Virtual Reality in Children with Cerebral Palsy: A Systematic Review (Protocol)

1. Introduction
1.1. Overview of Cerebral Palsy
Cerebral palsy (CP) is a non-progressive neurodevelopmental disorder which begins in the early stage of life[1]. It is defined as “a group of permanent disorders of the development of movement and posture, causing activity limitations, which are attributed to non-progressive disturbances that occur in the developing fetal or infant brain. The motor disorders are often accompanied by a disturbance of sensation, perception, cognition, communication, behaviour, epilepsy, and by secondary musculoskeletal problems”[1, 2]. The incident rate of CP per 1000 live births ranges from 2-3 in Europe[3]; 3.3 in four states in the US[4]; 2 to 2.5 in Australia[5]; 2-2.8 in China and India[6]; and 2-10 in Africa[7].

Children with CP have postural difficulties, changes in muscle tone (the resting state of muscle tension), and may have limited movement in the upper and/or lower limbs[8]. Affected children with increased tone usually develop muscle tightness and subsequently joint deformities. These issues contribute to the limited use of the extremities for functional activities. When the upper limbs are affected there is usually a limitation of fine motor skills such as writing and the manipulation of toys[9].

The International Classification of Functioning, Disability and Health (ICF) offers a conceptual biopsychosocial model that describes health and function[10]. The ICF has 4 components namely body functions; body structure; activities and participation; and environmental factors; all of which are organised into a hierarchical structure[11]. Figure-1 shows the hand function classification based on the ICF model[12]. This model can be applied for the CP population when hand function is affected.

![Figure-1: Hand function classification based on the ICF model[12].](image)

1.2 General Management
The typical management of the child with CP will include a conventional physiotherapy programme consisting of a variety of therapy methods[13, 14]. These
may include stretching, strengthening, positioning, splinting, casting and the facilitation of movement[13, 14]. Other modes of therapy may include baclofen, oral and intrathecal; botulinum toxin injections, for short term reduction of muscle tone[15, 16]; surgical intervention to correct musculoskeletal deformities and dorsal rhizotomy to manage increased muscle tone[17]. Less common are techniques such as acupuncture and constrain induced movement therapy that can be used to improve motor functions[14, 18].

1.3. Virtual Reality
The recent advances in computer technology have enabled clinicians to explore the use of Virtual reality (VR) as an alternative treatment modality[19, 20]. VR is defined as the “use of interactive simulations created with computer hardware and software to present users with opportunities to engage in environments that appear and feel similar to real-world objects and events”[21, 22]. It can help the user to focus on the virtual world through sound, image and touch stimuli[23]. It has recently been used to treat patients suffering from Parkinson’s disease[24], mental illness[25], stroke[21], and CP[13, 26-28].

1.4 VR mechanism
The VR system can be categorised as immersion and non-immersion[29]. In the immersive system, the person is encapsulated in the virtual environment and all of their senses (vision, touch and auditory) are blocked from the external environment[23]. Whereas in the non-immersive system the person’s senses are intact with the external world[23]. Some of the input devices which can be used in VR are the computer mouse; a data glove and in some cases position trackers[30]. The output devices may be computer and/or television screens, shutter glasses or head-mounted displays[30]. The elements of motor learning theory are integrated in VR intervention because it enables the users to gain feedback, thereby monitoring their performance, which is more likely to result in repeated practice[31].

1.5. How the intervention might work in children with CP?
VR is reported to augment the desirable motor performance because of a variety of factors[32, 33]. For the purpose of this review, the following possible mechanisms related to children with CP are described below.

1.5.1. Cortical reorganisation (brain learning)
Snider et al’s systematic review found that more than half of the reviewed studies reported desirable results in brain plasticity and brain reorganisation with the use of VR[31]. Active participation, receiving feedback, and repetition of movements assisted in motor learning and related cortical changes[34]. Neural plasticity through cortical reorganisation following VR intervention were also reported[35, 36].

1.5.2. Motor control
Luna-Oliva et al examined the effect of VR intervention on children with CP[27]. They showed statistical significant improvement in the motor and processing skills, including balance, gait speed, running, jumping and manual dexterity[27]. An explorative study that examined the upper limb functions using the commercially available VR intervention for a 6 week period reported no improvement of the quality of movement, but the participants reported an improvement in using their upper limbs for activities of daily living[37].
1.5.3. Motivation
VR increases the exercise compliance level in achieving selective motor control and enhances conventional physiotherapy effectiveness[38]. Participants were highly motivated by the challenge, variability and the competitive factors[39, 40]. Adults with CP and poor cognition showed a higher level of enthusiasm and some of them showed the appropriate goal oriented response[41]. VR as a therapeutic modality showed positive impact on children with CP[31].

