# THE UNIVERSITY OF MEDICINE AND PHARMACY "CAROL DAVILA", BUCHAREST DOCTORAL SCHOOL

**MEDICINE** 



Research on main methodological options in virtual reality (VR) mediated interventions for remedial treatment in balance disorders in adolescents with cerebral palsy (CP)

#### PHD THESIS SUMMARY

PhD supervisor:

PROF. UNIV. DR. ONOSE GELU

**PhD** student:

PHYSIOTHERAPIST AVRAM RADU-MIHAI

2023

"I thank God for the help offered through the people I met during my professional training and who unconditionally supported me in the scientific foundation as well as in the elaboration of this doctoral thesis - which would have been impossible without the help, the support and the guidance of these entities - who, through their high professional degree and dedication, contributed to my formation as a researcher, instilling in me the knowledge, perseverance and courage to move forward."

#### INTRODUCTION

The subject of the Doctoral Thesis "Research on the main methodological options in interventions mediated by virtual reality (VR), for recuperative treatment, in balance disorders in adolescents with cerebral palsy (CP)" I considered it appropriate, thinking that for people - due to specific posture and mobility: standing and walking, bipedal - the static and dynamic balance of the body and, respectively, its positioning in conditions of sequential stability [efficient/propensive, including for coordinated movements, sometimes extremely complex, performed with the upper limbs (1) – necessary for characteristic anthropic activities, such as ADL (activities of daily living) and/or lucrative], represents a feature and at the same time a key determinant of our functioning(2).

"... an item still incompletely resolved - and topical - remains the problem of managing and maintaining balance."(3) ... thus "recovery being a major component for fall prevention; ... part of the neuromotor impairment"(4), in existing pathologies; as such, I decided to choose the issue stated in the title as the main subject of this paper.

So, I have followed internationally – over the years – in the specialized literature [case studies(5–7), research / original works, websites, etc.] how numerous materials have been presented(8,9), in which the importance of Virtual Reality (VR/augmented) is exposed in various fields of significant importance: – military(10,11), cinematography(10) medicine(12,13), fitness(14), medical/aerospace/automotive engineering as well as in the areas of education and entertainment respectively(15), with the explanation and demonstration(16,17) of the applicability and benefits(18) - in the short and long term - of training, recovery of balance disorders and instability, as the main objective in patients with

PC – interventions focused on (re)performance(19) and (re)learning, motor(20), results reported as having favorable results(21,22).

"Beyond the distraction and entertainment created, virtual reality can deliver an artificial psychological and physiological, corrective environment and facilitate the recovery of pediatric patients suffering from cornic pain"(23) as well as the neuromotor recovery of children with cerebral palsy, spinal amyotrophies, muscular dystrophies (Duchenne, Becker), cranio-cerebral trauma(24), vertebro-medullary, etc.

At the same time, we mention the fact that in addition to RV/augmented, in the modern diagnostic and therapeutic-recuperative arsenal, with the purpose stated in the title, advanced, convergent devices and interventions are used - and we also use them - in the approach to balance disorders: "PRO-KIN 252"(25) (in order to encourage the active participation of the adolescent patient, we used one of the many assessment/stimulation and training devices on the market using augmented virtual reality, with which we were able to follow the proposed objectives and transpose the exercises necessary from classical physical therapy to that related to modern robotic recovery, with more joy, ease and intrinsic motivation(26) (I specify that I carry out my activity and I carried out this Doctoral Thesis within the National Clinical Center for Neuropsychomotor Recovery for Children "Dr. Nicolae Robănescu", this medical unit being the first in Romania to benefit from this medical device since 06-21-2016 - see annex 14), including for adolescents with CP.

"PRO-KIN 252" is a "top" medical device, as a technological innovation in the recovery of static and dynamic balance, with up to 50 levels/settings of electronically controlled instability; is equipped with: a sensitized platform containing 4 force cells, which measures COP (center of pressure) activity at the plant/leg level and a sensor applied to the patient's xiphoid appendage (TRUNK SENSOR) which measures trunk oscillations .



Annex no. 14. Physiomed commercial company declaration of uniqueness, delivery and surrender of the "PRO-KIN 252" Device in Romania within the CNCRNC Dr.

