scale. The test stopped if the score was higher than 5. The target velocity is 80% of the maximum speed achieved during the test.

The first 5 minutes are a warm-up time; the speed gradually increases until reaching the target velocity. The child walks for a maximum of 20 minutes at their target velocity. Then, the treadmill speed gradually diminishes over the final 5 minutes. Training could be interrupted at any time at the child's request or the therapist's judgment. Treadmill sessions are monitored by a physiotherapist, assistant physiotherapist, or a research staff member.

Randomization Procedure

After baseline measures, eligible participants are randomized to the intervention or control group based on a computerized randomization program. Block randomizations are calculated in block sizes of fours and six. The randomization procedure is only available to an independent researcher who will not be involved in the delivery of the interventions or the performance of the measurements.

Participants

All participants will be recruited from the Ellen Poidatz Rehabilitation Center. The children will be operated in several hospitals in Paris: Necker Enfants Malades University Hospital, Trousseau University Hospital, or Robert Debré University Hospital. The French Ethical Committee Sud-Est granted ethics approval. Additionally, all parents, and participants from 12 years of age, will provide informed consent prior to study initiation. All participants should have a cooling-off period prior to the inclusion (minimum 15 days between information and consent). The National Commission of Informatics (CNIL) guarantees confidentiality and data access. A Data Protection Officer has been designated for all research studies conducted in this rehabilitation center. According to the General Data Protection Regulation (EU) 2016/679 (GDPR), he guarantees the respect of data protection and the subject's rights. The study has been registered in ClinicalTrials.gov (Identifier: NCT04837105).

Inclusion criteria are children with CP admitted for inpatient rehabilitation following SEMLS, 12–18 years of age, functioning preoperatively at GMFCS I–III. The study's minimum time between surgery and inclusion is seven weeks (step 4 of the postoperative rehabilitation process). They should have a Functional Mobility Scale 50 meters rating superior or equal to 2 (ability to walk on 50m using a walker or frame without help from another person).

All children should cooperate, understand and follow simple instructions in French to practice the game. Only voluntary patients whose parents consent for their child's participation in the study are included. Criteria for non-inclusion include a diagnosis of photosensitive epilepsy in the medical record and the patient's case history mentioning seizures that occurred while playing a video game, visual cognitive or auditory impairment that would interfere with playing the game. The patient should have normal or corrected vision and hearing.

Patient and Public Involvement

Patient involvement. No public involved.

Outcomes

Outcome measures will take place at baseline (T0), immediately after four weeks of GT (T1), and six months later (T2).

See **Supplementary File 2** for outcomes details and criterion validity.

The 6 minutes walk test (6MWT)

The six-minute walk test is increasingly used in pediatrics clinics to monitor patients' abilities, or for clinical research as a criterion for evaluating the effectiveness of a rehabilitation protocol[27–29] The 6MWT assesses distance walked over six minutes as a submaximal test of aerobic capacity/endurance. The reference guide detailing the recommendations and instructions was updated in 2013.[30,31]

Muscle power sprint test (MPST)

The MPST evaluates the anaerobic performance of youth with CP over 6x15 meters at their maximal speed.[32] Velocity (m/s), acceleration (m/s2), force (kg/s2) and power (watts) are calculated.

Anaerobic performance is defined as peak and mean power. Peak power (PP) is the highest power of six sprints, and mean power (MP) averages over six sprints.

Shuttle Run Test (SRT)

The 10-meters shuttle run test is an adapted version of the 20-meter shuttle run test[33] to accommodate children with cerebral palsy (CP) classified Level I or Level II on the Gross Motor Function Classification System (GMFCS).[34] In this study, the SRT-II will be used because of the postoperative context. The SRT-II starts at 2 km/h. Speed is increased by 0.25 km/h at every level (minute). The test is over when the child cannot go to the next cone in time.

Questionnaire

The 16-items of the Physical Activity Enjoyment Scale (PACES) will be used to assess enjoyment for both the control and test groups.[35] The PACES is a valid and reliable measure of physical activity enjoyment.[36,37] It has been used in many studies assessing the effectiveness of VR therapy.[38,39] This questionnaire will be presented to the participant at the end of the last session.

Sample size and statistical analysis

According to a study by Grecco et al., an average augmentation of 83% (range 80-85%) in 6MWT was calculated following 12-weeks of treadmill training in a postoperative context.[13] The distance traveled during the 6MWT increases from before: 166.4 ± 39.1 m to after: 304.7 ± 75.8 m. The effect size was calculated: d= 2.29. We hypothesize that participants following the ARRoW CP protocol will show the same effect on the 6MWT.

With an $\alpha = 0.05$ and $\beta = 0.20$ (power = 0.80), a sample size of 6 subjects per group will be required.

When taking a failure rate of 10 % into account, 14 subjects should be included.

The required sample size was calculated with G.Power 3.1.9.7. The parameter was t-tests – Means; preliminary analysis was the difference between two independent means (two groups).

The effect of the GT protocol will be analyzed using a multivariate repeated-measures ANOVA. The differences between and within T0, T1, and T2 for the intervention and control groups will be calculated. A posthoc test will be executed to investigate group differences further. Quantitative descriptive statistics will be used to present patient characteristics and global results. All statistical analyses will be performed using R with a statistical significance level of $p = 0.05$.

DISCUSSION

This approach has evolved from two directions: interest to improve walking capacity after SEMLS for children with CP and from concern that the usual postoperative rehabilitation approach has not produced sustainable improvements in participation and activity in daily life for these children.[8]

Active video game development framework

This work followed the active video game development framework PROGame, proposed by Amenguai Alcover et al.[38] A participative process including both professional healthcare and patients has been conducted.

The first step was the *project initiation*. The team identified the need for an active video game, the stakeholders, and user categories (users and experts). They also clarified the game functionality and constraints. They selected the therapy to transfer into the active video game. The operational objectives were to be safe; to provide efficient gait training; to improve walking speed; to motivate the patient; to

be fun. These identifications were based upon prior experience and literature review.[12,39–41] The team used communication tools like an oral presentation of preliminary results, open debates, surveys, and meeting reports. The aim was to support incremental development between team members (with their specialty) and share knowledge. At this stage, the project proposed a general description. The second step was the *interaction mechanism,* all technical solutions were explored, and an algorithm for gait parameters detection was developed and tested.[40,41] During the third step, the *interactive elements,* the team investigated actual commercial or active video games to get inspired. Team exploration and discussion are aimed at games like Pokémon Go or Zelda, in which the gamer must explore the world and accomplish missions. These games appear very popular with the younger generation. The development team was composed of therapists (3 physiotherapists), researchers (2 in computer science, 1 in rehabilitation science, 1 in movement science), and a software engineer. These steps occurred between January 2020 and June 2021. All details are available in **Supplementary File 3**.

The aim was to think together about the best solution for improving postoperative results, especially walking capacity. New technologies were young people's preferred solution. These solutions seem to be an up-and-coming tool for rehabilitation purposes, allowing to manipulate the environment, offer interaction, optimize feedback, and many other potentialities.[42,43]

Feedback the critical point for motor learning

The feedback retraining paradigm is based on the conversion, supplementation, and augmentation of sensory information that are usually accessible only by an internal focus of attention to accessible information.[44–46] In this paradigm, augmented feedback is defined as augmented sensory information provided by an external resource (therapist or display) to the patient.[26,47] The information provided to the user could be relative to the movement's pattern or result on the environment or the outcome of a movement for the goal.[48–51] Sensory channels used to deliver information are visual, auditory, or haptic, linked to the proprioception properties of humans.[52] The timing of feedback delivery is critical. Concurrent feedback is delivered while the skill is being performed. Terminal feedback is delivered after the skill is performed with or without delay.[53,54] In most studies, even if feedback effectively improves motor activities, the characteristics applied during interventions were generally inconsistent with motor control feedback theory. Authors suggest that timing, frequency, and autonomy should be adjusted to optimize the long-term effect.[53–55] A strategy that provides feedback to the user on demand promotes learning. Then, by reducing the frequency and timing of the feedback, the user can develop a sense of self-regulation. [56]

The serious aspect of the ARRoW-CP game

ARRoW-CP active video game combines many of the motor learning theories: context-focused therapy and goal-directed training, task-specific, variable practice, high intensity, augmented feedback during therapy sessions, and motivation of the patient.[57] To find the best feedback modalities for our active video game, we have conducted preliminary studies exploring the impact of feedback modalities on walking speed, both in healthy adults and in children with CP. A study on healthy adults showed that specific feedback helped increase walking speed, provided that the game instruction was explicit. Typically, feedback combining a focus of attention with knowledge of results, a spatial representation with world-locked holograms, and a method of presentation with rich holographic content (like animation, color changes) increased walking speed in healthy subjects.[58] This step allowed us to modify and adapt feedback modalities. A second study has occurred with children with CP. Results showed that *scenarios* combining world-locked holograms that disappeared over time helped children with CP reach their target speed. On the other hand, a body-locked hologram that advances in front of the user at the target speed was better able to control the walking speed of the patient.[59]

ARRoW-CP is an adaptation of the validated protocol from Zwinkels et al. The original protocol consists of 8 weeks, twice a week.[25] Every training session consisted of a 30s walking sprints following the prescribed intensity, volume, and time: Week 1 to week 2: 8 sprints, work/rest ratio 1:4; Week 3 to week 4: 10 sprints, work/rest ratio 1:4; Week 5 to week 8: 12 sprints, work/rest ratio 1:3. Because of the postoperative context, the intensity should be reduced. At the beginning of the fourth step of the

rehabilitation process, even if gait training is recommended, children did not precisely recover to their pre-operative level; some children needed crutches or k-walkers. Moreover, a further aspect not to be underestimated: fatigue and pain.[60] The choice of intensity, volume, and time in the ARRoW CP protocol is based on practical experience from expert clinicians and literature[12,13,61]

CONCLUSION

This article presents in detail the gait training protocol tested through an RCT. Both the control group and experimental group have evidence-based physical therapy training. This article also presents the game development framework of the ARRoW-CP active video game. This game is based on the most recent motor learning approach. This is the first study assessing the efficacy of postoperative gait rehabilitation using an active video game. If our hypothesis is validated, the ARRoW-CP game will intensify gait training. This innovative strategy will have a significant clinical impact by improving walking capacity for children after SEMLS. Publishing the study protocol of the RCT offers the opportunity to collaborate with other teams and to give more details about the study. Results will be available in 2022.

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Authors' contributions: ALG, GB, and ED, conceived the study, participated in its design, and participated to the manuscript. SPT, MB, NK participated in the coordination of the study. All authors read and approved the final manuscript.

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Figure 1. Image capture from ARRoW-CP active video game. On the left, this is Yuki, the little dragon that children must follow during walking sprints, and Master Keito, who oversees providing Ninja gait training. A child wearing the Microsoft Hololens AR headset is in the middle to see holograms. On the right, game elements encourage participants, increase motivation and improve adherence to the therapy (game scoreboard)

	WEEK 1	WEEK 2	WEEK 3	WEEK4
Frequency (session/week)	3	3	3	3
Sprint Duration (s)	30	30	30	30
Rest Time (min:s)	2:00	2:00	1:30	1:30
Sprint Repetition	4	6	8	10
Total time (min)	10	15	18	22

Table I. Details of the gait training protocol deployed in the active video game ARRoW-CP

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Figure 1. Image capture from ARRoW-CP active video game. On the left, this is Yuki, the little dragon that children must follow during walking sprints, and Master Keito, who oversees providing Ninja gait training. A child wearing the Microsoft Hololens AR headset is in the middle to see holograms. On the right, game elements encourage participants, increase motivation and improve adherence to the therapy (game scoreboard)

447x137mm (38 x 38 DPI)

1. The Microsoft Hololens Headset is used for ARRoW-CP **(Figure 1)**. Game development was made with Unity 2019.4.8f1 and Mixed Reality Toolkit (MRTK). MRTK-Unity is a Microsoft-driven project that provides a set of components and features, used to accelerate cross-platform MR app development in Unity.

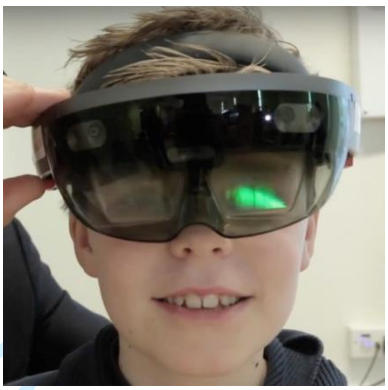

Figure 1. Microsoft Hololens Augmented reality headset.

2. The player is immersed in a samurai world. He meets the chief of the village that can no longer protect its population. The natural elements are unleashed, causing famine and various damages. The player's role is to develop his energy through ninja training to build a protective totem for the village's inhabitants (trailer: https://youtu.be/BbmniiiJuaA).

The software architecture is presented in **Figure 2**.

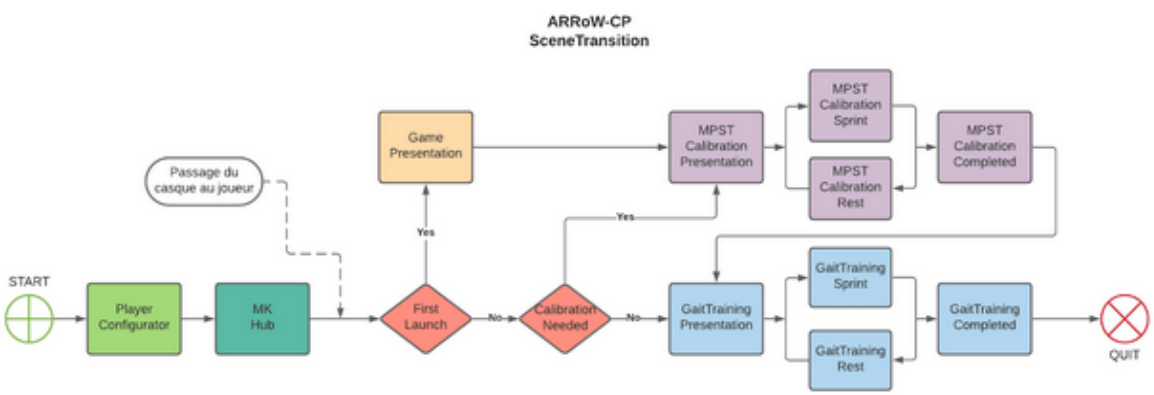

Figure 2. Game architecture of the ARRoW CP game. When the game starts, the AR headset is worn by the therapist. He creates the user profile of the player by entering his name, first name, age, height, and weight during session 1 week 1. Next session, he loads the existing user profile. The therapist then accesses the "MK Hub", which contains information about the performance of previous sessions and the number of sessions

3. The mechanism of feedback provided during sprints and rest time is detailed in **Figure 3**.

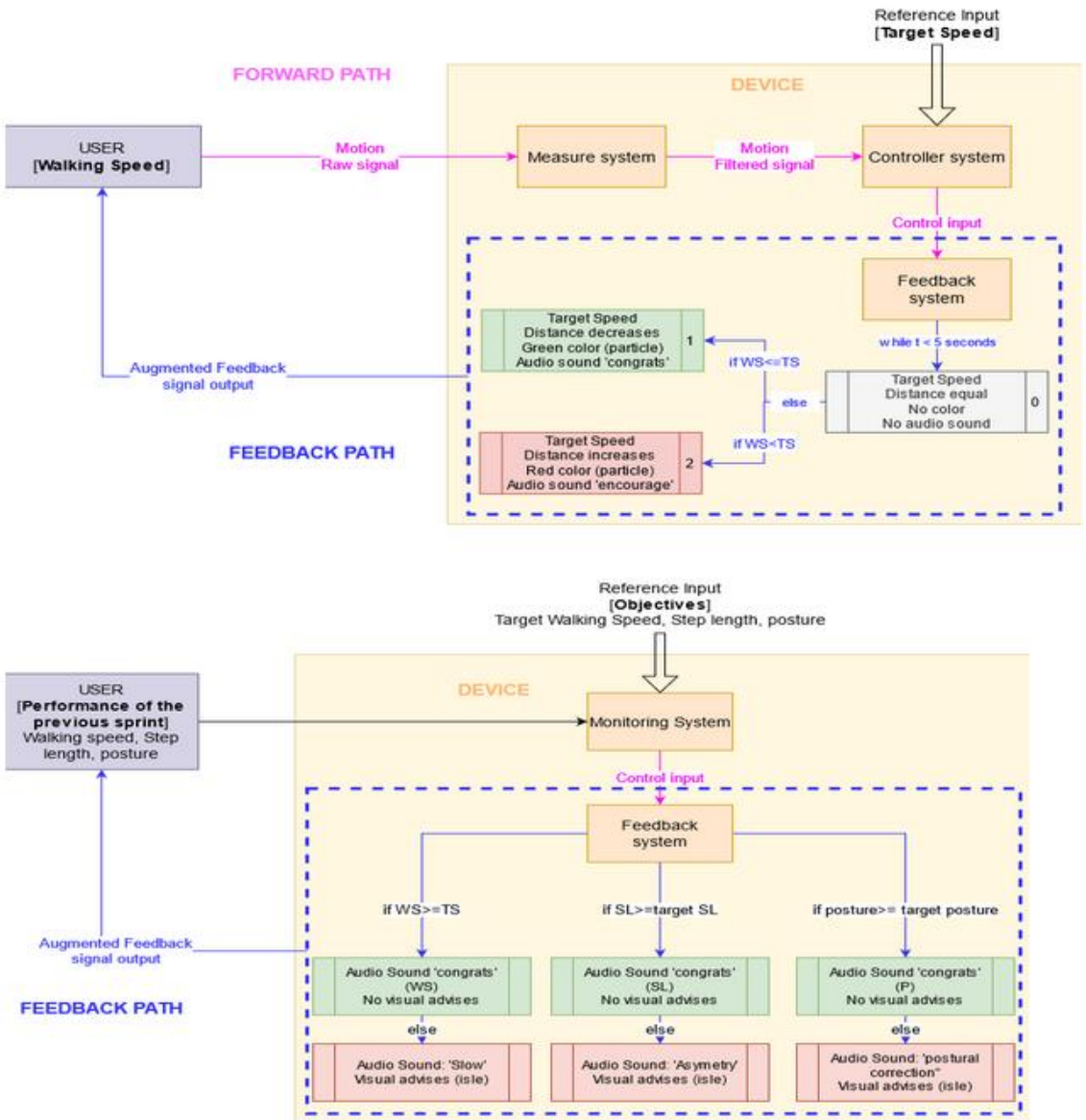

Figure 3. Feedback mechanism during sprints (A) and rest period (B).