1.5.4. Other factors
Improved cognitive function, concentration and levels of participation have been reported when using VR intervention[42]. It provides feedback which enables the participants to improve their performance by repetition, cognitive planning, and by giving them a sense of achievement[43]. The VR environment can allow creativity, it has been shown to have resulted in improved persistence with repetitive tasks; increased enjoyment in attaining the therapeutic objective; and it gives the participant a certain degree of control[44].

1.6. Why this review is needed?
VR combined with physiotherapy appears to be a promising new treatment approach with wider future applications. Research over the past decade using VR intervention has reported benefit to children with CP[31, 45]. It may assist in acquiring new motor skills, sustaining the exercise benefit and enabling children to use their hands for more functional skills. If this is indeed the case it will transform the daily life of the child with CP. It should improve their activity and independence as well as minimising secondary complications that are associated with growth and development. Currently there is no systematic review that evaluates the effectiveness of VR in the treatment of hand function in children with CP. This review will bridge the gap and may assist in guiding future designs and the therapeutic use of VR. We therefore intend to perform a systematic review with the aim of evaluating the effect of VR intervention when used in the treatment of hand function in children with CP.

1.7. Objective
Our objective is to determine how effective the use of VR intervention is on improving the hand function in children with CP. It will be compared with conventional physiotherapy treatment or other therapeutic interventions. The outcome of this review will be categorised according to the ICF dimensions.

2. Materials and methods
2.1. Search Strategy
The following strategy will be adopted for this review [14, 15, 18, 21, 24, 46].

2.1.1. Electronic database search: A comprehensive computerised bibliographic databases search will be performed in the following database:
- MEDLINE (1950–current)
- Cumulative Index to Nursing and Allied Health Literature
- ERIC
- Allied and Complementary Medicine (1985 to present)
- British Nursing Index (1992–present)
- Excerpta Medica Database (1980–present)
• PsycINFO (1806–current)
• Physiotherapy Evidence Database
• Cochrane Central Register
• DARE
• OTSeeker
• Scopus database
• Web of science

2.1.2. Trial registers: The unpublished and on-going clinical trial information will be gathered by searching the major trial register websites. These include www.clinicaltrial.gov, www.who.int/trialsearch and www.controlled-trials.com.

2.1.3. Contacting the corresponding authors of the selected articles and asking them to provide the details of any other VR related research studies in CP either by their team or by their associates and research group.

2.1.4. Citation Searching: Most of the journals track any other articles that cite their research studies.

2.1.5. This protocol will be published in PROSPERO website. A request to the wider research community will be made asking them to contact the review team with any relevant unpublished and/or on-going studies based on the inclusion and exclusion criteria.

2.1.6. Other sources
• Conference proceedings and abstracts related to VR (International Workshop on Virtual Rehabilitation, Virtual Rehabilitation Conference, International Conference Series on Disability, Virtual Reality and Associated Technologies and Cybertherapy) will be monitored. The review team will contact the corresponding authors of studies at these conferences and they will be asked to provide any additional information so that the relevant studies are included.
• The following VR equipment manufacturers will be contacted via email and asked for the details of any trials (Nintendo, Sony, GestureTek, NeuroVR, Hocoma, Motek, Virtual Realities, Haptic Master, Microsoft Xbox, Essential Reality, SensAble, Novint and Cyberglove). This may encourage the manufacturers to offer the review team any relevant unpublished in-house industrial research data, thus no potential study/data is missed for this review.

2.2. Search Terms
The reviews and protocol documents related to VR and CP were gathered[14-16, 24, 46-50]. The relevant search terms from these documents will be used to acquire all relevant articles for this review. A comprehensive list of search terms with the Boolean operation plan is provided in appendix-1. A broad search strategy including free-text words, medical subject heading and all thesauruses subject terms will be used in the database wherever applicable.

2.3. Type of studies
Only the RCTs will be included for this review, thus the higher level of evidence with minimal bias is ensured. All the other types of studies will be excluded.
2.4. Inclusion and Exclusion
In order to limit the number of results in the above database the searches will be confined to children with CP only[52]. All the subgroups of CP will be included and children with acquired neurological disorder and the adult population will be excluded. Some studies include adolescent population (15–25 years) and they may be considered for a review if more than 50% of the participants are less than 18 years old. If such information is not clearly available, the article will be excluded.