#### "Nicolae Robănescu"

Another advanced recuperative assistive device we used is the "G-EO EVOLUTION": this robotic system helps patients by supporting the correct movement compared, as feedback with corresponding representations from an immersive virtual environment, both during walking and in activities more complex such as going up and down the stairs, in an immersive virtual environment - by applying 3D virtual reality glasses with the aim of improving movement patterns (aiming to resume orthostatism and walking as close as possible to physiological) (27).

The "MYRO" interactive surface - equipped with tactile/haptic movement capture sensors, where the recovery plan becomes creative, engaging - activates and demands the cognitive system with a multitude of applications aimed at recovering the ability of the upper limbs (uni) bilaterally, including/in mainly in neurological, trauma recovery interventions and more(28).

I also used the "Nirvana" augmented VR system in neuro-motor recovery, including in patients with PC, this device through multisensory stimulation, with illustrations displayed on the wall or floor(29).

The doctoral research approach that I proposed aimed at the impact of RV/augmented in the traction and recovery of adolescents [it is important to specify that puberty begins

approximately at 8-10 years(30), being followed by adolescence between 13-19 years(31,32)] with CP and balance disorders, following two important aspects:

- 1. The attempt to clarify what is not fully standardized: the related "dosage" (8,33,34), in the context of a comprehensive approach to the physical methods of recuperative treatment in the mentioned pathology;
- 2. Considering/respecting, as a related but also priority objective, the safety of our patients regarding the application of RV/augmented procedures.

Of course, the achievement of these objectives is a complex approach that involves the subsumption of standardized clinical and instrumental assessment approaches and elements of advanced technology.

As will be seen both below and throughout the present PhD Thesis.

In order to carry out this doctoral work, I pursued and achieved:

- obtaining approval for the conduct of the related clinical study, from the Ethics Commission and respectively from the manager in charge of this Institution
- ensuring the information of the participants and completing the Informed Consent of the patient/his parent
- application of the following clinical-functional assessment scales including apparatus (see below).
- interpretation including objectification based on related statistical analysis of the data obtained.

We specify the fact that, unfortunately, given that, as is known, there is still no intervention modality (pharmacological, physiatry, neuro-surgical, regenerative medicine/tissue engineering, etc.) capable of effectively healing the injuries of the nervous system central (CNS)(35) - including CP - any attempt to improve/optimize therapeutic-recovery in this extremely difficult field of pathology is still of urgent relevance, considering also the marked disabling potential of this category of conditions.

At the same time, we mention the fact that in the literature - to the best of our knowledge - we have not found any works focused on this target population: adolescents with CP and consecutive balance disorders, with their therapeutic-recuperative approach, in a multi-level physiatry complex, including using advanced physical therapy devices and especially in association with RV/augmented procedures.

#### Working hypothesis:

If there are significant differences from the point of view of the recuperative results obtained between the doses used of RV/augmented, in the context of the complex, integrated recuperative physiatry approach, in adolescents with CP and consecutive balance disorders with CP, and if so, what is the related methodological formula more efficiency.

#### The thesis is structured in two parts:

The general part, containing 3 chapters, including theoretical data - including based on a systematic review of related literature ["Data on advanced physiatry approaches of stabilometry and virtual reality for assessment and (re)training of balance in cerebral palsy"(36) regarding CP and the consequent balance disorders, as well as ways of testing/quantified evaluation and respectively recuperative physical-kinetological interventions, including advanced apparatus, for the recovery/retraining of balance in adolescents with such pathology.

The special part (original - personal contributions) includes the working hypothesis, the established objectives - succinctly stated above - and the research methodology, used as well as: a pilot study (Study I) - "Evaluation modalities and physical therapy, apparatus, advanced, coordinated methodological, to address static and balance disorders in pediatric patients with cerebral palsy (CP) - preliminary results"; Study II, entitled "Our experience regarding the effects of some advanced physical - kinetological recuperative treatment methods in balance disorders in adolescents with cerebral palsy - (partial results)"; Study III, entitled: "Final data - on numerically increased groups/lots and with related optimization of the statistical analysis methodology - regarding the effects of some advanced methods of recuperative physical-kinetotherapy treatment in balance disorders, in adolescents with cerebral palsy".