At the beginning of each session, through the "Physio HUB", therapists know the previous performance of their patient and they can adjust their advice.

At the end of each session, feedback with delay is proposed to the child: they can choose to see their actual performance through the game scoreboard and totem construction (feedback on demand). These feedbacks were based on knowledge of results.

Test name	Instructions
The 6 minutes walk test (6MWT)	To summarize, patients are instructed to walk, not run, as far as they could along a 20-m level surface back during a 6-minute period. This shorter distance has been validated for children in order to be more focused on the task. They could use their usual walking aids. After each minute, participants are told the elapsed time and standardized encouragement is provided. Patients are allowed to stop and rest during the test but are instructed to resume walking as soon as they feel able to do so. The stopwatch is not stopped during this time. The 6MWT distance (in meters) is registered. Measured 6MWT distance could be compared with normative values for children with CP. It is recommended to monitor heart rate during the 6MWT.
Muscle power sprint test (MPST)	The 15-m distance is marked by 2 lines taped to the floor. Cones are placed at the end of each of the lines. Participants are instructed to walk as fast as possible from one line to the other, and to be sure to cross the line. Between each run, participants are allowed to rest for 10 seconds before turning around to allow them to prepare for the following sprint. Children should be encouraged to give maximal effort. The following variables are calculated for each of the 6 sprints: velocity (m/s) = distance/time, acceleration (m/s2) = velocity/time, force (kg/s2) = body mass × acceleration, and power (watts) = force × velocity. Anaerobic performance is defined as peak and mean power. Peak power (PP) is the highest power of 6 sprints and mean power (MP) is the average over 6 sprints.
10-meters Shuttle Run Test (SRT)	Description of the test is available here : “The course is 10 metres long; the end is marked with 2 cones and a measuring tape. Subjects should wear regular sports clothing and shoes, and orthoses, if applicable. Each child should also wear a heart rate monitor. Children walk or run between the 2 markers at a set incremental speed. These runs are synchronised with a pre-recorded sound. (…) As the test proceeds, the interval between each successive beep reduces, forcing the child to increase speed over the course of the test, until it is impossible to keep in sync with the recording.” We have developed a mobile application that beeps at regular intervals, indicates the time spent and allows the assessor to increment the number of shuttles made by the child.
Physical Activity Enjoyment Scale (PACES)	This is a 5-point Likert scale (from 1- I totally disagree to 5- I totally agree). A translation procedure from English to French language has been made using guidelines (figure).

Validity
In population of children with CP, test/retest reliability is excellent for distance output (ICC=0.98). The 6MWT is poorly related to VO2 peak in ambulatory adolescents and young adults with CP. The 6MWT is a more suitable measure of walking capacity than peak cardiopulmonary fitness in children with CP. The 6MWT outcome appears to be more strongly influenced by potential limits to walking speed rather than cardiopulmonary fitness.
The MPST is a valid test to assess the anaerobic performance in children with CP, significant correlations between the performance on these tests for both PP and MP were found. (PP: r = 0.731 ; MP: r = 0.903). Standard error of measurement (SEM), minimal detectable change (MDC) and normative data are available in Verschuren et al. The children with CP had impaired anaerobic performance as it was lower than that of their peers.
The SRT is a valid and reliable test. Test-retest is excellent (ICC=0.99) and high correlations were found for the relationship between data for both shuttle run tests and data for the treadmill test (r=0.96).
The PACES is a valid and reliable measure of physical activity enjoyment.

Global Aim

Operational objectives
describe the needs in general

Restrictions
detail economical, technical, operational, legal restrictions

Stakeholders
identify customers, special needs and required functionality ;
define experts and representatives end users

Therapy Selection

Project Initiation

to develop a walking rehabilitation serious game for children with motor disabilities and particularly cerebral palsy

to be safe; to provide efficient gait training; to improve walking speed; to motivate the patient; to be fun.

The development of the game must correspond to the duration of a 3-year thesis; grants are limited and predefined; the agreement of the ethics committee and written consents from participants are required before any test on humans ; all technical solution could be explored.

Customers :
- Children with cerebral palsy, 12-18 years old, GMFCS I-III, with cognitive skills to understand and follow simple instructions == END USERS
- Physiotherapists, occupational therapists, physiotherapist assistants, rehabilitation therapists == EXPERTS

Special needs and required functionalities :
- The serious game must include the principles of motor learning, which are task-specific practice, variable practice, high practice intensity, progressive difficulty, augmented feedback, and adaptability to user abilities.
- The serious game should allow the inclusion of motivational elements to increase engagement.
- Children must be free to move in the global environment, without restriction of movement.
- Children must be able to use their usual walking aids (crutches or posterior walker).
- Therapists should have access to the previous and global performance of their patient through the game
- The solution should be "ready to use" easily both for children and therapists

The team's members agreed on making walking speed the main variable input of the serious game. Meaningful reason is that intensive gait training focused on walking speed has shown their clinical efficacy.[12,39] The therapy to transfer into the serious game should include walking sprints.

Interaction Mechanism	
Aim of this phase	To select the interaction system and to capture the therapy into this system.
Device selection	Device: Microsoft Hololens AR headset version 1 was selected because its technical characteristics matched all identified specifications. Tools : - Unity software (version 2019.4.8f1) - Microsoft Visual Studio 2019 - Mixed Reality ToolKit for Unity (MRTK version 4.2.3)
Gait parameters detection *development and evaluation*	Algorithm development: HoloStep measuring the real-time gait parameters with the AR headset system[43] Evaluation : - The accuracy of the AR headset's sensors was sufficiently high to evaluate the position of the user without time drift in the global environment[42] - HoloStep was reliable for measuring and calculating walking speed, cadence, step length and global distance travelled in comparison to a reference motion analysis tracking system[43]

Aim of this phase

Feedback reflexion

Game selection & Universe

Interaction Elements

To design the interaction elements that force patients to perform the therapy correctly

After a debate between team development members, the choice was made to develop the game around the 'do not escape' scenario using body-locked hologram to follow. Main reasons were technical constraints (Microsoft Azure credits were required to build fixed and high-quality world-locked holograms) and experts point of view (physiotherapists judged that the world-locked holograms that disappeared over the time decreased the quality of walking). Feedback with delay was also choosen (game scoreboard). During rest periods, team members agreed to provide advice through animation.

The choice of the game universe (Samurai world) and reward panel were unanimously validated by experts and end users. All packages used to design the game were available in the Unity Asset Store: Polygon Samurai low poly 3D Art by Synty, Tiny Dragon by Suriyun, the GUI Kit - The Stone, and the Particle FX. Voice of game characters from volunteers were recorded in a professional radio studio (HandiFM – France 107.3 FM).

BMJ Open

Effect of an Augmented Reality Active Video Game for Gait Training in Children with Cerebral Palsy following Single-Event Multilevel Surgery : Protocol for a Randomized Controlled Trial

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OPEN ACCESS PROTOCOL

Effect of an Augmented Reality Active Video Game for Gait Training in Children with Cerebral Palsy following Single-Event Multilevel Surgery: Protocol for a Randomized Controlled Trial

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Abstract

Introduction: In paediatric rehabilitation, fun and motivation are also critical keys to successful therapy. A variety of interventions have shown positive effects, high level of interest, compliance and engagement with active video game (AVG).
This seems to be an interesting approach for the postoperative gait rehabilitation of children with CP. In this study, we will investigate if an overground gait training (GT) delivered through an AVG can improve walking capacity and anaerobic performance.

Methods and analysis: This study is a randomized clinical controlled trial. A total of 14 children and adolescents in the age of 12–18 years with CP will be included. The minimum time between surgery and inclusion will be 7 weeks. The test group will participate in the GT program with ARRoW-CP AVG (Augmented Reality Rehabilitation of Walking-Cerebral Palsy), control group will receive GT on a treadmill. The primary outcome is the 6-Minutes Walk Test assessing walking capacity; secondary outcomes are the Muscle Power Sprint Test for anaerobic performance and Shuttle Run Test for physical fitness level. Satisfaction is tested with the Physical Activity Enjoyment Scale. This study has been registered in ClinicalTrials.gov (NCT04837105).
The findings will be disseminated by publications in peer-reviewed journals and conferences.

Keywords: cerebral palsy; surgery; active video game; augmented reality; gait performance

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Strengths and limitations of this study

- This is the first randomized clinical trial to com- pare traditional rehabilitation and technology- delivered gait performance training in children with cerebral palsy after surgery.
- The control group receives treadmill therapy to counterbalance the additional dose effect of active video game use in the experimental group.
- The active video game intervention being investigated have been tailored to the needs of children with cerebral palsy based on feedback from patient and public involvement and expert review groups conducted during the first phase of this project.
- Patients and patient's physiotherapist cannot be blinded; however, the professional caregiver ad- ministering outcome measures and the trial statistician will remain blinded to group allocation until the database has been locked.
- The interventions require participants to have no visual, cognitive or auditory impairment that would interfere with playing the game.

Introduction

Cerebral palsy is commonly defined as a "group of permanent disorders of the development of movement and posture, causing activity limitation"[1]. The overall prevalence of CP remains constant (2.11 per 1000 births) [2] with an estimated prevalence of 17 million people worldwide.[3] Individuals with CP present various clinical symptoms including a non-exhaustive list of neurological, orthopaedic, movement, cognitive, vision/hearing, aero digestive disorders.

Musculoskeletal disorders are considered as a secondary impairment contributing to restricted mobility in childhood and adulthood.[4, 5, 6] Since 1985, therapeutic interventions to correct orthopaedic disorders include single-event multilevel surgery (SEMLS). This surgery proposes, during one operative period, to realign the musculoskeletal system, practicing tendon transfer, muscle lengthening, derotation and/or deflexion osteotomy and joint stabilization. Novak et al. classified SEMLS as effective intervention for children with CP for improving both Gross Motor, walking speed and walking capacity but also contracture and alignment deformities [7]. To date, systematic reviews on the effect of SEMLS reported improvement in passive range of motion, kinematics and kinematics gait parameters, overall gait index and energy efficiency [8, 9]. Results were more disputed about the long-term effect on spatio-temporal gait parameters, gross motor function and the activity and participation domain [10].

A recent literature review has proposed a model in five steps that could guide clinicians during the post- operative rehabilitation [11]. The authors suggested that the fourth phase, which included more intensive exercises, functional gait training and resistive muscle strengthening should be optimized to improve the gross motor function and walking speed after surgery. Functional gait training has been defined as 'actively practice the task of walking, to improve walking ability [12]. Intervention could be overground gait training (OGT), or treadmill gait training (TT), with or without body support.

Previously, Grecco et al. demonstrated the efficacy of treadmill gait training program including both on functional mobility and gross motor function on children with CP after SEMLS [13]. Recently, a systematic review showed that gait training was a safe and effective intervention to improve walking capacity in children with CP, outside postoperative context [12]. In particular, the minimal clinically important difference (MCID) for increase in walking speed (0.1m/s) was achieved after intervention in 12 studies/14 (studies level between II and III). Authors discussed two points: OGT could provide greater effect on locomotor abilities than TT because OGT is more representative of the natural walking, and the addition of feedback could enhance the patient outcomes. These points were important to consider after SEMLS, because the overall gait pattern of children was modified by the bone and muscle gestures. Novak et al. highlighted the importance of the context focused therapy and goal-directed training

for children with CP [7]. Functional gait training should therefore take into ac- count those recommendations and involve motor learning strategies: task-specific, variable practice, high intensity, augmented feedback during therapy sessions and motivation of the patient [14].

In recent years, new technologies have been introduced in rehabilitation practice, both for upper and lower limbs therapy. These systems include a large type of technology ranging from fully immersive virtual reality (VR) or augmented reality (AR) using commercially available head-mounted displays (HMD) (e.g., Oculus Quest; HTC VIVE, Microsoft HoloLens), Cave Automatic Virtual Environment where video is projected on the walls and floor20 to video game console on television screen (e.g., Nintendo Switch, PlayStation).

To 'actively practice the task of walking', systems combining treadmill training and active video game (AVG) delivered through a screen in a semi-immersive environment have been tested with good results [15]. However, motor learning principles are not always fully integrated into VR/AR systems because of the lack of knowledge about which feedback modality and which intensity level should be provided in the rehabilitation settings [16].

To our knowledge, even if OGT was recommended for functional gait training, no AR system with AVG exists to provide high-intensity, with progressive difficulty, and variable modalities including feedback. To this end, we have developed the active video game ARRoW-CP (Augmented Reality Rehabilitation of Walking-Cerebral Palsy) combining OGT based on previous results [12] and literature [17] and motor learning theory [14]. ARRoW-CP active video game has been developed for Microsoft Hololens headset (mixed reality headset). The team used the game development framework PROGame and all stakeholders have been involved through the process (children with CP, researchers, engineers, therapists)[18]. In most studies, even if feedback is effective to improve motor activities, the characteristics applied during interventions were generally inconsistent with motor control feedback theory. Authors suggest that timing, frequency and autonomy should be adjusted to optimize long-term effect [19]. A strategy that provides feed- back to the user on demand promotes learning. Then, by reducing the frequency and timing of the feedback, the user can develop a sense of self-regulation. In this AVG, continuous feedback as well as terminal feedback, both with different audio and visual modalities, are combined following the recommendations of the literature [20, 16]. The general principle for defining the feedback to be used is primarily defined by the results from a previous study that the team lead (article under review). Specific recommendations from this previous study included using feedback moving on in front of the player at the target speed to create a more challenging task that motivates participants to excel. In addition, our results highlighted that the temporary modification of visual aspect according to the performance (red light/too slow; green light/good speed) helped to improve walking speed creating a playful challenge. The feedback attached to the player seemed to be better to minimize visual discomfort and, by extension, fatigue. More details of ARRoW-CP game, architecture, framework development and feedback characteristics, are available in the Supplementary Files 1 and 3.

The current study, denoted as the ARRoW-CP study, will investigate whether a gait training protocol through an active video game in AR can:

1. Increase the walking capacity
2. Increase anaerobic performance & physical fitness level
3. Improve the level of satisfaction during therapy

Our hypothesis is that the AVG ARRoW-CP is at least as effective as treadmill training to improve walking performance and more enjoyable for children with CP following surgery.

Methods and analysis

Study Design

This study is a randomized control trial with two groups: OGT using the AVG ARRoW-CP in AR (OGT-AR) and Treadmill Training control group (TT). All children and adolescents participate in a four-week gait training intervention to improve their walking function in one of this two groups. During this period, children continue their usual physical therapy program (5 weekly 45-minutes session). This postoperative protocol has been standardized following a 5-step framework [11]. These usual rehabilitation sessions include muscle stretching exercises, muscle strengthening exercises (active resistance exercises), functional exercises (sit-to-stand, transfer, balance, walk, stairs). The study is planned to start in April 2021 and end in December 2023.

Description of the two gait training interventions

To standardize the session content as much as possible, the therapists involved in the study participate in the training sessions before the start of the study. During these sessions, a member of the project team presents them the process and objectives of this study, as well as the gait training protocol proposed for the two groups. A session is dedicated to the familiarization with Microsoft Hololens and the ARRoW-CP game via a tutorial application.

ARRoW-CP: Overground Gait Training in AR

Intervention group receives the OGT-AR protocol through the AVG ARRoW-CP using the Microsoft Hololens headset (Figure 1). ARRoW-CP sessions are monitored by physiotherapist, assistant physiotherapist, or research assistant.

The intervention consists of 4 weeks of OGT (3 sessions per week), including a series of walking sprints. These sessions are always performed indoors, along the same flat and straight 30m in length hallway with a hard surface that is seldom traveled. The starting point is marked with a round floor sticker ARRoW- CP. Children can see the real environment because of transparency of holograms and use of augmented reality (that is different from virtual reality), but some safety measures are taken to avoid collision with other people: the caregiver signals to others that a session is in progress, checking before starting the game that there are no obstacles in the hallway. This protocol is an adaptation from Zwinkels et al. [17]. Every training session consists of a prescribed intensity, volume and time (Table I).

Before the first session of each week, the target velocity is calculated during a Muscle Power Sprint Test (MPST) [21]. This test is made through the ARRoW- CP game and is presented as a "calibration" to the participant. During this test, no feedback is presented to the player. The target velocity is defined as the highest velocity of 6 sprints. This test is repeated every week to adapt the difficulty of the game to the child's progress.

Treadmill Gait Training

The control group protocol consists of 4 weeks of GT on a treadmill (3 sessions per week), with a maximal duration of 30 minutes. This protocol is an adaptation from Grecco et al.[13]

Before the first session, the target velocity is estimated during a treadmill speed test: participants are instructed to walk on a treadmill with increasing speed (initially 0.5 km/h and increased 0.5 km/h each minute). Each minute, children are asked about shortness of breath and the subjective responses are classified using the 1-10 Borg Rating of Perceived Exertion Scale. The test is stopped if the score is higher than 5. The target velocity is defined as 80% of the maximum speed achieved during the test.

The first 5 minutes is a warm-up time, the speed is gradually increased until reaching the target velocity. The child walks for a maximal 20 minutes at their target velocity. Then, the treadmill speed is gradually diminished over the final 5 minutes. Training could be interrupted at any time at the child's request or physical therapist judgement. Treadmill sessions are monitored by physiotherapist, assistant-physiotherapist, or a member of the research staff.

Randomization Procedure

After baseline measures, eligible participants are randomized to the intervention or control group based on a computerized randomization program. Blocks randomization are calculated in block sizes of fours and six. The randomization procedure is only available to an independent researcher who will not be involved in the delivery of the interventions or the performance of the measurements. Due to small sample size required, the randomization lists were not stratified.

Participants

All participants are recruited from the Poidatz Rehabilitation Centre. The children are operated in several hospitals in Paris: Necker Enfants Malades University Hospital, Trousseau University Hospital or Robert Debré University Hospital. Ethics approval is granted by the French Ethical Committee Sud-Est VI (Clermont-Ferrand). Additionally, all parents, and participants from 10 years of age, should provide informed consent prior to study initiation. All participants should have a cooling off period prior to the inclusion (minimum 15 days between information and consent). Confidentiality and data access are guaranteed by the National Commission of Informatic (CNIL). A Data Protection Officer has been designated for all research studies conducted in this rehabilitation centre. He guarantees that the data protection and the rights of the subject are respected according to the General Data Protection Regulation (EU) 2016/679 (GDPR). The study has been registered in ClinicalTrials.gov (Identifier: NCT04837105).
Inclusion criteria are children with CP admitted for inpatient rehabilitation following SEMLS, 10–18 years of age, functioning preoperatively at GMFCS I–III. The minimum time between surgery and inclusion in the study is 7 weeks (step 4 of post-SEMLS rehabilitation process), they should have a Functional Mobility Scale 50 meters rating superior or equal to 2 (ability to walk on 50m using a walker or frame without help from another person).