Research studies that include VR as one of the intervention methods will be included whilst those that do not involve VR as an intervention will be excluded. Studies that examine the effect of VR intervention on hand function as either a primary or secondary objective will be included. Only those studies that have used objective outcome measures to objectively measure the hand functions will be included.

No exclusion criteria will be set for language or publication years, however, the title and abstracts will need to have been published in English. This will enable the reviewers to make a decision about whether to include the full article for the final review. The review team will contact the corresponding authors and ask for the required information in English. Due to time constraints, the time for response to this request will be limited to two weeks only. If no response is received, those studies will be excluded and this will be documented.

3. Study selection
3.1 Review team
A review team that consists of four reviewers to select the studies will be formed to minimise discarding the relevant studies.

3.2. Identifying the articles
3.2.1 Stage-1: Once the electronic database search is completed, the collected titles and structured abstracts will be scrutinised independently by two reviewers to reduce search related bias[54]. In order to minimise the bias and the potential error of judgement, the set inclusion and exclusion criteria will be used to guide the selection of articles. The selection of the study process will be systematically documented to enable the same result to be reproduced. The excluded studies will be classified as irrelevant and the reasons will be documented using study eligibility form[55].

3.2.2 Stage-2: The other two independent reviewers will jointly search the potential research studies that were described in section 2.1.2 based on the study selection criteria by scanning the title and the abstracts. Any difference of opinion will be resolved through discussion.

3.2.3. Stage-3: Full articles that meet the selection criteria from the above source will be collected from the NHS library services. The reviewers will collectively decide which articles will be suitable for the final review.

The selection process will be piloting 20% of the collected electronic and grey literature at the beginning to ensure reliable interpretation and agreement between the reviewers. Disagreement will be resolved with a consensus meeting.

Lack of information usually leads to articles being excluded[54, 56]. To minimise this, the corresponding authors of the articles will be contacted via email and asked to
provide the missing data within two weeks. If no response is received, those potential studies will either be excluded or a sensitivity analysis will be carried out to determine the result’s influence on the review. Duplications of studies will be considered as a single study.

3.3. Data extraction
An electronic data extraction file with the required category will be created to suit this review. In order to verify that the required information is captured in the data extraction form and to maintain interrater reliability between the reviewers, 20% of the collected studies will be piloted. If any changes in the data extraction form are required, they will be made at this point. Interrater agreement will be calculated using kappa statistics and the outcome will be documented. The authors of the unpublished studies will be contacted and asked to provide the data related to their studies for data extraction within two weeks.

4. Quality assessment
This review will only include RCTs. The methodological quality of the included RCTs will be examined to find out how far they are free from bias[54]. The Cochrane collaboration’s risk assessment tool will be used to judge the quality of sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other domains[54]. Quality of risk will be judged and a risk of bias graph and a risk of bias table with the summary of the key domains will be constructed[54].

5. Data synthesis
Quantitative data synthesis through meta-analysis will be considered if the pooling of the results from different studies is possible. If meta-analysis is inappropriate, a narrative review approach will be opted for.

The RCTs are generally designed to compare the difference between the intervention and control groups. This review will therefore, gather the evidence of the effect size; and the consistency of the effect size across all of the included studies[54]. Meta-analysis will be considered to increase and improve the power and precision of the findings. In the first stage, summary statistics will be calculated. This is because this review will be examining a specific intervention (VR) that has been applied in different studies and the data from those studies is expected to be similar. A sensitivity analysis will be performed to determine whether the summary statistics are important to the meta-analysis conclusion.

The data analysis plan is expected to change, as it is dependent upon the number and quality of the studies included for the final review. It is difficult to anticipate the statistical issues but the following Cochrane recommendations will be adopted for this review[54].

- The analysis needs to address the objective.
- All suitable types of RCTs will be considered.
- The outcome measures need to be either ordinal (dichotomous) or interval (continuous) scales.
- The measures of effect for clinical trials with binary outcomes involve comparing either the risk or the odds ratio from the two intervention groups. Therefore, the corresponding odds ratio (relative measure) or the risk
difference (absolute measure) will be selected to report the clinical trial’s effect. An odds ratio value of greater than one will be interpreted as a positive outcome. Similarly, the mean difference between the intervention and the control groups will be reported for continuous variables.