This research took place between October 2017 - February 2023, within the CNCRNC "Dr. Nicolae Robănescu", Bucharest, on three target groups/groups: two study groups/groups (adolescents) and one control/control (all with CP and consecutive balance disorders), the study groups/groups totaling 163 patients and one control/ control, 89 such pediatric patients, respectively a control/ control subgroup/ subgroup of 13 adolescents with CP (see below).

As the only usable group/control group/control (pediatric patients with CP who only performed physical therapy, comprising 89 cases), we opted for its use in its entirety due to the statistical power provided by the relatively large number of such patients.

However, given the fact that there were only 13 teenagers in this group/batch, for added rigor we performed the same comparative statistical analyzes using this (sub)group/(sub)batch of teenagers with CP as a control.

Thus, we found that, although the statistical power was inevitably lower, from the point of view of the significance of the results obtained, they do not differ significantly from those found in the comparisons made using the initial control group/group (consisting, in total, of 13 teenagers and 76 children = 89 pediatric patients with PC, in total).

Concretely, from the comparative analysis of the effects obtained by the therapeutic-restorative methodology used - and objectified by the above-mentioned quantified clinical-functional assessment tools - we found that the patients in the "intensive" group/batch (see further) had overall statistically significant results better than those in the "moderate" group/lot and respectively from the control/control group (/subgroup)/lot(/sublot).

A possible limitation of the present research carried out/in the elaboration of this Doctoral Thesis, is (in addition to the mixed composition: children plus adolescents of the group/ control group/ control in its entirety and, respectively, the smaller number of cases of the adolescent patient component of within the control subgroup/subgroup) the options expressed by the respective parents regarding the voluntary placement in the "moderate" or "intensive" group/group, taking into account aspects of balance (including subjective elements) between the desire/confidence - of principle, natural - and the psychological "investment" in a procedural complex with a more pronounced profile and, respectively, the concern for a potential risk of additional patient fatigue - see below).

The results obtained constitute, we consider, a personal contribution to the objectification of the theoretical and practical knowledge base for the use of RV/augmented dosages, which can be used within the optimized, multimodal approach of modern complex, therapeutic-recuperative physiiatric treatment of cerebral palsy with consecutive disorders of balance, in teenagers.

#### GENERAL PART

# Theoretical aspects related to the researched pathology – cerebral palsy (CP)

#### **Definitions**

Several definitions have been added to it, over the years there have been conceptual and approach differences, several authors trying to reach an agreement on the definition and multidisciplinary approach of this pathology (37); thus some of the authors attribute the term "umbrella" (symbolistic association) to it, and refer to the vast group of non-progressive disorders, more precisely - neuro-psycho-motor type (38) - so PC is considered to be a disorder of posture, movement, voluntary control and motor development, which determines the limitation of activity over time (sometimes with changes along the way) - triggered in an immature brain (39).

#### Etiological data

The postnatal development of the brain takes place majorly in the first two years of life and that the lesions that occur in the immature brain are the ones that determine the appearance of CP, which can be: prenatal/congenital (before birth and represent approximately 75% of CP cases), perinatal (during birth/before term 6-8%), postnatal/time after birth (especially in the first 2 years of life 10-18% (40)).

#### Classification

In the relevant literature, a classification system approved by the American Academy for PC, used since 1956 (22,38), is found, which describes 7 mortic types of this morbid entity: spastic, athetic, rigid, with present tremor, hypotonic, mixed, unclassifiable (41).

Assessing the functioning of the adolescent with PC-generated disabilities

Currently, there are a number of scales or systems of quantified clinical motor classification, which highlight/measure the functional deficits within PC.

It should be noted that: a large number of such scales can be found in the literature (almost 30 - not used exclusively in PC "Communication at the National Congress of Physical Medicine, Recovery and Balneology - with International participation", Covasna 2021) (42).

We present here two such quantified clinical-functional evaluation scales, which we used, along with 5 instrumentally measured evaluation parameters (see below) in this Doctoral Thesis.