All children should be able to cooperate, understand and follow simple instructions in French to practice the game. Only voluntary patients whose parents give their consent for their child's participation in the study and patient affiliated to the French social security sys- tem are included. Criteria for exclusion include a diagnosis of photosensitive epilepsy in the medical record and/or patient's case history mentioning seizures that occurred while playing a video game, visual, cognitive or auditory impairment that would interfere with playing the game. The patient must have normal or corrected vision and hearing. During the 4-weeks, children can wear their orthotic device and their assistive device as prescribed by medical staff. In cases of evolution regarding the level of support (a patient going from walking with crutches to no walking aid, for example), the medical staff decides if patient is able to practice series of walking sprints safety and efficiently according the main objective of the study, then they inform the research staff. This change should only be made during the first session of the week to proceed with the new weekly calibration and thus adapt the objective walking speed to the child's abilities.

Patient and Public Involvement

Patient involved as described above. All patients meeting the study criteria were approached directly in the rehabilitation center when they were in the phase of walking recovery after surgery. Information about the study was given to them orally. They are given time to reflect. If they are interested, a physiotherapist contacts the family by phone to give them information about the study. Written consent is obtained after a further period of reflection. No public involved.

Outcomes

Outcome measures take place at baseline (T0), immediately after four weeks of GT (T1), and six months later (T2). The professional caregiver administering outcome measures remains blinded to group allocation. See Supplementary File 2 for outcomes details and criterion validity.

Primary outcome : The 6 minutes walk test (6MWT) The 6MWT is increasingly used in paediatrics, in clinics to monitor patients' abilities or in research as a criterion for evaluating the effectiveness of a rehabilitation protocol [22]. The 6MWT assesses distance walked over 6 minutes as a submaximal test of aerobic capacity/endurance. The reference guideline detailing the recommendations and instructions has been updated in 2013 [23, 24]. The 6MWT is a more suitable measure of walking capacity than peak cardiopulmonary fitness in children with CP [25, 26]. The 6MWT outcome appears to be more strongly influenced by potential limits to walking speed rather than cardiopulmonary fitness. This primary outcome is relative to the primary objective i.e. improve walking capacity.

Secondary outcome : Muscle power sprint test (MPST)
The MPST evaluates anaerobic performance of youth with CP over a 6x15 meters at their maximal speed [21]. Velocity (m/s), acceleration (m/s2), force (kg/s2) and power (watts) are calculated. Anaerobic performance is defined as peak and mean power. Peak power (PP) is the highest power of 6 sprints and mean power

(MP) is the average over 6 sprints. This secondary out- come is relative to the secondary objective i.e. improve anaerobic performance.

Secondary outcome : Shuttle Run Test (SRT)
The 10-meters shuttle run test is an adapted version of the 20-metre shuttle run test to accommodate children with cerebral palsy (CP) classified at Level I or Level II on the Gross Motor Function Classification System (GMFCS) [27]. This test evaluates cardiovascular endurance. In this study, the SRT-II will be used because of postoperative context. The SRT-II starts at 2 km/h. Speed is increased 0.25 km/h every level (minute). The test is over when the child cannot go to the next cone in time. This secondary outcome is relative to the secondary objective i.e. improve physical fitness level.

Secondary outcome : Questionnaire (PACES)
To assess enjoyment for both control and test group, the 16-items of the Physical Activity Enjoyment Scale (PACES) will be used. The PACES is a valid and reliable measure of physical activity enjoyment. It has been used in many studies assessing the effectiveness of VR therapy [28]. This questionnaire will be presented to the participant at the end of the last session. This secondary outcome is relative to the secondary objective i.e. improve satisfaction during therapy.

Sample size and statistical analysis

According to a study of Grecco et al. an average augmentation of 83% (range 80-85%) in 6MWT was calculated after following 12-weeks of treadmill training in postoperative context [13]. The distance travelled during the 6MWT increases from before: 166.4 ± 39.1 m to after: 304.7 ± 75.8 m. The effect size was calculated: d= 2.29. In this previous study, the mean number of training sessions throughout the 12-week period was 11.1 (around 1-session per week) i.e. total dose of 6h/12-weeks. It has been hypothesized that participants following a more intensive protocol (3 sessions/week i.e. total dose of 6h/4-weeks) will show the same effect on the 6MWT.

With an alpha = 0.05 and beta = 0.20 (power = 0.80), a sample size of 6 subjects per group will be required. When taking a failure rate of 10% into account, 14 subjects should be included.

The required sample size was calculated with G Power 3.1.9.7. Parameter was t-tests – Means; difference between two independent means (two groups) with a priori analysis.

The effect of the GT protocol will be analyzed using a multivariate repeated measures

ANOVA. The possible differences between and within T0, T1 and T2 for the intervention group and control group will be calculated with a statistical significance level of $p = 0.05$. If there is a significant difference, a post-hoc test will be executed to further investigate group differences. Quantitative descriptive statistics will be used to present patient characteristics and global results. Data from PACES questionnaire will be analyzed using normality test (deciding to use parametric / non-parametric statistics), descriptive statistics, reliability test (Cronbach Alpha / Composite Reliability), Pearson / Spearman correlational test. All statistical analyses will be performed using R with a statistical significance level of $p = 0.05$. Moreover, the trial statistician will remain blinded to group allocation until the database has been locked.

Discussion

This approach has evolved from two directions: interest to improve walking capacity after SEMLS for children with CP, and from concern that the usual post-operative rehabilitation approach has not produced sustainable improvements in participation and activity in daily life for these children [8].

AVG development framework

This work followed the AVG development framework PROGame, proposed by Amenguai Alcover et al. [18]. A participate process including both professional healthcare and patients has been conducted. The first step was the project initiation. The team identified the need for a AVG, the stakeholders, and user categories (users and experts). They also clarified the game functionality and constraints. They selected the therapy to transfer into the AVG. The operational objectives were to be safe; to provide efficient gait training; to improve walking speed; to motivate the patient; to be fun. These identifications were based upon prior experience and literature review [12, 29]. The team used communication tools like oral presentation of preliminary results, open debates, surveys and meeting reports. The aim was to support incremental development between team's members (that has their own specialty) and to share knowledge. At this stage, the project proposed a general description. The second step was the interaction mechanism, all technical solutions were explored and an algorithm for gait parameters detection was developed and tested [30, 31]. During the third step, the interactive elements, the team investigated actual commercial or AVGs to get inspired. Team exploration and discussion conducted to games like Pokemon Go or Zelda, in which the gamer must explore the world and accomplish missions. These games appear very popular with the younger generation. The development team was composed of therapists (3 physiotherapists), researchers (2 in computer science, 1 in rehabilitation science, 1 in movement science) and a software engineer. These steps occurred between January 2020 and June 2021. All details are available in Supplementary File 3.

The aim was to think together about the best solution for improving postoperative results, especially walking capacity. New technologies were young people's preferred solution. These solutions seem to be a very promising tools for rehabilitation purposes, allowing to manipulate the environment, to offer interaction, to optimize feedback and many other potentialities [19, 32]

Feedback, a key point for motor learning

Feedback retraining paradigm is based on the conversion, the supplementation and augmentation of sensory information that are usually accessible only by an internal focus of attention, to accessible information [32, 33]. In this paradigm, augmented feedback is defined as augmented sensory information provided by an external resource (therapist or display) to the patient [34]. The information provided to the user could be relative to the movement's pattern or result on the environment or the outcome of a movement with respect to the goal. Sensory channels used to deliver information are visual, auditory, or haptic, linked to the proprioception properties of humans. The timing of feedback delivery is critical. Concurrent feedback is delivered while the skill is being performed, terminal feedback is delivered after the skill is performed with or without delay [35]. In our previous study, we have con- firmed that children with CP can adapt their walking speed, and they can positively respond to the real-time AR feedback (article under review). However, we have observed that not all patients performed equally well with the scenarios. When we have looked at the individual responses of each participant for each scenario, we have observed some essential differences. Some people did not perform better with the feedback; others were helped by a particular feedback but disturbed with another. Some authors highlighted these inter- individual differences. Recently, Liu et al. have underscored different patient profiles: "non-responders" and "responders" to the feedback [19]. In their study, patients were people after stroke. They were instructed to walk on a treadmill while visualizing an avatar replicating their exact walking pattern in real-time on a large screen. Overall, patients improved step length and walking speed when the avatar was displayed on a side view. But results were not the same

for all participants; the authors distinguished non-responders and responders to the feedback. They hypothesized that the initial step length ratio could influence the result because patients with a larger paretic step length better responded. This study has shown that specific populations are more sensitive to the virtual environment.

Serious aspect of ARRoW-CP game

ARRoW-CP AVG combines many of the motor learning theories: context focused therapy and goal-directed training, task-specific, variable practice, high intensity, augmented feedback during therapy sessions and motivation of the patient [16]. To find the best feedback modalities for our AVG, we have conducted preliminary studies exploring the impact of feedback modalities on walking speed, both in healthy adults and in children with CP. Study on healthy adults showed that certain feedback helped to increase walking speed, provided that the game instruction was clear. Typically, feedback combining a focus of attention with knowledge of results, a spatial representation with world-locked holograms and a method of presentation with rich holographic content (like animation, colour changes) increased walking speed in healthy subject [36]. This step allowed us to modify and adapt feed- back modalities.

A second study has occurred with children with CP. Results showed that scenarios combining world-locked holograms that disappeared over the time helped children with CP to reach their tar- get speed. On the other hand, a body-locked hologram that advances in front of the user at the target speed was better able to control the walking speed of the patient[37].
ARRoW-CP is an adaptation of the validated protocol from Zwinkels et al. The original protocol consists of 8 weeks, twice a week [17]. Every training session consisted of a 30s walking sprints following the pre- scribed intensity, volume, and time: Week 1 to week 2: 8 sprints, work/rest ratio 1:4; Week 3 to week 4: 10 sprints, work/rest ratio 1:4; Week 5 to week 8: 12 sprints, work/rest ratio 1:3. Because of post-operative context, the intensity should be reduced. At the beginning of the fourth step of rehabilitation process, even if gait training is recommended, children did not recover to their pre-operative level, specifically some children needed crutches or k-walkers. Moreover, a further aspect not to be underestimated: fatigue and pain [38]. The choice of intensity, volume and time in the ARRoW CP protocol is based on practical experience from expert clinician and from literature [12, 17].

Limitations

The limited sample size limit the ability to balance the two groups according the gender, age, GMFCS level and type of surgery. The randomization lists were not stratified. But the next step in the ARRoW-CP project is to modify the game based on our initial results and to conduct a new RCT including more centers (and more children) worldwide. Using AR for therapy is not suitable for all children. We excluded patients with cognitive trouble and with patients high risks of fall based on medical recommendations.

Conclusion

This article presents in detail the gait training protocol tested through a RCT. Both control group and experimental group have an evidence-based physical therapy training. This article also presents the game development framework of the ARRoW-CP AVG. This game is based on the most recent motor learning approach. This is the first study assessing the efficacy of postoperative gait rehabilitation using an active video game. If our hypothesis is validated, ARRoW-CP game will make possible to intensify gait training. This innovative strategy will have significant clinical impact by improving walking capacity for children after SEMLS. Publishing study protocol of the RCT offers the opportunity to collaborate with other teams and to give more details about the study. Results will be available in 2023.

Tables

Table 1 Details of the gait training protocol deployed in the active video game ARRoW-CP

	WEEK 1	WEEK 2	WEEK 3	WEEK 4
Session Number per week	3	3	3	3
Sprint Time (s)	30	30	30	30
Rest Time (min:s)	2:00	2:00	1:30	1:30
Sprint Number	4	6	8	10
Total time of the session	10	15	18	22

Figure 1. Image capture from ARRoW-CP active video game. On the left, this is Yuki, the little dragon that children must follow during walking sprints, and Master Keito, who oversees providing Ninja gait training. On the middle, an adult (not a patient) wearing the Microsoft Hololens AR headset to see holograms. On the right, game elements encourage participants, increase motivation and improve adherence to the therapy (game scoreboard).

Supplementary Files

Supplementary file 1 — ARRoW-CP Active Video Game
Supplementary file 2 — Main Outcomes details and criterion validity. Additional file 3 — Active Video game development framework

Competing interests

Not applicable.

Author's contributions

ALG, GB, SO and ED conceived the study, participated in its design and helped to draft the manuscript. SPT, NK and MB participated in the acquisition and coordination of the study. All authors read, revisit it critically and approved the final manuscript.

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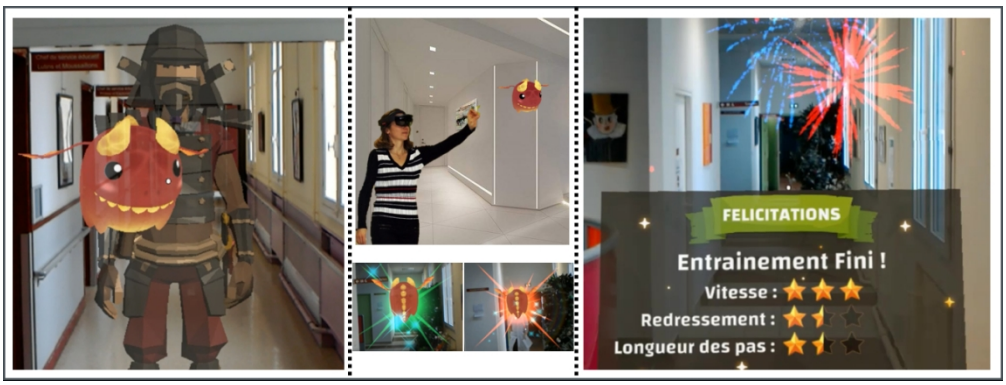

Caption : Figure 1. Image capture from ARRoW-CP active video game. On the left, this is Yuki, the little dragon that children must follow during walking sprints, and Master Keito, who oversees providing Ninja gait training. On the middle, an adult (not a patient) wearing the Microsoft Hololens AR headset to see holograms. On the right, game elements encourage participants, increase motivation and improve adherence to the therapy (game scoreboard)

577x216mm (59 x 59 DPI)

1. The Microsoft Hololens Headset is used for ARRoW-CP **(Figure 1)**. Game development was made with Unity 2019.4.8f1 and Mixed Reality Toolkit (MRTK). MRTK-Unity is a Microsoft-driven project that provides a set of components and features, used to accelerate cross-platform MR app development in Unity.

Figure 1. Microsoft Hololens Augmented reality headset.

2. The player is immersed in a samurai world. He meets the chief of the village that can no longer protect its population. The natural elements are unleashed, causing famine and various damages. The player's role is to develop his energy through ninja training to build a protective totem for the village's inhabitants (trailer: https://youtu.be/BbmniiiJuaA).

The software architecture is presented in **Figure 2**.

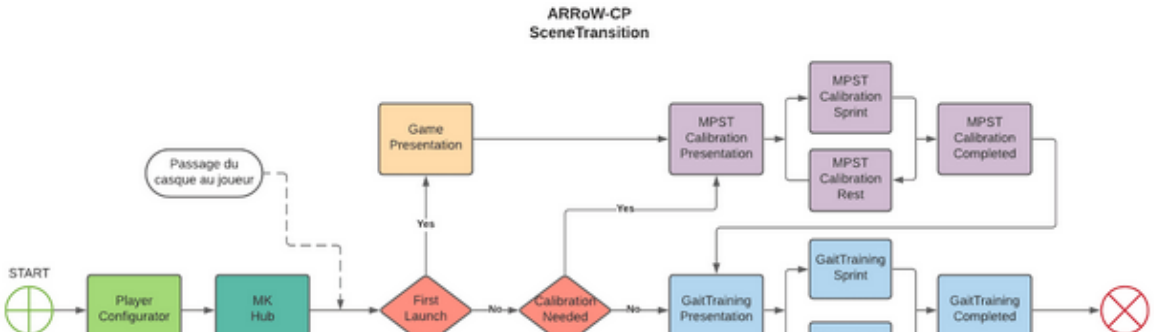

Figure 2. Game architecture of the ARRoW CP game. When the game starts, the AR headset is worn by the therapist. He creates the user profile of the player by entering his name, first name, age, height, and weight during session 1 week 1. Next session, he loads the existing user profile. The therapist then accesses the "MK Hub", which contains information about the performance of previous sessions and the number of sessions

3. The mechanism of feedback provided during sprints and rest time is detailed in **Figure 3**.

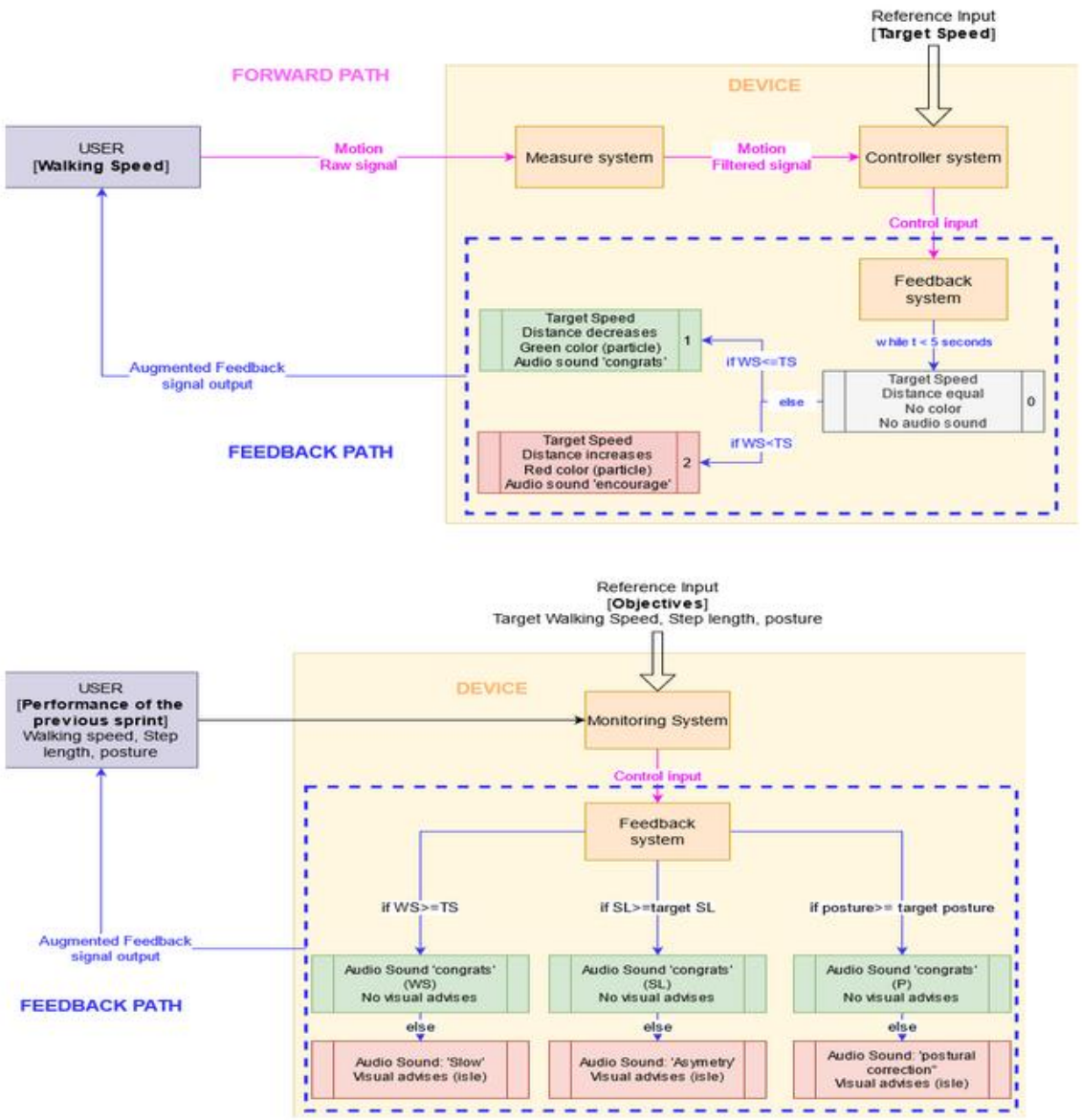

Figure 3. Feedback mechanism during sprints (A) and rest period (B).

