Effect of an augmented reality active video game for gait training in children with cerebral palsy following single-event multilevel surgery: protocol for a randomised controlled trial

Anne-Laure Guinet, Michel Bams, Sandrine Payan-Terral, Néjib Khouri, Samir Otmane, Guillaume Bouyer, Eric Desailly

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 cerebral palsy (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 randomised 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 programme with Augmented Reality Rehabilitation of Walking-Cerebral Palsy AVG, control group will receive GT on a treadmill. The primary outcome is the 6-Min 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.

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).

INTRODUCTION
Cerebral palsy (CP) is commonly defined as a ‘group of permanent disorders of the development of movement and posture, causing activity limitation’. The overall prevalence of CP remains constant (2.11 per 1000 births) with an estimated prevalence of 17 million people worldwide. 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. 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, practising tendon transfer, muscle lengthening, derototation and/or deflexion osteotomy and joint stabilisation. 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. 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.\textsuperscript{8,9} Results were more disputed about the long-term effect on spatiotemporal gait parameters, gross motor function and the activity and participation domain.\textsuperscript{10} A recent literature review has proposed a model in five steps that could guide clinicians during the postoperative rehabilitation.\textsuperscript{11} The authors suggested that the fourth phase, which included more intensive exercises, functional gait training (GT) and resistive muscle strengthening should be optimised to improve the gross motor function and walking speed after surgery. Functional GT has been defined as ‘actively practise the task of walking’, to improve walking ability.\textsuperscript{12} Intervention could be over-ground GT (OGT) or treadmill gait training (TT), with or without body support.

Previously, Grecco et al demonstrated the efficacy of TT programme including both functional mobility and gross motor function on children with CP after SEMLS.\textsuperscript{13} Recently, a systematic review showed that GT was a safe and effective intervention to improve walking capacity in children with CP, outside postoperative context.\textsuperscript{12} In particular, the minimal clinically important difference for increase in walking speed (0.1 m/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.\textsuperscript{7} Functional GT should therefore take into account those recommendations and involve motor learning strategies: task-specific, variable practice, high intensity; augmented feedback during therapy sessions and motivation of the patient.\textsuperscript{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 (eg, Oculus Quest; HTC VIVE, Microsoft HoloLens), Cave Automatic Virtual Environment where video is projected on the walls and floor\textsuperscript{20} to video game console on television screen (eg, Nintendo Switch, PlayStation).

To ‘actively practise the task of walking’, systems combining TT and active video game (AVG) delivered through a screen in a semi-immersive environment have been tested with good results.\textsuperscript{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.\textsuperscript{16}

To our knowledge, even if OGT was recommended for functional GT, 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 AVG Augmented Reality Rehabilitation of Walking-Cerebral Palsy (ARRoW-CP) combining OGT based on previous results\textsuperscript{12} and literature\textsuperscript{17} and motor learning theory.\textsuperscript{14} ARRoW-CP AVG 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).\textsuperscript{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 optimise long-term effect.\textsuperscript{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.\textsuperscript{16,17} 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 minimise visual discomfort and, by extension, fatigue. More details of ARRoW-CP game, architecture, framework development and feedback characteristics are available in online supplemental files 1 and 2.

The current study, denoted as the ARRoW-CP study, will investigate whether a GT protocol through an AVG in AR can:
1. Increase the walking capacity.
2. Increase anaerobic performance and 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 TT to improve walking performance and more enjoyable for children with CP following surgery.

\textbf{METHODS AND ANALYSIS}

\textbf{Study design}

This study is a randomised controlled trial (RCT) with two groups: OGT using the AVG ARRoW-CP in AR (OGT-AR) and TT control group. All children and adolescents participate in a 4-week GT intervention to improve their walking function in one of this two groups. During this period, children continue their usual physical therapy programme (5 weekly 45 min session). This postoperative
protocol has been standardised following a five-step framework. 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 GT interventions
To standardise 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 GT protocol proposed for the two groups. A session is dedicated to the familiarisation with Microsoft Hololens and the ARRoW-CP game via a tutorial application.

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

The intervention consists of 4 weeks of OGT (three sessions per week), including a series of walking sprints. These sessions are always performed indoors, along the same flat and straight 30 m length hallway with a hard surface that is seldom travelled. 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 AR (ie, different from VR), 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. Every training session consists of a prescribed intensity, volume and time (table 1).

Before the first session of each week, the target velocity is calculated during a Muscle Power Sprint Test (MPST). 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 (three sessions per week), with a maximal duration of 30 min. This protocol is an adaptation from Grecco et al.

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/hour and increased 0.5 km/hour 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 min is a warm-up time, the speed is gradually increased until reaching the target velocity. The child walks for a maximal 20 min at their target velocity. Then, the treadmill speed is gradually diminished over the final 5 min. 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.