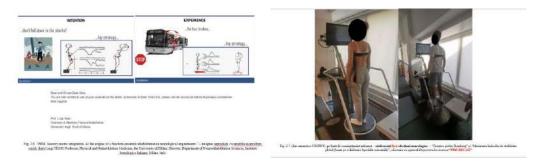
# Synthetic notions of morpho-physiology regarding postural balance and its main changes in adolescents with CP

Morpho-physiological aspects regarding human postural balance – in orthostatism and walking

Ostrostatism and biped walking, human, with the required postural balance - static and dynamic - related, are extremely complex and efficient physiological functions but not easy to achieve (with increased risk - as the "price" of this decisive biological advance of ours in / compared to the animal kingdom - of falls, especially when there are/ appear disturbances/ dysfunctions within one or more of the numerous and subtle components of this function), which represents, as a whole, a brilliant progress and phylogenetic success, constituting at the same time, defining features of our species.

Achieving balance in standing and walking and (through recovery and/or support reactions) its restoration, under the conditions of inevitable dynamic challenges, generated by very varied and important constituents of our current activities, is ensured "infrastructurally", synthetically - subsumed by a pattern of bio-cybernetic functioning and control, based on feedback/ forward processes - of components of the "neuromyoarthrokinetic apparatus" (43) - more precisely of "musculo-skeletal" structures, respectively - n. n.

- "visual, vestibular" as well as "cutaneous" but also "psycho-emotional" interferences) (44)



### Physiopathological data regarding static and dynamic balance disorders – in adolescents with CP

CP is the most "common" cause of motor disability in children (45) and as it is a chronic/"permanent" condition (46) - as is known, unfortunately, at the present time there is

still no pharmacological, natural or synthetic agent or type of therapeutic intervention (including surgical or physiatric) able to effectively cure CNS lesions (35) - its sequelae [(CP being defined as "a neurological disorder generated by a brain injury non-progressive or by a malformation, which occurs during the time when the child's brain is developing" (47) disabling - are "primarily affected": "body motility and muscle coordination" (47) - continue to exist even in adolescence.

#### Morpho-/physio-pathological bases.

As a morpho-dysfunctional substrate, the main tissue types/areas of localization of neurolesions in PC (identifiable by imaging - especially nuclear magnetic resonance (NMR) is considered, including for this purpose, a very contributing investigation - are: "predominantly of the substance periventricular white matter, predominantly of the gray matter, cerebral malformations, others" (48); they appear predominantly in affected areas of the brain with topographical distributions corresponding to the neurodysfunctions/consecutive disabilities - such as: the parietal lobe (found in clinicaldysfunctional correlation with " gait profile score"); the periventricular shell (found in correlation with the Gross Motor Function Classification System - GMFCS score); the anterior part of the corpus callosum (found in correlation with "variable gait scores") (49) in the cerebellum - associated with some ataxic forms (in "extrapyramidal/non-spastic" PC) -(50), with presence, also encountered, variable, in such forms - for example, on CT: "frequent but variable", widespread in " simple ataxia" (and with - n. n.) "imbalance" including (but) in the parietal lobes, posterior fossa, vermis, in hydrocephalus (51).

#### **Clinical-dysfunctional aspects**

More detailed clinical-functional classifications of CP are those belonging to the 'Surveillance of Cerebral Palsy in Europe (SCPE) Collaborative Group, CP' - according to which this condition can be: spastic, ataxic-dyskinetic and unclassifiable (52) - and respectively, the one developed by Swedish authors, which proposes the taxonomic division of CP even more thoroughly: "spastic (hemiplegic, tetraplegic, diplegic), dyskinetic (dystonic and athetotic), ataxic and unclassifiable/mixed".

So, postural balance is "a key problem for children with CP"(53).

Methods of testing and, respectively, physical therapy interventions, including advanced equipment, for the recovery/retraining of balance in adolescents with CP.

### Concept-methodological aspects related to the clinical (non-apparatus) testing of balance disorders

In order to be able to evaluate the state and conditions of equilibrium/re-equilibration, numerous tests for detection/quantification of disorders of this function can be used.

The use of such tests - including those of the apparatus type - also helped to a more comprehensive description and understanding of the complex processes that compete to maintain stability.

Generally, such a test is repeated three times and the best result is chosen; eg: Sensitized Romberg, Leg Test, Berg Scale, Movement Skills Scale, Fukuda Test, Bass Test, Timed Up & go Test, Tinetti Test.