At the beginning of each session, through the "Physio HUB", therapists know the previous performance of their patient and they can adjust their advice.

At the end of each session, feedback with delay is proposed to the child: they can choose to see their actual performance through the game scoreboard and totem construction (feedback on demand). These feedbacks were based on knowledge of results.

Test name	Instructions	Validity
[PRIMARY OUTCOME] *The 6 minutes walk test (6MWT)*	To summarize, patients are instructed to walk, not run, as far as they could along a 20-m level surface track during a 6-minute period. This shorter distance has been validated for children in order to be more focused on the task. They could use their usual walking aids. After each minute, participants are told the elapsed time and standardized encouragement is provided. Patients are allowed to stop and rest during the test but are instructed to resume walking as soon as they feel able to do so. The stopwatch is not stopped during this time. The 6MWT distance (in meters) is registered. Measured 6MWT distance could be compared with normative values for children with CP. It is recommended to monitor heart rate during the 6MWT.	In population of children with CP, test/retest reliability is excellent for distance output (ICC=0.98). The 6MWT is poorly related to VO2 peak in ambulatory adolescents and young adults with CP. The 6MWT is a more suitable measure of walking capacity than peak cardiopulmonary fitness in children with CP. The 6MWT outcome appears to be more strongly influenced by potential limits to walking speed rather than cardiopulmonary fitness.
[SECONDARY OUTCOME] *Muscle power sprint test (MPST)*	The 15-m distance is marked by 2 lines taped to the floor. Cones are placed at the end of each of the lines. Participants are instructed to walk as fast as possible from one line to the other, and to be sure to cross each line. Between each run, participants are allowed to rest for 10 seconds before turning around to allow them to prepare for the following sprint. Children should be encouraged to give maximal effort. The following variables are calculated for each of the 6 sprints: velocity (m/s) = distance/time, acceleration (m/s2) = velocity/time, force (kg/s2) = body mass × acceleration, and power (watts) = force × velocity. Anaerobic performance is defined as peak and mean power. Peak power (PP) is the highest power of 6 sprints and mean power (MP) is the average over 6 sprints.	The MPST is a valid test to assess the anaerobic performance in children with CP, significant correlations between the performance on these tests for both PP and MP were found. (PP: r = 0.731 ; MP: r = 0.903). Standard error of measurement (SEM), minimal detectable change (MDC) and normative data are available in Verschuren et al. The children with CP had impaired anaerobic performance as it was lower than that of their peers.
[SECONDARY OUTCOME] *10-meters Shuttle Run Test (SRT)*	Description of the test is available here : “The course is 10 metres long; the end is marked with 2 cones and measuring tape. Subjects should wear regular sports clothing and shoes, and orthoses, if applicable. Each child should also wear a heart rate monitor. Children walk or run between the 2 markers at a set incremental speed. These runs are synchronised with a pre-recorded sound. (…) As the test proceeds, the interval between each successive beep reduces, forcing the child to increase speed over the course of the test, until it is impossible to keep in sync with the recording.” We have developed a mobile application that beeps at regular intervals, indicates the time spent and allows the assessor to increment the number of shuttles made by the child.	The SRT is a valid and reliable test. Test-retest is excellent (ICC=0.99) and high correlations were found for the relationship between data for both shuttle run tests and data for the treadmill test (r=0.96).
[SECONDARY OUTCOME] *Physical Activity Enjoyment Scale (PACES)*	This is a 5-point Likert scale (from 1- I totally disagree to 5- I totally agree). A translation procedure from English to French language has been made using guidelines (figure).	The PACES is a valid and reliable measure of physical activity enjoyment.

Project Initiation		Interaction Mechanism		Interaction Elements	
Global Aim	to develop an active video game for gait rehabilitation for children with motor disabilities and particularly cerebral palsy	**Aim of this phase**	To select the interaction system and to capture the therapy in the system.	**Aim of this phase**	To design the interaction elements that force patients to perform the therapy correctly
Operational objectives *describe the needs in general*	To be safe; to provide efficient gait training; to improve walking speed; to motivate the patient; to be fun.	**Device selection**	Device: Microsoft Hololens AR headset version 1 was selected because its technical characteristics matched all identified specifications. Tools : - Unity software (version 2019.4.8f1) -Microsoft Visual studio 2019 - Mixed Reality ToolKit for Unity (MRTK version 4.2.3)	**Feedback reflexion**	We have proposed a model of feedback in Augmented Reality (AR) for Motor Rehabilitation (article not published yet). Indeed, AR feedback can be displayed to the user through different characteristics. This theoretical work was necessary before designing feedback and testing specific characteristics of the model. The final aim was to optimize the augmented information provided to the patient. To carry out this work, we extended and adapted the biofeedback model described by Macintosh et al., and the qualitative model from Martinez et al., to the AR context. Our descriptive model of feedback in AR application helped us design an AR application, called Best-Of ARRoW. We have tested with this app, the impact of different virtual feedback characteristics on walking speed of children with CP. The results of this first study will be published soon (article under review). This help us to better design the feedback used in ARRoW-CP AVG.
Restrictions *detail economical, technical, operational, legal restrictions*	The development of the game must correspond to the duration of a 3-year thesis; grants are limited and predefined; the agreement of the ethics committee and written consents from participants are required before any test on humans ; all technical solution could be explored.				
Stakeholders *identify customers, special needs and required functionality ; define experts and representatives end users*	Customers : - Children with cerebral palsy, 10-18 years old, GMFCS I-III, with cognitive skills to understand and follow simple instructions == END USERS - Physiotherapists, occupational therapists, physiotherapist assistants, rehabilitation therapists == EXPERTS Special needs and required functionalities : - The active video game must include the principles of motor learning, which are task-specific practice, variable practice, high practice intensity, progressive difficulty, augmented feedback, and adaptability to user abilities. - The active video game should allow the inclusion of motivational elements to increase engagement. - Children must be free to move in the global environment, without restriction of movement. - Children must be able to use their usual walking aids (crutches or posterior walker). - Therapists should have access to the previous and global performance of their patient through the game - The solution should be "ready to use" easily both for children and therapists	**Gait parameters detection development and evaluation**	Algorithm development: HoloStep measuring the real-time gait parameters with the AR headset system[43] Evaluation : - The accuracy of the AR headset's sensors was sufficiently high to evaluate the position of the user without time drift in the global environment[42] - HoloStep was reliable for measuring and calculating walking speed, cadence, step length and global distance travelled in comparison to a reference motion analysis tracking system[43]	**Game selection & Universe**	The choice of the game universe (Samurai world) and reward panel were unanimously validated by experts and end users. All packages used to design the game were available in the Unity Asset Store: Polygon Samurai low poly 3D Art by Synty, Tiny Dragon by Suriyun, the GUI Kit - The Stone, and the Particle FX. Voice of game characters from volunteers were recorded in a professional radio studio (HandiFM – France 107.3 FM).
Therapy Selection	The team's members agreed on making walking speed the main variable input of the serious game. Meaningful reason is that intensive gait training focused on walking speed has shown their clinical efficacy.[12,39] The therapy to transfer into the serious game should include walking sprints.				

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
	2b	All items from the World Health Organization Trial Registration Data Set	1
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	na
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	7
	5b	Name and contact information for the trial sponsor	na
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	na
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	7
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	1-3
	6b	Explanation for choice of comparators	1-3
Objectives	7	Specific objectives or hypotheses	3
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	3

Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	3
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	2-3
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	na
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	na
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	na
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	4-5
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	4
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	5
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	5
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	5

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	na
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	4-5
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	4-5
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	4-5
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	5
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	5
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	5
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	5
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	5
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	5
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	na

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	na
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	5
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	na
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	1
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	na
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	3
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	na
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	na
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	7
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	na
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	na
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	na
	31b	Authorship eligibility guidelines and any intended use of professional writers	na
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	na

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	na
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	na

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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Effect of an Augmented Reality Active Video Game for Gait Training in Children with Cerebral Palsy following Single-Event Multilevel Surgery : Protocol for a Randomized Controlled Trial

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OPEN ACCESS PROTOCOL

Effect of an Augmented Reality Active Video Game for Gait Training in Children with Cerebral Palsy following Single-Event Multilevel Surgery : Protocol for a Randomized Controlled Trial

Anne-Laure Guinet[1,2*†], Michel Bams[1], Sandrine Payan-Terral[1], Neijib Khouri[3], Samir Otmane[2], Guillaume Bouyer[2] and Eric Desailly[1†]

Abstract

Introduction: In paediatric rehabilitation, fun and motivation are also critical keys to successful therapy. A variety of interventions have shown positive effects, high level of interest, compliance and engagement with active video game (AVG).
This seems to be an interesting approach for the postoperative gait rehabilitation of children with CP. In this study, we will investigate if an overground gait training (GT) delivered through an AVG can improve walking capacity and anaerobic performance.

Methods and analysis: This study is a randomized clinical controlled trial. A total of 14 children and adolescents in the age of 10–18 years with CP will be included. The minimum time between surgery and inclusion will be 7 weeks. The test group will participate in the GT program with ARRoW-CP AVG (Augmented Reality Rehabilitation of Walking-Cerebral Palsy), control group will receive GT on a treadmill. The primary outcome is the 6-Minutes Walk Test assessing walking capacity; secondary outcomes are the Muscle Power Sprint Test for anaerobic performance and Shuttle Run Test for physical fitness level. Satisfaction is tested with the Physical Activity Enjoyment Scale. This study has been registered in ClinicalTrials.gov (NCT04837105).
The findings will be disseminated by publications in peer-reviewed journals and conferences.

Keywords: cerebral palsy; surgery; active video game; augmented reality; gait performance

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Strengths and limitations of this study

- This is the first randomized clinical trial to compare traditional rehabilitation and technology delivered gait performance training in children with cerebral palsy after surgery.
- The control group receives treadmill therapy to counterbalance the additional dose effect of active video game use in the experimental group.
- The active video game intervention being investigated have been tailored to the needs of children with cerebral palsy based on feedback from patient and public involvement and expert review groups conducted during the first phase of this project.
- Patients and patient's physiotherapist cannot be blinded; however, the professional caregiver administering outcome measures and the trial statistician will remain blinded to group allocation until the database has been locked.
- The interventions require participants to have no visual, cognitive or auditory impairment that would interfere with playing the game.

Introduction

Cerebral palsy is commonly defined as a "group of permanent disorders of the development of movement and posture, causing activity limitation"[1]. The overall prevalence of CP remains constant (2.11 per 1000 births) [2] with an estimated prevalence of 17 million people worldwide.[3] Individuals with CP present various clinical symptoms including a non-exhaustive list of neurological, orthopaedic, movement, cognitive, vision/hearing, aero digestive disorders.

Musculoskeletal disorders are considered as a secondary impairment contributing to restricted mobility in childhood and adulthood.[4, 5, 6] Since 1985, therapeutic interventions to correct orthopaedic disorders include single-event multilevel surgery (SEMLS). This surgery proposes, during one operative period, to realign the musculoskeletal system, practicing tendon transfer, muscle lengthening, derotation and/or deflexion osteotomy and joint stabilization. Novak et al. classified SEMLS as effective intervention for children with CP for improving both Gross Motor, walking speed and walking capacity but also contracture and alignment deformities [7]. To date, systematic reviews on the effect of SEMLS reported improvement in passive range of motion, kinematics and kinematics gait parameters, overall gait index and energy efficiency [8, 9]. Results were more disputed about the long-term effect on spatio-temporal gait parameters, gross motor function and the activity and participation domain [10].

A recent literature review has proposed a model in five steps that could guide clinicians during the post- operative rehabilitation [11]. The authors suggested that the fourth phase, which included more intensive exercises, functional gait training and resistive muscle strengthening should be optimized to improve the gross motor function and walking speed after surgery. Functional gait training has been defined as 'actively practice the task of walking, to improve walking ability [12]. Intervention could be overground gait training (OGT), or treadmill gait training (TT), with or without body support.

Previously, Grecco et al. demonstrated the efficacy of treadmill gait training program including both on functional mobility and gross motor function on children with CP after SEMLS [13]. Recently, a systematic review showed that gait training was a safe and effective intervention to improve walking capacity in children with CP, outside postoperative context [12]. In particular, the minimal clinically important difference (MCID) for increase in walking speed (0.1m/s) was achieved after intervention in 12 studies/14 (studies level between II and III). Authors discussed two points: OGT could provide greater effect on locomotor abilities than TT because OGT is more representative of the natural walking, and the addition of feedback could enhance the patient outcomes. These points were important to consider after SEMLS, because the overall gait pattern of children was modified by the bone and muscle gestures. Novak et al. highlighted the importance of the context focused therapy and goal-directed training for children with CP [7]. Functional gait training should therefore take into ac- count those recommendations and involve motor learning strategies: task-specific, variable practice, high intensity, augmented

feedback during therapy sessions and motivation of the patient [14].
In recent years, new technologies have been introduced in rehabilitation practice, both for upper and lower limbs therapy. These systems include a large type of technology ranging from fully immersive virtual reality (VR) or augmented reality (AR) using commercially available head-mounted displays (HMD) (e.g., Oculus Quest; HTC VIVE, Microsoft HoloLens), Cave Automatic Virtual Environment where video is projected on the walls and floor20 to video game console on television screen (e.g., Nintendo Switch, PlayStation).
To 'actively practice the task of walking', systems combining treadmill training and active video game (AVG) delivered through a screen in a semi-immersive environment have been tested with good results [15]. However, motor learning principles are not always fully integrated into VR/AR systems because of the lack of knowledge about which feedback modality and which intensity level should be provided in the rehabilitation settings [16].

To our knowledge, even if OGT was recommended for functional gait training, no AR system with AVG exists to provide high-intensity, with progressive difficulty, and variable modalities including feedback. To this end, we have developed the active video game ARRoW-CP (Augmented Reality Rehabilitation of Walking-Cerebral Palsy) combining OGT based on previous results [12] and literature [17] and motor learning theory [14]. ARRoW-CP active video game has been developed for Microsoft Hololens headset (mixed reality headset). The team used the game development framework PROGame and all stakeholders have been involved through the process (children with CP, researchers, engineers, therapists)[18]. In most studies, even if feedback is effective to improve motor activities, the characteristics applied during interventions were generally inconsistent with motor control feedback theory. Authors suggest that timing, frequency and autonomy should be adjusted to optimize long-term effect [19]. A strategy that provides feedback to the user on demand promotes learning. Then, by reducing the frequency and timing of the feedback, the user can develop a sense of self-regulation. In this AVG, continuous feedback as well as terminal feedback, both with different audio and visual modalities, are combined following the recommendations of the literature [20, 16]. The general principle for defining the feedback to be used is primarily defined by the results from a previous study that the team lead (article under review). Specific recommendations from this previous study included using feedback moving on in front of the player at the target speed to create a more challenging task that motivates participants to excel. In addition, our results highlighted that the temporary modification of visual aspect according to the performance (red light/too slow; green light/good speed) helped to improve walking speed creating a playful challenge. The feedback attached to the player seemed to be better to minimize visual discomfort and, by extension, fatigue. More details of ARRoW-CP game, architecture, framework development and feedback characteristics, are available in the Supplementary Files 1 and 2.

The current study, denoted as the ARRoW-CP study, will investigate whether a gait training protocol through an active video game in AR can:

1. Increase the walking capacity
2. Increase anaerobic performance & physical fitness level
3. Improve the level of satisfaction during therapy

Our hypothesis is that the AVG ARRoW-CP is at least as effective as treadmill training to improve walking performance and more enjoyable for children with CP following surgery.

Methods and analysis

Study Design

This study is a randomized control trial with two groups: OGT using the AVG ARRoW-CP in AR (OGT-AR) and Treadmill Training control group (TT). All children and adolescents participate in a four-week gait training intervention to improve their walking function in one of this two groups. During this period, children continue their usual physical

therapy program (5 weekly 45-minutes session). This postoperative protocol has been standardized following a 5-step framework [11]. These usual rehabilitation sessions include muscle stretching exercises, muscle strengthening exercises (active resistance exercises), functional exercises (sit-to-stand, transfer, balance, walk, stairs). The study is planned to start in April 2021 and end in December 2023.

Description of the two gait training interventions

To standardize the session content as much as possible, the therapists involved in the study participate in the training sessions before the start of the study. During these sessions, a member of the project team presents them the process and objectives of this study, as well as the gait training protocol proposed for the two groups. A session is dedicated to the familiarization with Microsoft Hololens and the ARRoW-CP game via a tutorial application.