- Clinical heterogeneity will be determined by analysing the extracted data. Narrative analysis will be considered if the differences among the studies are wider. If homogeneity between studies is identified, a meta-analysis approach will be considered. Statistical heterogeneity will be determined further and a fixed effect model will be considered if no heterogeneity is observed. A fixed effect model assumes only the sampling error is the source of variation among effect sizes, which is plausible when the selected studies are very similar, using the same procedures and measures. A random effect model will be adopted if statistical heterogeneity is observed. In a random effect model the assumption is that effect sizes are sampled from an underlying population of effect sizes and that the studies will have more differences in the way that they were conducted.
- The Mantel-Haenszel method will be used to calculate binary variable data. The inverse-variance (fixed/random effect)) method will be used to calculate the continuous variable (mean difference).
- Heterogeneity will be statistically analysed using the Chi square test, and the p-value will inform the extent of the VR intervention’s effect. The I² value will be calculated to detect the extent of heterogeneity. A fixed or random effect meta-analysis may be used to incorporate the heterogeneity.

6. **Limitation**

- Some of the research studies may include children with other motor disorders such as head injuries alongside children with CP. Excluding these studies may result in some data being missed.
- It may be possible that more quasi-experimental studies (non-RCTs, before and after study and interrupted time series) and cohort studies may be available in this area. Excluding these studies will prevent reporting of some important findings.
- This review will be less likely to report the adverse effects from the RCTs as such information is usually reported in the observational studies.
- Although this review is aimed at including all languages, the chances of using reviews in other languages are limited by the study authors’ ability to provide the information in English. This could introduce language and publication bias, which will be reported in the result.
- Searching Dissertation Abstracts will not be done and this may lead to excluding some of the relevant studies.

7. **Dissemination**

This review will be disseminated to practitioners and policy makers. This will enable them to make an evidence based decision on whether or not to use VR intervention in their therapy. This will improve the quality of health care, thereby directly benefitting children with CP. The research findings will be published in a peer reviewed academic journal and at rehabilitation conferences. These traditional mediums have only a limited chance of reaching a wider audience group, therefore,
the Centre for Review and Dissemination (CRD) framework will also be used to disseminate the review results[58].

8. References
8. Thorley, M., et al., Evaluation of the effects of botulinum toxin A injections when used to improve ease of care and comfort in children with cerebral palsy whom are non-ambulant: a double blind randomized controlled trial. (1471-2431 (Electronic)).
30. Novák-Marcinčín, J., HARDWARE DEVICES USED IN VIRTUAL REALITY TECHNOLOGIES.


53. Hoare, B., et al., Linking cerebral palsy upper limb measures to the International Classification of Functioning, Disability and Health. (1651-2081 (Electronic)).

**Appendix-1: Search Terms**

1 exp child/
2 exp infant/
3 exp adolescent/
4 exp minors/
5 exp pediatrics/
6 (child* or infant* or newborn* or neonat* or baby or babies or adolescen* or pediatric* or paediatric* or youth* or teen*).tw.
7 or/1-6
8 randomized controlled trial.pt.
9 controlled clinical trial.pt.
10 randomized.ab.
11 placebo.ab.
12 randomly.ab.
13 trial.ab.
14 groups.ab.
15 or/8-14
16 virtual reality exposure therapy/
17 (virtual or virtually or VR).tw.
18 exp user computer interface/
19 exp computer simulation/
20 computer simulat*.tw.
21 ((simulat* or augement* or mediat*) adj3 (world* or realit* or environment*)).tw. (5593)
22 exp video games/
23 (videogame* or ((video or computer or electronic or online or on-line or simulation or role playing) adj game)).tw.
24 wii.tw. (356)
25 ((head or helmet) adj mounted).tw.
26 (immersi* or spatial presence or lifelike or life-like).tw.
27 interactive*.tw.
28 augment*.tw.
29 computer*.tw.
30 "serious gaming".tw.
software.tw.
"user-computer interface**".tw.
exergam*.tw.
"reality system**".tw.
(Nintendo or Sony or "GestureTek" or NeuroVR or Hocoma or Motek or "Virtual Realities" or "Haptic Master" or Microsoft or Xbox or "Essential Reality" or SensAble or Novint or Cyberglove).ti,ab.
or/16-35
exp cerebral palsy/
exp central nervous system diseases/
"little* disease**".tw.
exp nervous system diseases/
"nervous system disease**".tw.
"nervous system disorder**".tw.
(cerebral adj3 pals*).tw.
((spastic* or dipleg* or monopleg* or quadripleg*) and (hypoton* or dyston* or dyskinetic*)).tw.
or/37-44
7 and 15 and 36 and 45
Repeat 46 in other database
Remove duplicate by combine 46 and 47

Unique number of studies from step 48 (title, abstract and journal information) will be saved in EndNote software.