## Conceptual and methodological aspects related to testing and, respectively, to physical-kinetic therapy interventions of the apparatus type, advanced

Modern instrumental movement evaluation techniques offer the possibility of inclusive quantification of the effects of the pathology involved in orthostatic balance and gait disorders as well as the establishment of recovery/ reeducation strategies, on coherent, scientific bases.

Stabilometry is the objective study, through force plates, of the balancing/balancing of the body during the rest/ "quiet" state, with possibilities for quantified evaluation. Stabilometric analyzes in addition to orthostatism, without active movements, can also target passive/externally induced movements, for the trunk and upper extremities; such assessments can also be done from a sitting position (54).

Thus, the "hard" infrastructure of an apparatus such as the "PRO-KIN 252" (mentioned and presented previously) ensures the passive balancing - challenging for rebalancing - the movements generated by the force plates of the apparatus together with its dedicated software/ applications, provides – as continuous guidance/ training feedback – the ideal/optimal line that the patient must follow to recover balance, posture and then/also gait and related dynamic rebalancing – with the consequent decrease in the risk of falling (55) – and, furthermore, autonomy, as well as quality of life (QOL).

Some specific considerations, within the related activity and ours respectively: Assessment and intervention facilities mediated by virtual/augmented reality:

As elements of the Classification of VR/augmented facilities/interventions, we consider necessary in advance some considerations regarding evaluation and intervention facilities:

"Virtual reality (VR - or virtual environment, MV) - can be defined as a computer/computing technology that generates a three-dimensional (3D) simulated/artificial environment that imitates reality"; in principle, its infrastructure (hardware and software) must produce a "convincing" virtual environment capable of allowing the user to interfere with it in the most "naturalistic" way possible(56).

From the beginning, a related detail is also necessary: in addition to VR there is Augmented Reality (AR), which includes a series of facilities, also based on computer science, to enhance multisensory perceptions, through additional stimuli such as - apart from those visual – auditory, olfactory and respectively tactile/haptic stimuli, many of which combine with the physical/real, surrounding environment (from which the user is not disconnected) specifically, by adding/superimposing on reality, of "...a synthetic elements such as 3D images, multimedia content elements or/and text information superimposed on real-world images", to improve multimodal interactivity in a new-complex environment: digital-human... (57).

Types/virtual reality devices - provided by CNCRNC "Dr. Nicolae Robănescu" and used in the Clinical Study related to my Doctoral Thesis.

Specialized device for evaluation, quantification and stimulation/retraining of static and dynamic balance (based on proprioceptive and visual feedback) "PRO-KIN 252" (25).



Fig. 3.1. (din carnistica CNCRNC "Dr. Nicolae Robânescu" po bază de consimțiamint informat – adolescenți cu PC: – "Testarea probei Romberg" și măsuzurea "Indiceliu de stabilitat global (bazza pu echilibrare bijudală orzontală)", efectuate cu ajutorul Dispozitivului Avansat "PRO-KIN 152"



Fig. 3.5. (din cazuistica CNCRNC, pe bază de consimilământ informat – adolescenți cu PC: stimularea și antrenarea miscărilor globale ale membrelor inferioare (reeducarea mersului și implicit al echilibrului postural static și dinamic efectuate cu ajutorul dispozitivului – asistiv recuperator robotic "G-EO EVOLUTION" și RV

#### The main arguments in favor of choosing these interventional options were:

As a fundamental first stage condition – serious games (SG) feature complex and interactive graphics, an attractive/engaging environment for the user.

They ensure for the user/patient an important role of cognitive stimulation, through which we aim to maximize his active and conscious involvement, the prolongation of the procedural period - as an echo of the improvement of the motor system (positive feedback) - obtaining favorable results by completing the tasks (58).

Through a series of assistive-multimodal tools, SG have the property to recognize and assist body movements (passive, passive-active, active, active with resistance, coarse and/or fine) in real time.

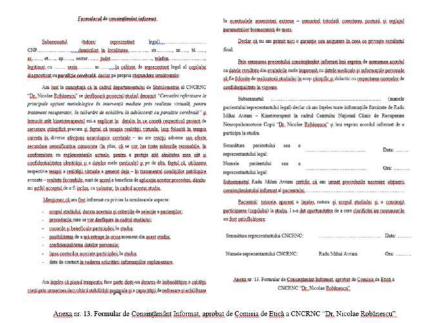
At the same time, they enable the user's attention and change the behavioral attitude, through motivation and the desire to overcome oneself - to slow down and accelerate the recovery period (59).