ARRoW-CP: Overground Gait Training in AR

Intervention group receives the OGT-AR protocol through the AVG ARRoW-CP using the Microsoft Hololens headset (Figures 1A-C). ARRoW-CP sessions are monitored by physiotherapist, assistant physiotherapist, or research assistant.

The intervention consists of 4 weeks of OGT (3 sessions per week), including a series of walking sprints. These sessions are always performed indoors, along the same flat and straight 30m in length hallway with a hard surface that is seldom traveled. The starting point is marked with a round floor sticker ARRoW- CP. Children can see the real environment because of transparency of holograms and use of augmented reality (that is different from virtual reality), but some safety measures are taken to avoid collision with other people: the caregiver signals to others that a session is in progress, checking before starting the game that there are no obstacles in the hallway. This protocol is an adaptation from Zwinkels et al. [17]. Every training session consists of a prescribed intensity, volume and time (Table I).

Before the first session of each week, the target velocity is calculated during a Muscle Power Sprint Test (MPST) [21]. This test is made through the ARRoW- CP game and is presented as a "calibration" to the participant. During this test, no feedback is presented to the player. The target velocity is defined as the highest velocity of 6 sprints. This test is repeated every week to adapt the difficulty of the game to the child's progress.

Treadmill Gait Training

The control group protocol consists of 4 weeks of GT on a treadmill (3 sessions per week), with a maximal duration of 30 minutes. This protocol is an adaptation from Grecco et al.[13]

Before the first session, the target velocity is estimated during a treadmill speed test: participants are instructed to walk on a treadmill with increasing speed (initially 0.5 km/h and increased 0.5 km/h each minute). Each minute, children are asked about short- ness of breath and the subjective responses are classified using the 1-10 Borg Rating of Perceived Exertion Scale. The test is stopped if the score is higher than 5. The target velocity is defined as 80% of the maximum speed achieved during the test.

The first 5 minutes is a warm-up time, the speed is gradually increased until reaching the target velocity. The child walks for a maximal 20 minutes at their target velocity. Then, the treadmill speed is gradually diminished over the final 5 minutes. Training could be interrupted at any time at the child's request or physical therapist judgement. Treadmill sessions are monitored by physiotherapist, assistant-physiotherapist, or a member of the research staff.

Randomization Procedure

After baseline measures, eligible participants are randomized to the intervention or control group based on a computerized randomization program. Blocks randomization are calculated in block sizes of fours and six. The randomization procedure is only available to an independent researcher who will not be involved in the delivery of the interventions or the performance of the measurements. Due to small sample size required, the

randomization lists were not stratified.

Participants

All participants are recruited from the Poidatz Rehabilitation Centre. The children are operated in several hospitals in Paris: Necker Enfants Malades University Hospital, Trousseau University Hospital or Robert Debré University Hospital. Ethics approval is granted by the French Ethical Committee Sud-Est VI (Clermont-Ferrand). All patients meeting the study criteria were approached directly in the rehabilitation center when they were in the phase of walking recovery after surgery. Information about the study was given to them orally. They are given time to reflect. If they are interested, a physiotherapist contacts the family by phone to give them information about the study. Written consent is obtained after a further period of reflection. Additionally, all parents, and participants from 10 years of age, should provide informed consent prior to study initiation. All participants should have a cooling off period prior to the inclusion (minimum 15 days between information and consent). Confidentiality and data access are guaranteed by the National Commission of Informatic (CNIL). A Data Protection Officer has been designated for all research studies conducted in this rehabilitation centre. He guarantees that the data protection and the rights of the subject are respected according to the General Data Protection Regulation (EU) 2016/679 (GDPR). The study has been registered in ClinicalTrials.gov (Identifier: NCT04837105).
Inclusion criteria are children with CP admitted for inpatient rehabilitation following SEMLS, 10–18 years of age, functioning preoperatively at GMFCS I–III. The minimum time between surgery and inclusion in the study is 7 weeks (step 4 of post-SEMLS rehabilitation process), they should have a Functional Mobility Scale 50 meters rating superior or equal to 2 (ability to walk on 50m using a walker or frame without help from another person).

All children should be able to cooperate, understand and follow simple instructions in French to practice the game. Only voluntary patients whose parents give their consent for their child's participation in the study and patient affiliated to the French social security system are included. Criteria for exclusion include a diagnosis of photosensitive epilepsy in the medical record and/or patient's case history mentioning seizures that occurred while playing a video game, visual, cognitive or auditory impairment that would interfere with playing the game. The patient must have normal or corrected vision and hearing. During the 4-weeks, children can wear their orthotic device and their assistive device as prescribed by medical staff. In cases of evolution regarding the level of support (a patient going from walking with crutches to no walking aid, for example), the medical staff decides if patient is able to practice series of walking sprints safety and efficiently according the main objective of the study, then they inform the research staff. This change should only be made during the first session of the week to proceed with the new weekly calibration and thus adapt the objective walking speed to the child's abilities.

Patient and Public Involvement

Patient involved as described above. Throughout the development phase of the ARRoW-CP active video game, test sessions were organized with some of the patients of the rehabilitation centre to collect their opinion on the game. The results of the RCT will be disseminated to the international community through the publication of articles and conference papers. It is also planned to spread these results to communicate them to parents, families, and children with motor disabilities (regional or national newspapers in French, social networks, patient associations).

Outcomes

Outcome measures take place at baseline (T0), immediately after four weeks of GT (T1), and six months later (T2). The professional caregiver administering outcome measures remains blinded to group allocation. See Supplementary File 3 for outcomes details and criterion validity.

Primary outcome : The 6 minutes walk test (6MWT) The 6MWT is increasingly used in paediatrics, in clinics to monitor patients' abilities or in research as a criterion for evaluating the effectiveness of a rehabilitation protocol [22]. The 6MWT assesses distance walked over 6 minutes as a submaximal test of aerobic capacity/endurance. The reference guideline detailing the recommendations and instructions has been updated in 2013 [23,

24]. The 6MWT is a more suitable measure of walking capacity than peak cardiopulmonary fitness in children with CP [25, 26]. The 6MWT outcome appears to be more strongly influenced by potential limits to walking speed rather than cardiopulmonary fitness. This primary outcome is relative to the primary objective i.e. improve walking capacity.

Secondary outcome : Muscle power sprint test (MPST)
The MPST evaluates anaerobic performance of youth with CP over a 6x15 meters at their maximal speed [21]. Velocity (m/s), acceleration (m/s2), force (kg/s2) and power (watts) are calculated. Anaerobic performance is defined as peak and mean power. Peak power (PP) is the highest power of 6 sprints and mean power (MP) is the average over 6 sprints. This secondary outcome is relative to the secondary objective i.e. improve anaerobic performance.

Secondary outcome : Shuttle Run Test (SRT)
The 10-meters shuttle run test is an adapted version of the 20-metre shuttle run test to accommodate children with cerebral palsy (CP) classified at Level I or Level II on the Gross Motor Function Classification System (GMFCS) [27]. This test evaluates cardiovascular endurance. In this study, the SRT-II will be used because of postoperative context. The SRT-II starts at 2 km/h. Speed is increased 0.25 km/h every level (minute). The test is over when the child cannot go to the next cone in time. This secondary outcome is relative to the secondary objective i.e. improve physical fitness level.

Secondary outcome : Questionnaire (PACES)
To assess enjoyment for both control and test group, the 16-items of the Physical Activity Enjoyment Scale (PACES) will be used. The PACES is a valid and reliable measure of physical activity enjoyment. It has been used in many studies assessing the effectiveness of VR therapy [28]. This questionnaire will be presented to the participant at the end of the last session. This secondary outcome is relative to the secondary objective i.e. improve satisfaction during therapy.

Sample size and statistical analysis
According to a study of Grecco et al. an average augmentation of 83% (range 80-85%) in 6MWT was calculated after following 12-weeks of treadmill training in postoperative context [13]. The distance travelled during the 6MWT increases from before: 166.4 ± 39.1 m to after: 304.7 ± 75.8 m. The effect size was calculated: d= 2.29. In this previous study, the mean number of training sessions throughout the 12-week period was 11.1 (around 1-session per week) i.e. total dose of 6h/12-weeks. It has been hypothesized that participants following a more intensive protocol (3 sessions/week i.e. total dose of 6h/4-weeks) will show the same effect on the 6MWT.

With an alpha = 0.05 and beta = 0.20 (power = 0.80), a sample size of 6 subjects per group will be required. When taking a failure rate of 10% into account, 14 subjects should be included.

The required sample size was calculated with G Power 3.1.9.7. Parameter was t-tests – Means; difference between two independent means (two groups) with a priori analysis.

The effect of the GT protocol will be analyzed using a multivariate repeated measures ANOVA. The possible differences between and within T0, T1 and T2 for the intervention group and control group will be calculated with a statistical significance level of p = 0.05. If there is a significant difference, a post-hoc test will be executed to further investigate group differences. Quantitative descriptive statistics will be used to present patient characteristics and global results. Data from PACES questionnaire will be analyzed using normality test (deciding to use parametric / non-parametric statistics), descriptive statistics, reliability test (Cronbach Alpha / Composite Reliability), Pearson / Spearman correlational test. All statistical analyses will be performed using R with a statistical significance level of p = 0.05. Moreover, the trial statistician will remain blinded to group allocation until the database has been locked.

Discussion

This approach has evolved from two directions: interest to improve walking capacity after SEMLS for children with CP, and from concern that the usual post-operative rehabilitation approach has not produced sustainable improvements in participation and activity in daily life for these children [8].

AVG development framework

This work followed the AVG development framework PROGame, proposed by Amenguai Alcover et al. [18]. A participate process including both professional healthcare and patients has been conducted. The first step was the project initiation. The team identified the need for a AVG, the stakeholders, and user categories (users and experts). They also clarified the game functionality and constraints. They selected the therapy to transfer into the AVG. The operational objectives were to be safe; to provide efficient gait training; to improve walking speed; to motivate the patient; to be fun. These identifications were based upon prior experience and literature review [12, 29]. The team used communication tools like oral presentation of preliminary results, open debates, surveys and meeting reports. The aim was to support incremental development between team's members (that has their own specialty) and to share knowledge. At this stage, the project proposed a general description. The second step was the interaction mechanism, all technical solutions were explored and an algorithm for gait parameters detection was developed and tested [30, 31]. During the third step, the interactive elements, the team investigated actual commercial or AVGs to get inspired. Team exploration and discussion conducted to games like Pokemon Go or Zelda, in which the gamer must explore the world and accomplish missions. These games appear very popular with the younger generation. The development team was composed of therapists (3 physiotherapists), researchers (2 in computer science, 1 in rehabilitation science, 1 in movement science) and a software engineer. These steps occurred between January 2020 and June 2021. All details are available in Supplementary File 2.

The aim was to think together about the best solution for improving postoperative results, especially walking capacity. New technologies were young people's preferred solution. These solutions seem to be a very promising tools for rehabilitation purposes, al- lowing to manipulate the environment, to offer inter- action, to optimize feedback and many other potentialities [19, 32]

Feedback, a key point for motor learning

Feedback retraining paradigm is based on the conversion, the supplementation and augmentation of sensory information that are usually accessible only by an internal focus of attention, to accessible information [32, 33]. In this paradigm, augmented feedback is defined as augmented sensory information provided by an external resource (therapist or display) to the patient [34]. The information provided to the user could be relative to the movement's pattern or result on the environment or the outcome of a movement with respect to the goal. Sensory channels used to deliver information are visual, auditory, or haptic, linked to the proprioception properties of humans. The timing of feedback delivery is critical. Concurrent feedback is delivered while the skill is being performed, terminal feedback is delivered after the skill is performed with or without delay [35]. In our previous study, we have confirmed that children with CP can adapt their walking speed, and they can positively respond to the real-time AR feedback (article under review). However, we have observed that not all patients performed equally well with the scenarios. When we have looked at the individual responses of each participant for each scenario, we have observed some essential differences. Some people did not perform better with the feedback; others were helped by a particular feedback but disturbed with another. Some authors highlighted these inter- individual differences. Recently, Liu et al. have underscored different patient profiles: "non-responders" and "responders" to the feedback [19]. In their study, patients were people after stroke. They were instructed to walk on a treadmill while visualizing an avatar replicating their exact walking pattern in real-time on a large screen. Overall, patients improved step length and walking speed when the avatar was displayed on a side view. But results were not the same for all participants; the authors distinguished non-responders and

responders to the feedback. They hypothesized that the initial step length ratio could influence the result because patients with a larger paretic step length better responded. This study has shown that specific populations are more sensitive to the virtual environment.

Serious aspect of ARRoW-CP game

ARRoW-CP AVG combines many of the motor learning theories: context focused therapy and goal-directed training, task-specific, variable practice, high intensity, augmented feedback during therapy sessions and motivation of the patient [16]. To find the best feedback modalities for our AVG, we have conducted preliminary studies exploring the impact of feedback modalities on walking speed, both in healthy adults and in children with CP. Study on healthy adults showed that certain feedback helped to increase walking speed, provided that the game instruction was clear. Typically, feedback combining a focus of attention with knowledge of results, a spatial representation with world-locked holograms and a method of presentation with rich holographic content (like animation, colour changes) increased walking speed in healthy subject [36]. This step allowed us to modify and adapt feedback modalities (Figures 1A-C).

A second study has occurred with children with CP. Results showed that scenarios combining world-locked holograms that disappeared over the time helped children with CP to reach their target speed. On the other hand, a body-locked hologram that advances in front of the user at the target speed was better able to control the walking speed of the patient[37].
ARRoW-CP is an adaptation of the validated protocol from Zwinkels et al. The original protocol consists of 8 weeks, twice a week [17]. Every training session consisted of a 30s walking sprints following the pre- scribed intensity, volume, and time: Week 1 to week 2: 8 sprints, work/rest ratio 1:4; Week 3 to week 4: 10 sprints, work/rest ratio 1:4; Week 5 to week 8: 12 sprints, work/rest ratio 1:3. Because of post-operative context, the intensity should be reduced. At the beginning of the fourth step of rehabilitation process, even if gait training is recommended, children did not recover to their pre-operative level, specifically some children needed crutches or k-walkers. Moreover, a further aspect not to be underestimated: fatigue and pain [38]. The choice of intensity, volume and time in the ARRoW CP protocol is based on practical experience from expert clinician and from literature [12, 17].

Limitations

The limited sample size limit the ability to balance the two groups according the gender, age, GMFCS level and type of surgery. The randomization lists were not stratified. But the next step in the ARRoW-CP project is to modify the game based on our initial results and to conduct a new RCT including more centers (and more children) worldwide. Using AR for therapy is not suitable for all children. We excluded patients with cognitive trouble and with patients high risks of fall based on medical recommendations.

Conclusion

This article presents in detail the gait training protocol tested through a RCT. Both control group and experimental group have an evidence-based physical therapy training. This article also presents the game development framework of the ARRoW-CP AVG. This game is based on the most recent motor learning approach. This is the first study assessing the efficacy of postoperative gait rehabilitation using an active video game. If our hypothesis is validated, ARRoW-CP game will make possible to intensify gait training. This innovative strategy will have significant clinical impact by improving walking capacity for children after SEMLS. Publishing study protocol of the RCT offers the opportunity to collaborate with other teams and to give more details about the study. Results will be available in 2023.

Tables

Table 1 Details of the gait training protocol deployed in the active video game ARRoW-CP

	WEEK 1	WEEK 2	WEEK 3	WEEK 4
Session Number per week	3	3	3	3
Sprint Time (s)	30	30	30	30
Rest Time (min:s)	2:00	2:00	1:30	1:30
Sprint Number	4	6	8	10
Total time of the session	10	15	18	22

Figures 1A-C. Image capture from ARRoW-CP active video game. On the left (A), this is Yuki, the little dragon that children must follow during walking sprints, and Master Keito, who oversees providing Ninja gait training. On the middle (B), an adult (not a patient) wearing the Microsoft Hololens AR headset to see holograms. On the right (C), game elements encourage participants, increase motivation and improve adherence to the therapy (game scoreboard).

Supplementary Files

Supplementary file 1 — ARRoW-CP Active Video Game
Supplementary file 2 — Active Video game development framework
Supplementary file 3 — Main Outcomes details and criterion validity.

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a. Contributorship

ALG, GB, SO and ED conceived the study, participated in its design, and helped to draft the manuscript. SPT, NK and MB participated in the acquisition and coordination of the study. All authors read, revisit it critically and approved the final manuscript. All of them affirm that the manuscript is an honest, accurate, and transparent account of the study being reported.

b. Funding statement

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c. Competing interests

There are no competing interests for any author.

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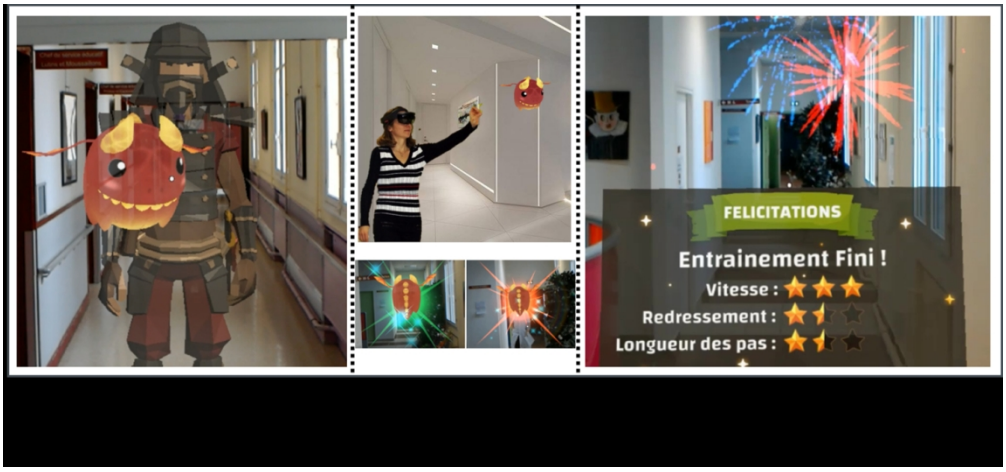

Figures 1A-C. Image capture from ARRoW-CP active video game. On the left (A), this is Yuki, the little dragon that children must follow during walking sprints, and Master Keito, who oversees providing Ninja gait training. On the middle (B), an adult (not a patient) wearing the Microsoft Hololens AR headset to see holograms. On the right (C), game elements encourage participants, increase motivation and improve adherence to the therapy (game scoreboard)

289x134mm (130 x 130 DPI)

1. The Microsoft Hololens Headset is used for ARRoW-CP **(Figure 1)**. Game development was made with Unity 2019.4.8f1 and Mixed Reality Toolkit (MRTK). MRTK-Unity is a Microsoft-driven project that provides a set of components and features, used to accelerate cross-platform MR app development in Unity.