Randomisation procedure
After baseline measures, eligible participants are randomised to the intervention or control group based

| Table 1 Details of the gait training protocol deployed in the active video game ARRoW-CP |
|-----------------|--------|--------|--------|--------|
| **Session number per week** | Week 1 | Week 2 | Week 3 | Week 4 |
| 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 |

ARRoW-CP, Augmented Reality Rehabilitation of Walking-Cerebral Palsy.
on a computerised randomisation programme. Blocks randomisation are calculated in block sizes of 4 and 6. The randomisation 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 randomisation 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. All patients meeting the study criteria were approached directly in the rehabilitation centre 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. 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. The study has been registered in ClinicalTrials.gov.

Inclusion criteria are children with CP admitted for inpatient rehabilitation following SEMLS, 10–18 years of age, functioning preoperatively at Gross Motor Function Classification System (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 m rating superior or equal to 2 (ability to walk on 50 m 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 practise 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 practise 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 AVG, test sessions were organised 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 4 weeks of GT (T1) and 6 months later (T2). The professional caregiver administering outcome measures remains blinded to group allocation. See online supplemental file 3 for outcomes details and criterion validity.

**Primary outcome: the 6-Min 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.

The 6MWT assesses distance walked over 6 min as a submaximal test of aerobic capacity/endurance. The reference guideline detailing the recommendations and instructions has been updated in 2013. 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 cardio-pulmonary fitness. This primary outcome is relative to the primary objective that is, improve walking capacity.

**Secondary outcome: MPST**  
The MPST evaluates anaerobic performance of youth with CP over a 6×15 m at their maximal speed. Velocity (m/s), acceleration (m/s²), force (kg/s²) and power (W) are calculated. Anaerobic performance is defined as peak and mean power. Peak power is the highest power of 6 sprints and mean power is the average over 6 sprints. This secondary outcome is relative to the secondary objective that is, improve anaerobic performance.

**Secondary outcome: Shuttle Run Test (SRT)**  
The 10-m SRT is an adapted version of the 20-m SRT to accommodate children with CP classified at Level I or Level II on the GMFCS. 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/hour. Speed is increased 0.25 km/hour every level
(min). The test is over when the child cannot go to the next cone in time. This secondary outcome is relative to the secondary objective that is, 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. This questionnaire will be presented to the participant at the end of the last session. This secondary outcome is relative to the secondary objective that is, 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 TT in postoperative context. 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) that is, total dose of 6hours/12weeks. It has been hypothesised that participants following a more intensive protocol (3 sessions/week that is, total dose of 6hours/4weeks) 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 analysed using a multivariate repeated measures analysis of variance (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 analysed 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 postoperative rehabilitation approach has not produced sustainable improvements in participation and activity in daily life for these children.

**AVG development framework**

This work followed the AVG development framework PROGame, proposed by Amengual Alcover et al. 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 an 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 GT; to improve walking speed; to motivate the patient; to be fun. These identifications were based on prior experience and literature review. 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. 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 online supplemental 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, allowing to manipulate the environment, to offer interaction, to optimise feedback and many other potentialities.

**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. In this
paradigm, augmented feedback is defined as augmented sensory information provided by an external resource (therapist or display) to the patient. 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. 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. In their study, patients were people after stroke. They were instructed to walk on a treadmill while visualising 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 hypothesised 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. 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. This step allowed us to modify and adapt feedback modalities (figure 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.

ARRoW-CP is an adaptation of the validated protocol from Zwinkels et al. The original protocol consists of 8 weeks, twice a week. 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 postoperative context, the intensity should be reduced. At the beginning of the fourth step of rehabilitation process, even if GT is recommended, children did not recover to their preoperative level, specifically some children needed crutches or k-walkers. Moreover, a further aspect not to be underestimated: fatigue and pain. The choice of intensity, volume and time in the ARRoW CP protocol is based on practical experience from expert clinician and from literature.

This article presents in detail the GT protocol tested through an 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 AVG. If our hypothesis is validated, ARRoW-CP game will make possible to intensify GT. 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 limits the ability to balance the two groups according the gender, age, GMFCS level and type of surgery. The randomisation 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 centres (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.

Contributors A-LG, GB, SO and ED conceived the study, participated in its design and helped to draft the manuscript. SP-T, 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.

Funding This study is a part of the ARRoW CP project supported by the Fondation Ellen Podatz, the Société d’Etudes et de Soins pour les Enfants Paralysés et Polyvalents et la Association Nationale Recherche et Technologie (ANRT) ID CIFRE 2018/09/73.

Competing interests None declared.

Patient and public involvement Throughout the development phase of the ARRoW-CP active video gameAVG, test sessions were organized in collaboration 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).

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID ID
Anne-Laure Guinet http://orcid.org/0000-0002-2957-1849

REFERENCES