#### General research methodology

The study was carried out in the fourth quarter of 2017 - the approval was obtained from the Ethics Commission - No: 7661 of: 19.10.2017 - within the CNCRNC "Dr. Nicolae Robănescu", Bucharest and targets teenagers with CP, to address the re-education of their consistent balance disorders, using, as a therapeutic-recovery means, key tools of motivation/participation and related improved re-learning, VR/augmented facilities (VR/AR) and robotics.



Appendix no. 12. Favorable opinion from the Ethics Commission of CNCRNC "Dr. Nicolae Robănescu" for conducting the clinical study related to the Doctoral Thesis - 19.10.2017



Statistical processing methodology

For statistical processing, demographic data and descriptive statistics were calculated and comparison tests were used - Kolmogorov-Smirnov (K-S) and Shapiro Walik (S-W) - for normality, respectively parametric (type t/ ANOVA - with situational adaptations specific through post-hoc tests: Tamhane, respectively Fisher's Least Significant Difference), non-parametric (Mann-Whitney U.,/ Wilcoxon W./ Z. Kruskal-Wallis H.).

We first calculated the delta concept for each of the four variables associated with the Romberg test, performed both in the situation with O.E. as well as in the situation with C.E.; for this purpose the formula applied was: (T1-T0) \* 100 / T0.

The personal scientific research carried out within this Doctoral Thesis consists of three clinical studies:

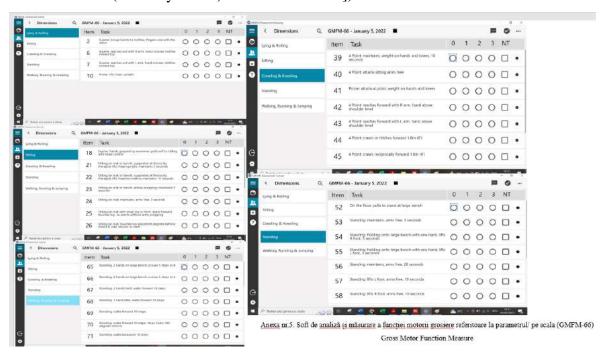
- Pilot study (I) on "Methodologically coordinated, apparatus-based, advanced physical therapy assessment methods for addressing static and balance disorders in pediatric patients with cerebral palsy (CP) preliminary results" (poster awarded in the section for doctoral students of the Congress of the Romanian Association from 2019;
- Study II "Our experience regarding the effects of some advanced physiokinetic recovery methods on balance disorders in adolescents with cerebral palsy partial results; (Data regarding physiiatric advanced approaches of stabilometric and virtual reality for balance assessment and (re)training in cerebral palsy"); where I published a synthesis of the documentation base, knowledge in the issue addressed in this doctoral work in the form of a systematic literature review (rigorously carried out according to the widely accepted and used international methodology: "Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA);
- Study III "Final results, on extended groups/lots with increased statistical power, regarding the results obtained by applying some advanced physical-kinetotherapy recovery methods on balance movements in adolescents with cerebral palsy (CP)":

The Pilot Study (I) concerned a group/batch of 14 patients aged between 13-18 years (156-216 months) who underwent the "intensive" methodological formula for a total duration of recuperative treatment of 90 minutes - (see May far annex no. 1); Study II included 89 patients - (of which 14 representing adolescents with CP and consecutive balance disorders from the Pilot study) - 40 in the "moderate" group/lot, with a methodological dosing algorithm related to a total duration of recuperative treatment of 75 minutes and 34 in the "intensive" group/batch, with a methodological dosing algorithm related to a total recovery treatment duration of 90 minutes [of which 14 from the Pilot Study(I)]; we remind you that all patients in the two groups/study groups were teenagers, aged between 13-18 years (156-216 months); Study III (final) "Final results on extended groups/lots with increased statistical power", was started by adding patients (34 in the "moderate" group/lot, respectively 55 in the "intensive" group/lot) - to the two groups/lots study [(reaching a total number of 163

patients) 74 in the "moderate" group/lot and 89 patients in the "intensive" group/lot)], all adolescents aged between 13-18 years (156-216 months).