Figure 1. Microsoft Hololens Augmented reality headset.

2. The player is immersed in a samurai world. He meets the chief of the village that can no longer protect its population. The natural elements are unleashed, causing famine and various damages. The player's role is to develop his energy through ninja training to build a protective totem for the village's inhabitants (trailer: https://youtu.be/BbmniiiJuaA).

The software architecture is presented in **Figure 2**.

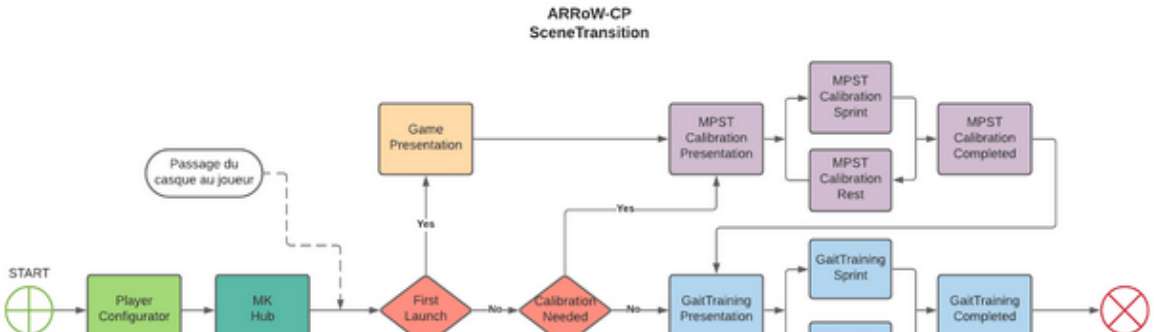

Figure 2. Game architecture of the ARRoW CP game. When the game starts, the AR headset is worn by the therapist. He creates the user profile of the player by entering his name, first name, age, height, and weight during session 1 week 1. Next session, he loads the existing user profile. The therapist then accesses the "MK Hub", which contains information about the performance of previous sessions and the number of sessions

3. The mechanism of feedback provided during sprints and rest time is detailed in **Figure 3**.

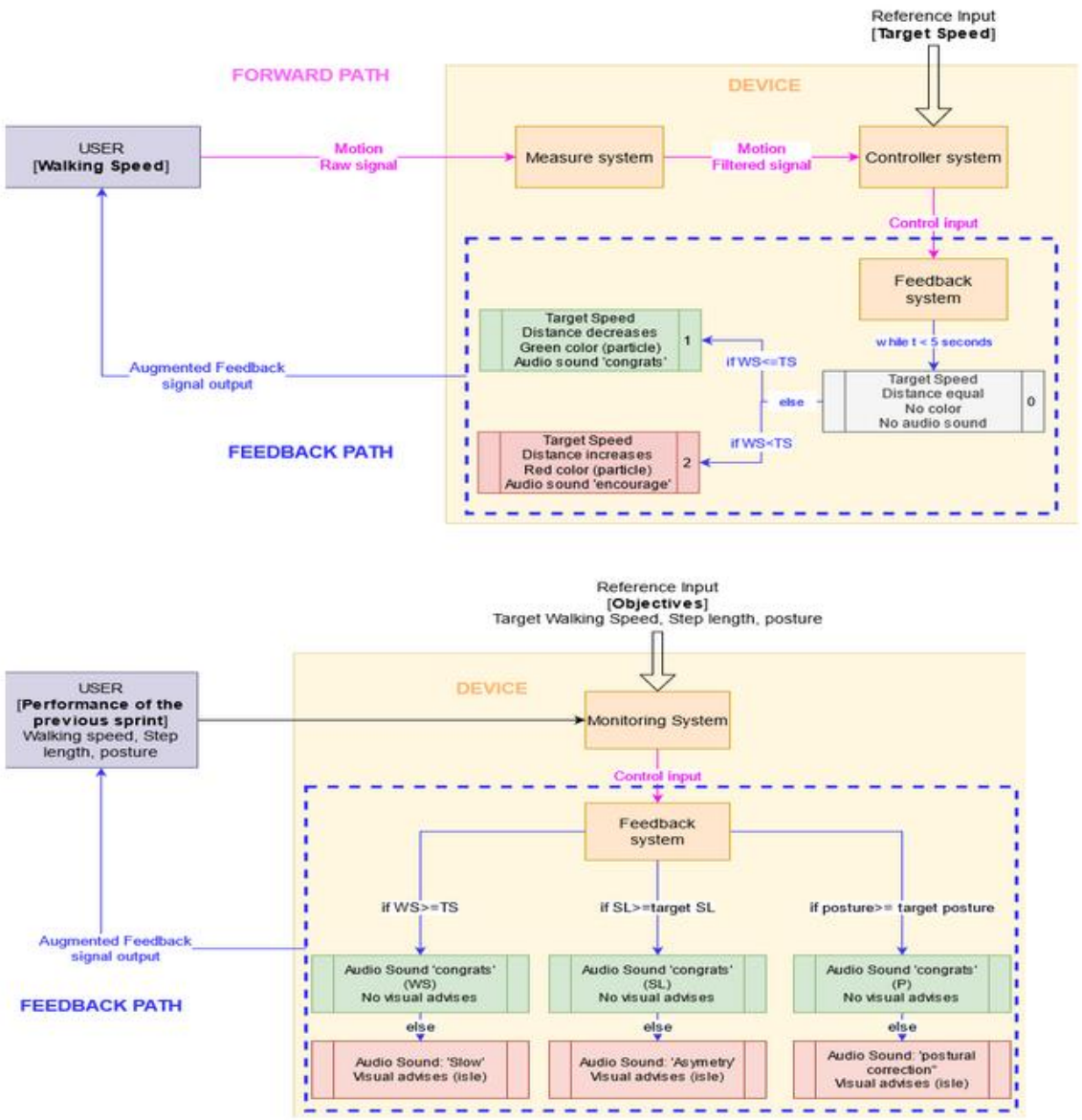

Figure 3. Feedback mechanism during sprints (A) and rest period (B).

At the beginning of each session, through the "Physio HUB", therapists know the previous performance of their patient and they can adjust their advice.

At the end of each session, feedback with delay is proposed to the child: they can choose to see their actual performance through the game scoreboard and totem construction (feedback on demand). These feedbacks were based on knowledge of results.

Project Initiation

Global Aim	to develop an active video game for gait rehabilitation for children with motor disabilities and particularly cerebral palsy
Operational objectives *describe the needs in general*	To be safe; to provide efficient gait training; to improve walking speed; to motivate the patient; to be fun.
Restrictions *detail economical, technical, operational, legal restrictions*	The development of the game must correspond to the duration of a 3-year thesis; grants are limited and predefined; the agreement of the ethics committee and written consents from participants are required before any test on humans ; all technical solution could be explored.
Stakeholders *identify customers, special needs and required functionality ; define experts and representatives end users*	Customers : - Children with cerebral palsy, 10-18 years old, GMFCS I-III, with cognitive skills to understand and follow simple instructions == END USERS - Physiotherapists, occupational therapists, physiotherapist assistants, rehabilitation therapists == EXPERTS Special needs and required functionalities : - The active video game must include the principles of motor learning, which are task-specific practice, variable practice, high practice intensity, progressive difficulty, augmented feedback, and adaptability to user abilities. - The active video game should allow the inclusion of motivational elements to increase engagement. - Children must be free to move in the global environment, without restriction of movement. - Children must be able to use their usual walking aids (crutches or posterior walker). - Therapists should have access to the previous and global performance of their patient through the game - The solution should be "ready to use" easily both for children and therapists
Therapy Selection	The team's members agreed on making walking speed the main variable input of the serious game. Meaningful reason is that intensive gait training focused on walking speed has shown their clinical efficacy.[12,39] The therapy to transfer into the serious game should include walking sprints.

Interaction Mechanism

Aim of this phase	To select the interaction system and to capture the therapy into the system.
Device selection	Device: Microsoft Hololens AR headset version 1 was selected because its technical characteristics matched all identified specifications. Tools : - Unity software (version 2019.4.8f1) -Microsoft Visual studio 2019 - Mixed Reality ToolKit for Unity (MRTK version 4.2.3)
Gait parameters detection development and evaluation	Algorithm development: HoloStep measuring the real-time gait parameters with the AR headset system[43] Evaluation : - The accuracy of the AR headset's sensors was sufficiently high to evaluate the position of the user without time drift in the global environment[42] - HoloStep was reliable for measuring and calculating walking speed, cadence, step length and global distance travelled in comparison to a reference motion analysis tracking system[43]

Interaction Elements

Aim of this phase	To design the interaction elements that force patients to perform the therapy correctly
Feedback reflexion	We have proposed a model of feedback in Augmented Reality (AR) for Motor Rehabilitation (article not published yet). Indeed, AR feedback can be displayed to the user through different characteristics. This theoretical work was necessary before designing feedback and testing specific characteristics of the model. The final aim was to optimize the augmented information provided to the patient. To carry out this work, we extended and adapted the biofeedback model described by Macintosh et al., and the qualitative model from Martinez et al., to the AR context. Our descriptive model of feedback in AR application helped us design an AR application, called Best-Of ARRoW. We have tested with this app, the impact of different virtual feedback characteristics on walking speed of children with CP. The results of this first study will be published soon (article under review). This help us to better design the feedback used in ARRoW-CP AVG.
Game selection & Universe	The choice of the game universe (Samurai world) and reward panel were unanimously validated by experts and end users. All packages used to design the game were available in the Unity Asset Store: Polygon Samurai low poly 3D Art by Synty, Tiny Dragon by Suriyun, the GUI Kit - The Stone, and the Particle FX. Voice of game characters from volunteers were recorded in a professional radio studio (HandiFM – France 107.3 FM).

Test name	Instructions	Validity
[PRIMARY OUTCOME] *The 6 minutes walk test (6MWT)*	To summarize, patients are instructed to walk, not run, as far as they could along a 20-m level surface track during a 6-minute period. This shorter distance has been validated for children in order to be more focused on the task. They could use their usual walking aids. After each minute, participants are told the elapsed time and standardized encouragement is provided. Patients are allowed to stop and rest during the test but are instructed to resume walking as soon as they feel able to do so. The stopwatch is not stopped during this time. The 6MWT distance (in meters) is registered. Measured 6MWT distance could be compared with normative values for children with CP. It is recommended to monitor heart rate during the 6MWT.	In population of children with CP, test/retest reliability is excellent for distance output (ICC=0.98). The 6MWT is poorly related to VO2 peak in ambulatory adolescents and young adults with CP. The 6MWT is a more suitable measure of walking capacity than peak cardiopulmonary fitness in children with CP. The 6MWT outcome appears to be more strongly influenced by potential limits to walking speed rather than cardiopulmonary fitness.
[SECONDARY OUTCOME] *Muscle power sprint test (MPST)*	The 15-m distance is marked by 2 lines taped to the floor. Cones are placed at the end of each of the lines. Participants are instructed to walk as fast as possible from one line to the other, and to be sure to cross each line. Between each run, participants are allowed to rest for 10 seconds before turning around to allow them to prepare for the following sprint. Children should be encouraged to give maximal effort. The following variables are calculated for each of the 6 sprints: velocity (m/s) = distance/time, acceleration (m/s2) = velocity/time, force (kg/s2) = body mass × acceleration, and power (watts) = force × velocity. Anaerobic performance is defined as peak and mean power. Peak power (PP) is the highest power of 6 sprints and mean power (MP) is the average over 6 sprints.	The MPST is a valid test to assess the anaerobic performance in children with CP, significant correlations between the performance on these tests for both PP and MP were found. (PP: r = 0.731 ; MP: r = 0.903). Standard error of measurement (SEM), minimal detectable change (MDC) and normative data are available in Verschuren et al. The children with CP had impaired anaerobic performance as it was lower than that of their peers.
[SECONDARY OUTCOME] *10-meters Shuttle Run Test (SRT)*	Description of the test is available here : “The course is 10 metres long; the end is marked with 2 cones and measuring tape. Subjects should wear regular sports clothing and shoes, and orthoses, if applicable. Each child should also wear a heart rate monitor. Children walk or run between the 2 markers at a set incremental speed. These runs are synchronised with a pre-recorded sound. (…) As the test proceeds, the interval between each successive beep reduces, forcing the child to increase speed over the course of the test, until it is impossible to keep in sync with the recording.” We have developed a mobile application that beeps at regular intervals, indicates the time spent and allows the assessor to increment the number of shuttles made by the child.	The SRT is a valid and reliable test. Test-retest is excellent (ICC=0.99) and high correlations were found for the relationship between data for both shuttle run tests and data for the treadmill test (r=0.96).
[SECONDARY OUTCOME] *Physical Activity Enjoyment Scale (PACES)*	This is a 5-point Likert scale (from 1- I totally disagree to 5- I totally agree). A translation procedure from English to French language has been made using guidelines (figure).	The PACES is a valid and reliable measure of physical activity enjoyment.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
	2b	All items from the World Health Organization Trial Registration Data Set	1
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	na
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	7
	5b	Name and contact information for the trial sponsor	na
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	na
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	7
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	1-3
	6b	Explanation for choice of comparators	1-3
Objectives	7	Specific objectives or hypotheses	3
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	3

Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	3
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	2-3
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	na
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	na
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	na
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	4-5
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	4
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	5
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	5
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	5

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	na
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	4-5
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	4-5
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	4-5
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	5
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	5
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	5
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	5
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	5
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	5
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	na

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	na
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	5
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	na
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	1
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	na
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	3
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	na
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	na
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	7
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	na
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	na
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	na
	31b	Authorship eligibility guidelines and any intended use of professional writers	na
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	na

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	na
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	na

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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Effect of an Augmented Reality Active Video Game for Gait Training in Children with Cerebral Palsy following Single-Event Multilevel Surgery : Protocol for a Randomized Controlled Trial

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OPEN ACCESS PROTOCOL

Effect of an Augmented Reality Active Video Game for Gait Training in Children with Cerebral Palsy following Single-Event Multilevel Surgery : Protocol for a Randomized Controlled Trial

Anne-Laure Guinet[1,2*†], Michel Bams[1], Sandrine Payan-Terral[1], Neijib Khouri[3], Samir Otmane[2], Guillaume Bouyer[2] and Eric Desailly[1†]

Abstract

Introduction: In paediatric rehabilitation, fun and motivation are also critical keys to successful therapy. A variety of interventions have shown positive effects, high level of interest, compliance and engagement with active video game (AVG).
This seems to be an interesting approach for the postoperative gait rehabilitation of children with CP. In this study, we will investigate if an overground gait training (GT) delivered through an AVG can improve walking capacity and anaerobic performance.

Methods and analysis: This study is a randomized clinical controlled trial. A total of 14 children and adolescents in the age of 10–18 years with CP will be included. The minimum time between surgery and inclusion will be 7 weeks. The test group will participate in the GT program with ARRoW-CP AVG (Augmented Reality Rehabilitation of Walking-Cerebral Palsy), control group will receive GT on a treadmill. The primary outcome is the 6-Minutes Walk Test assessing walking capacity; secondary outcomes are the Muscle Power Sprint Test for anaerobic performance and Shuttle Run Test for physical fitness level. Satisfaction is tested with the Physical Activity Enjoyment Scale. This study has been registered in ClinicalTrials.gov (NCT04837105).
Ethics and dissemination: The findings will be disseminated by publications in peer-reviewed journals and conferences. This study received agreement from French ethic committee (Comité de Protection des Personnes Sud-Est VI – Number 2020-A02959-30)

Keywords: cerebral palsy; surgery; active video game; augmented reality; gait performance

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Strengths and limitations of this study

- This is the first randomized clinical trial to compare traditional rehabilitation and technology delivered gait performance training in children with cerebral palsy after surgery.
- The control group receives treadmill therapy to counterbalance the additional dose effect of active video game use in the experimental group.
- The active video game intervention being investigated have been tailored to the needs of children with cerebral palsy based on feedback from patient and public involvement and expert review groups conducted during the first phase of this project.
- Patients and patient's physiotherapist cannot be blinded; however, the professional caregiver administering outcome measures and the trial statistician will remain blinded to group allocation until the database has been locked.
- The interventions require participants to have no visual, cognitive or auditory impairment that would interfere with playing the game.

Introduction

Cerebral palsy is commonly defined as a "group of permanent disorders of the development of movement and posture, causing activity limitation"[1]. The overall prevalence of CP remains constant (2.11 per 1000 births) [2] with an estimated prevalence of 17 million people worldwide.[3] Individuals with CP present various clinical symptoms including a non-exhaustive list of neurological, orthopaedic, movement, cognitive, vision/hearing, aero digestive disorders.

Musculoskeletal disorders are considered as a secondary impairment contributing to restricted mobility in childhood and adulthood.[4, 5, 6] Since 1985, therapeutic interventions to correct orthopaedic disorders include single-event multilevel surgery (SEMLS). This surgery proposes, during one operative period, to realign the musculoskeletal system, practicing tendon transfer, muscle lengthening, derotation and/or deflexion osteotomy and joint stabilization. Novak et al. classified SEMLS as effective intervention for children with CP for improving both Gross Motor, walking speed and walking capacity but also contracture and alignment deformities [7]. To date, systematic reviews on the effect of SEMLS reported improvement in passive range of motion, kinematics and kinematics gait parameters, overall gait index and energy efficiency [8, 9]. Results were more disputed about the long-term effect on spatio-temporal gait parameters, gross motor function and the activity and participation domain [10].

A recent literature review has proposed a model in five steps that could guide clinicians during the post- operative rehabilitation [11]. The authors suggested that the fourth phase, which included more intensive exercises, functional gait training and resistive muscle strengthening should be optimized to improve the gross motor function and walking speed after surgery. Functional gait training has been defined as 'actively practice the task of walking, to improve walking ability [12]. Intervention could be overground gait training (OGT), or treadmill gait training (TT), with or without body support.

Previously, Grecco et al. demonstrated the efficacy of treadmill gait training program including both on functional mobility and gross motor function on children with CP after SEMLS [13]. Recently, a systematic review showed that gait training was a safe and effective intervention to improve walking capacity in children with CP, outside postoperative context [12]. In particular, the minimal clinically important difference (MCID) for increase in walking speed (0.1m/s) was achieved after intervention in 12 studies/14 (studies level between II and III). Authors discussed two points: OGT could provide greater effect on locomotor abilities than TT because OGT is more representative of the natural walking, and the addition of feedback could enhance the patient outcomes. These points were important to consider after SEMLS, because the overall gait pattern of children was modified by the bone and muscle gestures. Novak et al. highlighted the importance of the context focused therapy and goal-directed training for children with CP [7]. Functional gait training should therefore take into ac- count those recommendations and involve motor learning strategies: task-specific, variable practice, high intensity, augmented

feedback during therapy sessions and motivation of the patient [14].
In recent years, new technologies have been introduced in rehabilitation practice, both for upper and lower limbs therapy. These systems include a large type of technology ranging from fully immersive virtual reality (VR) or augmented reality (AR) using commercially available head-mounted displays (HMD) (e.g., Oculus Quest; HTC VIVE, Microsoft HoloLens), Cave Automatic Virtual Environment where video is projected on the walls and floor20 to video game console on television screen (e.g., Nintendo Switch, PlayStation).
To 'actively practice the task of walking', systems combining treadmill training and active video game (AVG) delivered through a screen in a semi-immersive environment have been tested with good results [15]. However, motor learning principles are not always fully integrated into VR/AR systems because of the lack of knowledge about which feedback modality and which intensity level should be provided in the rehabilitation settings [16].

To our knowledge, even if OGT was recommended for functional gait training, no AR system with AVG exists to provide high-intensity, with progressive difficulty, and variable modalities including feedback. To this end, we have developed the active video game ARRoW-CP (Augmented Reality Rehabilitation of Walking-Cerebral Palsy) combining OGT based on previous results [12] and literature [17] and motor learning theory [14]. ARRoW-CP active video game has been developed for Microsoft Hololens headset (mixed reality headset). The team used the game development framework PROGame and all stakeholders have been involved through the process (children with CP, researchers, engineers, therapists)[18]. In most studies, even if feedback is effective to improve motor activities, the characteristics applied during interventions were generally inconsistent with motor control feedback theory. Authors suggest that timing, frequency and autonomy should be adjusted to optimize long-term effect [19]. A strategy that provides feedback to the user on demand promotes learning. Then, by reducing the frequency and timing of the feedback, the user can develop a sense of self-regulation. In this AVG, continuous feedback as well as terminal feedback, both with different audio and visual modalities, are combined following the recommendations of the literature [20, 16]. The general principle for defining the feedback to be used is primarily defined by the results from a previous study that the team lead (article under review). Specific recommendations from this previous study included using feedback moving on in front of the player at the target speed to create a more challenging task that motivates participants to excel. In addition, our results highlighted that the temporary modification of visual aspect according to the performance (red light/too slow; green light/good speed) helped to improve walking speed creating a playful challenge. The feedback attached to the player seemed to be better to minimize visual discomfort and, by extension, fatigue. More details of ARRoW-CP game, architecture, framework development and feedback characteristics, are available in the Supplementary Files 1 and 2.

The current study, denoted as the ARRoW-CP study, will investigate whether a gait training protocol through an active video game in AR can:

1. Increase the walking capacity
2. Increase anaerobic performance & physical fitness level
3. Improve the level of satisfaction during therapy

Our hypothesis is that the AVG ARRoW-CP is at least as effective as treadmill training to improve walking performance and more enjoyable for children with CP following surgery.

Methods and analysis

Study Design

This study is a randomized control trial with two groups: OGT using the AVG ARRoW-CP in AR (OGT-AR) and Treadmill Training control group (TT). All children and adolescents participate in a four-week gait training intervention to improve their walking function in one of this two groups. During this period, children continue their usual physical

therapy program (5 weekly 45-minutes session). This postoperative protocol has been standardized following a 5-step framework [11]. These usual rehabilitation sessions include muscle stretching exercises, muscle strengthening exercises (active resistance exercises), functional exercises (sit-to-stand, transfer, balance, walk, stairs). The study is planned to start in April 2021 and end in December 2023.

Description of the two gait training interventions

To standardize the session content as much as possible, the therapists involved in the study participate in the training sessions before the start of the study. During these sessions, a member of the project team presents them the process and objectives of this study, as well as the gait training protocol proposed for the two groups. A session is dedicated to the familiarization with Microsoft Hololens and the ARRoW-CP game via a tutorial application.

ARRoW-CP: Overground Gait Training in AR

Intervention group receives the OGT-AR protocol through the AVG ARRoW-CP using the Microsoft Hololens headset (Figures 1A-C). ARRoW-CP sessions are monitored by physiotherapist, assistant physiotherapist, or research assistant.

The intervention consists of 4 weeks of OGT (3 sessions per week), including a series of walking sprints. These sessions are always performed indoors, along the same flat and straight 30m in length hallway with a hard surface that is seldom traveled. The starting point is marked with a round floor sticker ARRoW- CP. Children can see the real environment because of transparency of holograms and use of augmented reality (that is different from virtual reality), but some safety measures are taken to avoid collision with other people: the caregiver signals to others that a session is in progress, checking before starting the game that there are no obstacles in the hallway. This protocol is an adaptation from Zwinkels et al. [17]. Every training session consists of a prescribed intensity, volume and time (Table I).

Before the first session of each week, the target velocity is calculated during a Muscle Power Sprint Test (MPST) [21]. This test is made through the ARRoW- CP game and is presented as a "calibration" to the participant. During this test, no feedback is presented to the player. The target velocity is defined as the highest velocity of 6 sprints. This test is repeated every week to adapt the difficulty of the game to the child's progress.

Treadmill Gait Training

The control group protocol consists of 4 weeks of GT on a treadmill (3 sessions per week), with a maximal duration of 30 minutes. This protocol is an adaptation from Grecco et al.[13]

Before the first session, the target velocity is estimated during a treadmill speed test: participants are instructed to walk on a treadmill with increasing speed (initially 0.5 km/h and increased 0.5 km/h each minute). Each minute, children are asked about short- ness of breath and the subjective responses are classified using the 1-10 Borg Rating of Perceived Exertion Scale. The test is stopped if the score is higher than 5. The target velocity is defined as 80% of the maximum speed achieved during the test.

The first 5 minutes is a warm-up time, the speed is gradually increased until reaching the target velocity. The child walks for a maximal 20 minutes at their target velocity. Then, the treadmill speed is gradually diminished over the final 5 minutes. Training could be interrupted at any time at the child's request or physical therapist judgement. Treadmill sessions are monitored by physiotherapist, assistant-physiotherapist, or a member of the research staff.

Randomization Procedure

After baseline measures, eligible participants are randomized to the intervention or control group based on a computerized randomization program. Blocks randomization are calculated in block sizes of fours and six. The randomization procedure is only available to an independent researcher who will not be involved in the delivery of the interventions or the performance of the measurements. Due to small sample size required, the

randomization lists were not stratified.

Participants

All participants are recruited from the Poidatz Rehabilitation Centre. The children are operated in several hospitals in Paris: Necker Enfants Malades University Hospital, Trousseau University Hospital or Robert Debré University Hospital. Ethics approval is granted by the French Ethical Committee Sud-Est VI (Clermont-Ferrand). All patients meeting the study criteria were approached directly in the rehabilitation center when they were in the phase of walking recovery after surgery. Information about the study was given to them orally. They are given time to reflect. If they are interested, a physiotherapist contacts the family by phone to give them information about the study. Written consent is obtained after a further period of reflection. Additionally, all parents, and participants from 10 years of age, should provide informed consent prior to study initiation. All participants should have a cooling off period prior to the inclusion (minimum 15 days between information and consent). Confidentiality and data access are guaranteed by the National Commission of Informatic (CNIL). A Data Protection Officer has been designated for all research studies conducted in this rehabilitation centre. He guarantees that the data protection and the rights of the subject are respected according to the General Data Protection Regulation (EU) 2016/679 (GDPR). The study has been registered in ClinicalTrials.gov (Identifier: NCT04837105).
Inclusion criteria are children with CP admitted for inpatient rehabilitation following SEMLS, 10–18 years of age, functioning preoperatively at GMFCS I–III. The minimum time between surgery and inclusion in the study is 7 weeks (step 4 of post-SEMLS rehabilitation process), they should have a Functional Mobility Scale 50 meters rating superior or equal to 2 (ability to walk on 50m using a walker or frame without help from another person).

All children should be able to cooperate, understand and follow simple instructions in French to practice the game. Only voluntary patients whose parents give their consent for their child's participation in the study and patient affiliated to the French social security system are included. Criteria for exclusion include a diagnosis of photosensitive epilepsy in the medical record and/or patient's case history mentioning seizures that occurred while playing a video game, visual, cognitive or auditory impairment that would interfere with playing the game. The patient must have normal or corrected vision and hearing. During the 4-weeks, children can wear their orthotic device and their assistive device as prescribed by medical staff. In cases of evolution regarding the level of support (a patient going from walking with crutches to no walking aid, for example), the medical staff decides if patient is able to practice series of walking sprints safety and efficiently according the main objective of the study, then they inform the research staff. This change should only be made during the first session of the week to proceed with the new weekly calibration and thus adapt the objective walking speed to the child's abilities.

Patient and Public Involvement

Patient involved as described above. Throughout the development phase of the ARRoW-CP active video game, test sessions were organized with some of the patients of the rehabilitation centre to collect their opinion on the game. The results of the RCT will be disseminated to the international community through the publication of articles and conference papers. It is also planned to spread these results to communicate them to parents, families, and children with motor disabilities (regional or national newspapers in French, social networks, patient associations).

Outcomes

Outcome measures take place at baseline (T0), immediately after four weeks of GT (T1), and six months later (T2). The professional caregiver administering outcome measures remains blinded to group allocation. See Supplementary File 3 for outcomes details and criterion validity.

Primary outcome : The 6 minutes walk test (6MWT) The 6MWT is increasingly used in paediatrics, in clinics to monitor patients' abilities or in research as a criterion for evaluating the effectiveness of a rehabilitation protocol [22]. The 6MWT assesses distance walked over 6 minutes as a submaximal test of aerobic capacity/endurance. The reference guideline detailing the recommendations and instructions has been updated in 2013 [23,

24]. The 6MWT is a more suitable measure of walking capacity than peak cardiopulmonary fitness in children with CP [25, 26]. The 6MWT outcome appears to be more strongly influenced by potential limits to walking speed rather than cardiopulmonary fitness. This primary outcome is relative to the primary objective i.e. improve walking capacity.

Secondary outcome : Muscle power sprint test (MPST)
The MPST evaluates anaerobic performance of youth with CP over a 6x15 meters at their maximal speed [21]. Velocity (m/s), acceleration (m/s2), force (kg/s2) and power (watts) are calculated. Anaerobic performance is defined as peak and mean power. Peak power (PP) is the highest power of 6 sprints and mean power (MP) is the average over 6 sprints. This secondary outcome is relative to the secondary objective i.e. improve anaerobic performance.

Secondary outcome : Shuttle Run Test (SRT)
The 10-meters shuttle run test is an adapted version of the 20-metre shuttle run test to accommodate children with cerebral palsy (CP) classified at Level I or Level II on the Gross Motor Function Classification System (GMFCS) [27]. This test evaluates cardiovascular endurance. In this study, the SRT-II will be used because of postoperative context. The SRT-II starts at 2 km/h. Speed is increased 0.25 km/h every level (minute). The test is over when the child cannot go to the next cone in time. This secondary outcome is relative to the secondary objective i.e. improve physical fitness level.

Secondary outcome : Questionnaire (PACES)
To assess enjoyment for both control and test group, the 16-items of the Physical Activity Enjoyment Scale (PACES) will be used. The PACES is a valid and reliable measure of physical activity enjoyment. It has been used in many studies assessing the effectiveness of VR therapy [28]. This questionnaire will be presented to the participant at the end of the last session. This secondary outcome is relative to the secondary objective i.e. improve satisfaction during therapy.

Sample size and statistical analysis
According to a study of Grecco et al. an average augmentation of 83% (range 80-85%) in 6MWT was calculated after following 12-weeks of treadmill training in postoperative context [13]. The distance travelled during the 6MWT increases from before: 166.4 ± 39.1 m to after: 304.7 ± 75.8 m. The effect size was calculated: d= 2.29. In this previous study, the mean number of training sessions throughout the 12-week period was 11.1 (around 1-session per week) i.e. total dose of 6h/12-weeks. It has been hypothesized that participants following a more intensive protocol (3 sessions/week i.e. total dose of 6h/4-weeks) will show the same effect on the 6MWT.

With an alpha = 0.05 and beta = 0.20 (power = 0.80), a sample size of 6 subjects per group will be required. When taking a failure rate of 10% into account, 14 subjects should be included.

The required sample size was calculated with G Power 3.1.9.7. Parameter was t-tests – Means; difference between two independent means (two groups) with a priori analysis.

The effect of the GT protocol will be analyzed using a multivariate repeated measures ANOVA. The possible differences between and within T0, T1 and T2 for the intervention group and control group will be calculated with a statistical significance level of p = 0.05. If there is a significant difference, a post-hoc test will be executed to further investigate group differences. Quantitative descriptive statistics will be used to present patient characteristics and global results. Data from PACES questionnaire will be analyzed using normality test (deciding to use parametric / non-parametric statistics), descriptive statistics, reliability test (Cronbach Alpha / Composite Reliability), Pearson / Spearman correlational test. All statistical analyses will be performed using R with a statistical significance level of p = 0.05. Moreover, the trial statistician will remain blinded to group allocation until the database has been locked.

Ethics and dissemination: The findings will be disseminated by publications in peer-reviewed journals and conferences. This study received agreement from French ethic committee (Comité de Protection des Personnes Sud-Est VI – Number 2020-A02959-30)

Discussion

This approach has evolved from two directions: interest to improve walking capacity after SEMLS for children with CP, and from concern that the usual post-operative rehabilitation approach has not produced sustainable improvements in participation and activity in daily life for these children [8].

AVG development framework

This work followed the AVG development framework PROGame, proposed by Amenguai Alcover et al. [18]. A participate process including both professional healthcare and patients has been conducted. The first step was the project initiation. The team identified the need for a AVG, the stakeholders, and user categories (users and experts). They also clarified the game functionality and constraints. They selected the therapy to transfer into the AVG. The operational objectives were to be safe; to provide efficient gait training; to improve walking speed; to motivate the patient; to be fun. These identifications were based upon prior experience and literature review [12, 29]. The team used communication tools like oral presentation of preliminary results, open debates, surveys and meeting reports. The aim was to support incremental development between team's members (that has their own specialty) and to share knowledge. At this stage, the project proposed a general description. The second step was the interaction mechanism, all technical solutions were explored and an algorithm for gait parameters detection was developed and tested [30, 31]. During the third step, the interactive elements, the team investigated actual commercial or AVGs to get inspired. Team exploration and discussion conducted to games like Pokemon Go or Zelda, in which the gamer must explore the world and accomplish missions. These games appear very popular with the younger generation. The development team was composed of therapists (3 physiotherapists), researchers (2 in computer science, 1 in rehabilitation science, 1 in movement science) and a software engineer. These steps occurred between January 2020 and June 2021. All details are available in Supplementary File 2.

The aim was to think together about the best solution for improving postoperative results, especially walking capacity. New technologies were young people's preferred solution. These solutions seem to be a very promising tools for rehabilitation purposes, al- lowing to manipulate the environment, to offer inter- action, to optimize feedback and many other potentialities [19, 32]

Feedback, a key point for motor learning

Feedback retraining paradigm is based on the conversion, the supplementation and augmentation of sensory information that are usually accessible only by an internal focus of attention, to accessible information [32, 33]. In this paradigm, augmented feedback is defined as augmented sensory information provided by an external resource (therapist or display) to the patient [34]. The information provided to the user could be relative to the movement's pattern or result on the environment or the outcome of a movement with respect to the goal. Sensory channels used to deliver information are visual, auditory, or haptic, linked to the proprioception properties of humans. The timing of feedback delivery is critical. Concurrent feedback is delivered while the skill is being performed, terminal feedback is delivered after the skill is performed with or without delay [35]. In our previous study, we have confirmed that children with CP can adapt their walking speed, and they can positively respond to the real-time AR feedback (article under review). However, we have observed that not all patients performed equally well with the scenarios. When we have looked at the individual responses of each participant for each scenario, we have observed some essential differences. Some people did not perform better with the feedback; others were helped by a particular feedback but disturbed with another. Some authors highlighted these inter- individual differences. Recently, Liu et al. have underscored different patient

profiles: ”non-responders” and ”responders” to the feedback [19]. In their study, patients were people after stroke. They were instructed to walk on a treadmill while visualizing an avatar replicating their exact walking pattern in real-time on a large screen. Overall, patients improved step length and walking speed when the avatar was displayed on a side view. But results were not the same for all participants; the authors distinguished non-responders and responders to the feedback. They hypothesized that the initial step length ratio could influence the result because patients with a larger paretic step length better responded. This study has shown that specific populations are more sensitive to the virtual environment.

Serious aspect of ARRoW-CP game

ARRoW-CP AVG combines many of the motor learning theories: context focused therapy and goal-directed training, task-specific, variable practice, high intensity, augmented feedback during therapy sessions and motivation of the patient [16]. To find the best feedback modalities for our AVG, we have conducted preliminary studies exploring the impact of feedback modalities on walking speed, both in healthy adults and in children with CP. Study on healthy adults showed that certain feedback helped to increase walking speed, provided that the game instruction was clear. Typically, feedback combining a focus of attention with knowledge of results, a spatial representation with world-locked holograms and a method of presentation with rich holographic content (like animation, colour changes) increased walking speed in healthy subject [36]. This step allowed us to modify and adapt feedback modalities (Figures 1A-C).

A second study has occurred with children with CP. Results showed that scenarios combining world-locked holograms that disappeared over the time helped children with CP to reach their target speed. On the other hand, a body-locked hologram that advances in front of the user at the target speed was better able to control the walking speed of the patient[37].
ARRoW-CP is an adaptation of the validated protocol from Zwinkels et al. The original protocol consists of 8 weeks, twice a week [17]. Every training session consisted of a 30s walking sprints following the pre- scribed intensity, volume, and time: Week 1 to week 2: 8 sprints, work/rest ratio 1:4; Week 3 to week 4: 10 sprints, work/rest ratio 1:4; Week 5 to week 8: 12 sprints, work/rest ratio 1:3. Because of post-operative context, the intensity should be reduced. At the beginning of the fourth step of rehabilitation process, even if gait training is recommended, children did not recover to their pre-operative level, specifically some children needed crutches or k-walkers. Moreover, a further aspect not to be underestimated: fatigue and pain [38]. The choice of intensity, volume and time in the ARRoW CP protocol is based on practical experience from expert clinician and from literature [12, 17].

This article presents in detail the gait training protocol tested through a RCT. Both control group and experimental group have an evidence-based physical therapy training. This article also presents the game development framework of the ARRoW-CP AVG. This game is based on the most recent motor learning approach. This is the first study assessing the efficacy of postoperative gait rehabilitation using an active video game. If our hypothesis is validated, ARRoW-CP game will make possible to intensify gait training. This innovative strategy will have significant clinical impact by improving walking capacity for children after SEMLS. Publishing study protocol of the RCT offers the opportunity to collaborate with other teams and to give more details about the study. Results will be available in 2023.

Limitations

The limited sample size limit the ability to balance the two groups according the gender, age, GMFCS level and type of surgery. The randomization lists were not stratified. But the next step in the ARRoW-CP project is to modify the game based on our initial results and to conduct a new RCT including more centers (and more children) worldwide. Using

AR for therapy is not suitable for all children. We excluded patients with cognitive trouble and with patients high risks of fall based on medical recommendations.

Tables

Table 1 Details of the gait training protocol deployed in the active video game ARRoW-CP

	WEEK 1	WEEK 2	WEEK 3	WEEK 4
Session Number per week	3	3	3	3
Sprint Time (s)	30	30	30	30
Rest Time (min:s)	2:00	2:00	1:30	1:30
Sprint Number	4	6	8	10
Total time of the session	10	15	18	22

Figures 1A-C. Image capture from ARRoW-CP active video game. On the left (A), this is Yuki, the little dragon that children must follow during walking sprints, and Master Keito, who oversees providing Ninja gait training. On the middle (B), an adult (not a patient) wearing the Microsoft Hololens AR headset to see holograms. On the right (C), game elements encourage participants, increase motivation and improve adherence to the therapy (game scoreboard).

Supplementary Files

Supplementary file 1 — ARRoW-CP Active Video Game
Supplementary file 2 — Active Video game development framework
Supplementary file 3 — Main Outcomes details and criterion validity.

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a. Contributorship

ALG, GB, SO and ED conceived the study, participated in its design, and helped to draft the manuscript. SPT, NK and MB participated in the acquisition and coordination of the study. All authors read, revisit it critically and approved the final manuscript. All of them affirm that the manuscript is an honest, accurate, and transparent account of the study being reported.

b. Funding statement

This study is a part of the ARRoW CP project supported by the Association Nationale Recherche et Technologie (ANRT) ID CIFRE 2018/0973. This is a public sponsor that does not influence the study.

c. Competing interests

There are no competing interests for any author.

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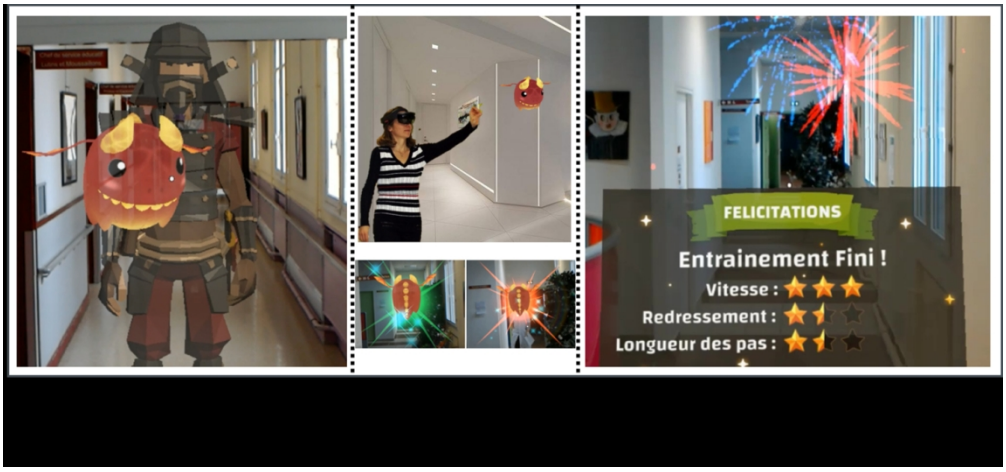

Figures 1A-C. Image capture from ARRoW-CP active video game. On the left (A), this is Yuki, the little dragon that children must follow during walking sprints, and Master Keito, who oversees providing Ninja gait training. On the middle (B), an adult (not a patient) wearing the Microsoft Hololens AR headset to see holograms. On the right (C), game elements encourage participants, increase motivation and improve adherence to the therapy (game scoreboard)

289x134mm (130 x 130 DPI)

1. The Microsoft Hololens Headset is used for ARRoW-CP **(Figure 1)**. Game development was made with Unity 2019.4.8f1 and Mixed Reality Toolkit (MRTK). MRTK-Unity is a Microsoft-driven project that provides a set of components and features, used to accelerate cross-platform MR app development in Unity.

Figure 1. Microsoft Hololens Augmented reality headset.

2. The player is immersed in a samurai world. He meets the chief of the village that can no longer protect its population. The natural elements are unleashed, causing famine and various damages. The player's role is to develop his energy through ninja training to build a protective totem for the village's inhabitants (trailer: https://youtu.be/BbmniiiJuaA).

The software architecture is presented in **Figure 2**.

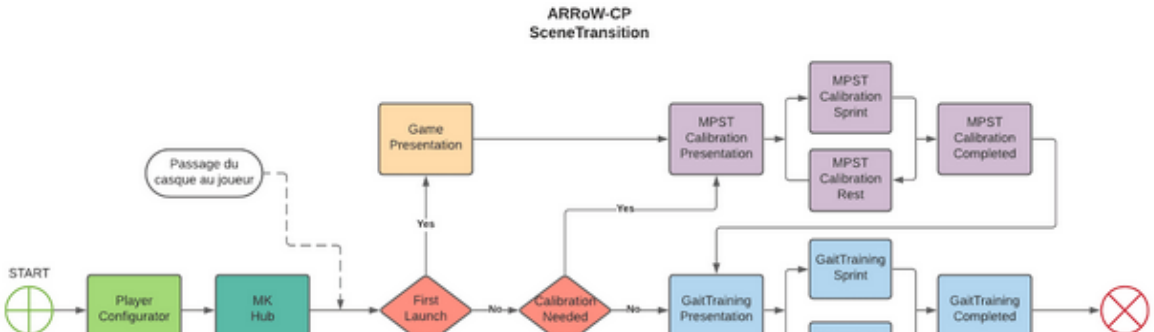

Figure 2. Game architecture of the ARRoW CP game. When the game starts, the AR headset is worn by the therapist. He creates the user profile of the player by entering his name, first name, age, height, and weight during session 1 week 1. Next session, he loads the existing user profile. The therapist then accesses the "MK Hub", which contains information about the performance of previous sessions and the number of sessions

3. The mechanism of feedback provided during sprints and rest time is detailed in **Figure 3**.

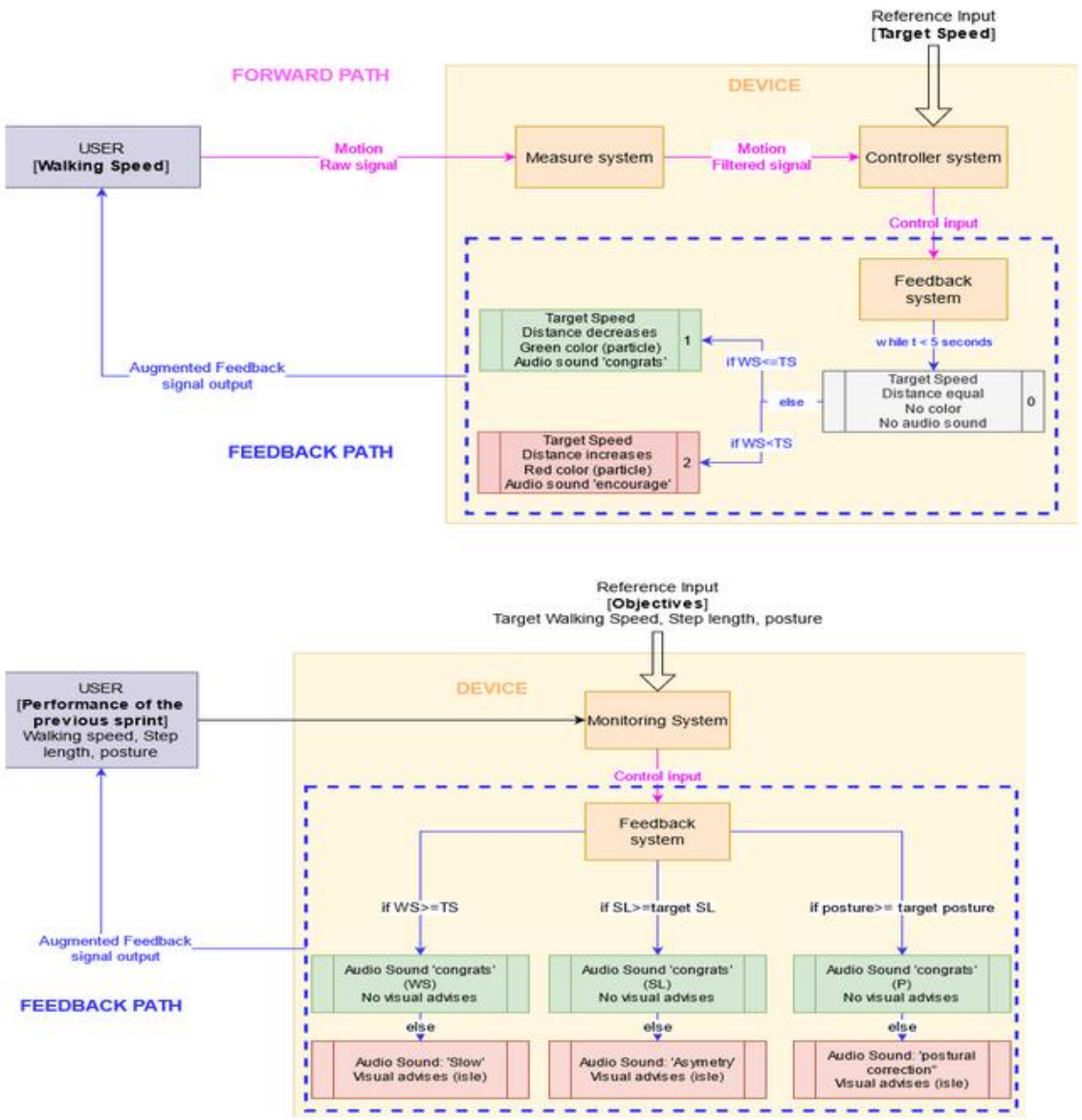

Figure 3. Feedback mechanism during sprints (A) and rest period (B).

At the beginning of each session, through the "Physio HUB", therapists know the previous performance of their patient and they can adjust their advice.

At the end of each session, feedback with delay is proposed to the child: they can choose to see their actual performance through the game scoreboard and totem construction (feedback on demand). These feedbacks were based on knowledge of results.

Project Initiation		Interaction Mechanism		Interaction Elements	
Global Aim	to develop an active video game for gait rehabilitation for children with motor disabilities and particularly cerebral palsy	**Aim of this phase**	To select the interaction system and to capture the therapy in the system.	**Aim of this phase**	To design the interaction elements that force patients to perform the therapy correctly
Operational objectives *describe the needs in general*	To be safe; to provide efficient gait training; to improve walking speed; to motivate the patient; to be fun.	**Device selection**	Device: Microsoft Hololens AR headset version 1 was selected because its technical characteristics matched all identified specifications. Tools : - Unity software (version 2019.4.8f1) -Microsoft Visual studio 2019 - Mixed Reality ToolKit for Unity (MRTK version 4.2.3)	**Feedback reflexion**	We have proposed a model of feedback in Augmented Reality (AR) for Motor Rehabilitation (article not published yet). Indeed, AR feedback can be displayed to the user through different characteristics. This theoretical work was necessary before designing feedback and testing specific characteristics of the model. The final aim was to optimize the augmented information provided to the patient. To carry out this work, we extended and adapted the biofeedback model described by Macintosh et al., and the qualitative model from Martinez et al., to the AR context. Our descriptive model of feedback in AR application helped us design an AR application, called Best-Of ARRoW. We have tested with this app, the impact of different virtual feedback characteristics on walking speed of children with CP. The results of this first study will be published soon (article under review). This help us to better design the feedback used in ARRoW-CP AVG.
Restrictions *detail economical, technical, operational, legal restrictions*	The development of the game must correspond to the duration of a 3-year thesis; grants are limited and predefined; the agreement of the ethics committee and written consents from participants are required before any test on humans ; all technical solution could be explored.				
Stakeholders *identify customers, special needs and required functionality ; define experts and representatives end users*	Customers : - Children with cerebral palsy, 10-18 years old, GMFCS I-III, with cognitive skills to understand and follow simple instructions == END USERS - Physiotherapists, occupational therapists, physiotherapist assistants, rehabilitation therapists == EXPERTS Special needs and required functionalities : - The active video game must include the principles of motor learning, which are task-specific practice, variable practice, high practice intensity, progressive difficulty, augmented feedback, and adaptability to user abilities. - The active video game should allow the inclusion of motivational elements to increase engagement. - Children must be free to move in the global environment, without restriction of movement. - Children must be able to use their usual walking aids (crutches or posterior walker). - Therapists should have access to the previous and global performance of their patient through the game - The solution should be "ready to use" easily both for children and therapists	**Gait parameters detection development and evaluation**	Algorithm development: HoloStep measuring the real-time gait parameters with the AR headset system[43] Evaluation : - The accuracy of the AR headset's sensors was sufficiently high to evaluate the position of the user without time drift in the global environment[42] - HoloStep was reliable for measuring and calculating walking speed, cadence, step length and global distance travelled in comparison to a reference motion analysis tracking system[43]	**Game selection & Universe**	The choice of the game universe (Samurai world) and reward panel were unanimously validated by experts and end users. All packages used to design the game were available in the Unity Asset Store: Polygon Samurai low poly 3D Art by Synty, Tiny Dragon by Suriyun, the GUI Kit - The Stone, and the Particle FX. Voice of game characters from volunteers were recorded in a professional radio studio (HandiFM – France 107.3 FM).
Therapy Selection	The team's members agreed on making walking speed the main variable input of the serious game. Meaningful reason is that intensive gait training focused on walking speed has shown their clinical efficacy.[12,39] The therapy to transfer into the serious game should include walking sprints.				

Test name	Instructions	Validity
[PRIMARY OUTCOME] *The 6 minutes walk test (6MWT)*	To summarize, patients are instructed to walk, not run, as far as they could along a 20-m level surface track during a 6-minute period. This shorter distance has been validated for children in order to be more focused on the task. They could use their usual walking aids. After each minute, participants are told the elapsed time and standardized encouragement is provided. Patients are allowed to stop and rest during the test but are instructed to resume walking as soon as they feel able to do so. The stopwatch is not stopped during this time. The 6MWT distance (in meters) is registered. Measured 6MWT distance could be compared with normative values for children with CP. It is recommended to monitor heart rate during the 6MWT.	In population of children with CP, test/retest reliability is excellent for distance output (ICC=0.98). The 6MWT is poorly related to VO2 peak in ambulatory adolescents and young adults with CP. The 6MWT is a more suitable measure of walking capacity than peak cardiopulmonary fitness in children with CP. The 6MWT outcome appears to be more strongly influenced by potential limits to walking speed rather than cardiopulmonary fitness.
[SECONDARY OUTCOME] *Muscle power sprint test (MPST)*	The 15-m distance is marked by 2 lines taped to the floor. Cones are placed at the end of each of the lines. Participants are instructed to walk as fast as possible from one line to the other, and to be sure to cross each line. Between each run, participants are allowed to rest for 10 seconds before turning around to allow them to prepare for the following sprint. Children should be encouraged to give maximal effort. The following variables are calculated for each of the 6 sprints: velocity (m/s) = distance/time, acceleration (m/s2) = velocity/time, force (kg/s2) = body mass × acceleration, and power (watts) = force × velocity. Anaerobic performance is defined as peak and mean power. Peak power (PP) is the highest power of 6 sprints and mean power (MP) is the average over 6 sprints.	The MPST is a valid test to assess the anaerobic performance in children with CP, significant correlations between the performance on these tests for both PP and MP were found. (PP: r = 0.731 ; MP: r = 0.903). Standard error of measurement (SEM), minimal detectable change (MDC) and normative data are available in Verschuren et al. The children with CP had impaired anaerobic performance as it was lower than that of their peers.
[SECONDARY OUTCOME] *10-meters Shuttle Run Test (SRT)*	Description of the test is available here : “The course is 10 metres long; the end is marked with 2 cones and measuring tape. Subjects should wear regular sports clothing and shoes, and orthoses, if applicable. Each child should also wear a heart rate monitor. Children walk or run between the 2 markers at a set incremental speed. These runs are synchronised with a pre-recorded sound. (…) As the test proceeds, the interval between each successive beep reduces, forcing the child to increase speed over the course of the test, until it is impossible to keep in sync with the recording.” We have developed a mobile application that beeps at regular intervals, indicates the time spent and allows the assessor to increment the number of shuttles made by the child.	The SRT is a valid and reliable test. Test-retest is excellent (ICC=0.99) and high correlations were found for the relationship between data for both shuttle run tests and data for the treadmill test (r=0.96).
[SECONDARY OUTCOME] *Physical Activity Enjoyment Scale (PACES)*	This is a 5-point Likert scale (from 1- I totally disagree to 5- I totally agree). A translation procedure from English to French language has been made using guidelines (figure).	The PACES is a valid and reliable measure of physical activity enjoyment.

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
	2b	All items from the World Health Organization Trial Registration Data Set	1
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	na
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	7
	5b	Name and contact information for the trial sponsor	na
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	na
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	7
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	1-3
	6b	Explanation for choice of comparators	1-3
Objectives	7	Specific objectives or hypotheses	3
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	3

Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	3
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	2-3
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	na
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	na
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	na
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	4-5
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	4
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	5
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	5
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	5

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	na
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	4-5
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	4-5
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	4-5
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	5
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	5
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	5
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	5
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	5
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	5
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	na

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	na
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	5
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	na
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	1
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	na
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	3
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	na
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	na
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	7
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	na
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	na
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	na
	31b	Authorship eligibility guidelines and any intended use of professional writers	na
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	na

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	na
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	na

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.