Thus, a numerically consistent increase was achieved in each of the two study groups/lots corresponding to a propensity statistical power for valid/reliable results of the related mathematical processing.

In order to quantify the functional status of the patients enrolled in the two study groups/groups and to objectively evaluate the effectiveness of the applied physical-kinetic therapy programs, we performed standardized measurements using seven quantification scales, of which two clinics (those numbered 6. respectively 7. - see below) and equipment - stabilometric/posturographic type measurements [(five measurements performed using the PRO-KIN 252 Device, provided with: a platform containing 4 force cells, which measures the activity of the COP (center of pressure/ pressure center) at the level of the plants and a sensor applied to the patient's xiphoid appendage (TRUNCK SENSOR)] – extracted from the tests performed: "Romberg" and "Global stability index (ISG)" based on horizontal bipodal balancing, expressed in degrees platform inclination [(within the device it is found under the name ('Stability Index') - "PRO-KIN 252"]).





Anexa nr.6. Licetà individualà de utilizare a Scalei de masurare a funcției motorii grosiere Gross Motor Function Measure (GMFM)-66

#### Inclusion criteria:

- When establishing the groups/groups analyzed in this Doctoral Thesis, we considered the following: pediatric patient (in the two study groups/groups mainly adolescents) with a medically confirmed PC diagnosis; no neurological conditions other than CP; stable clinical-biological general condition, without organ failure; the informed consent signed by the parent/legal guardian - a measure fulfilled since admission for all patients admitted to CNCRNC "Dr. Nicolae Robănescu", aged between (13-19 years - eminently teenagers); patient able to understand and cooperate in all the procedures of the complex therapeutic-recovery program;

#### **Exclusion criteria:**

- Refusal of patients/legal guardians to be included in the study; the presence of associated severe musculoskeletal/algic pathology; altered general condition and/or organ failure; cognitive-behavioral disorders capable of affecting the therapeutic-recuperative act; patient who underwent surgery less than 12 months ago;

After considering the inclusion and exclusion criteria, we constituted the two study groups/groups totaling 163 patients (74 in the "moderate" group/group - 75-minute algorithm of the therapeutic-recovery program - 89 in the "intensive" group/group - with the algorithm of the 90-minute therapeutic-recuperative program; it should be noted that we initially recruited 170 teenagers with CP and consecutive balance disorders, but 7 of them did not complete the "moderate" therapeutic-recuperative programs, respectively "intensive.

We specify the fact that the group/ control group/ control of 89 patients (constituted retrospectively) was taken from the Doctoral Thesis of the Associate Professor Doctor Andrada Mirea with the kind consent of her lordship - being selected precisely because it lends itself to the comparison between the groups/ study groups, patients being tested with the Gross Motor Function Measure evaluation scale (as a link and comparability element) and the second argument – these patients performed only 22 (2/day on weekdays and 1/day

on weekends, respectively) physical therapy sessions, which are carried out during a hospitalization (with a 12-day hospitalization) within the CNCRNC "Dr. Nicolae

Robănescu" - each meeting lasted 30 minutes and we did not take new cases as a witness/control because - considering the accentuated and sustained dynamics of upgrading the level of equipment of the CNCRNC "Dr. Nicolae Robănescu", in recent years, practically all patients with CP, in addition to physical therapy, also had one or more procedures such as: "G-EO", "NIRVANA", "LOCOMAT", "HYDROTERAPIE", "MYRO", "ARMEO", "ANDAGO", "PABLO", "VIBRAMOV"; so that as a group/ control group/ effective comparison control (which only performed physical therapy), I considered this one the most appropriate.

Subsemnata Dr. Andrada Mirea, sunt de acord ca datele din grupul de control din cadrul tezei mele de doctorat, in care a fost utilizata scala "Gross Motor Function Measure" (GMFM) să fie preluate, în scopuri comparative – de către colegul meu drd. Radu Mihai Avram în lucrarea sa de doctorat.

09-10-2017 Dr. Andrada Mirea

Anexa nr.7. Acord de utilizare a datelor din cadrul prestigioasei Teze de Doctorat a Doamnei Conf. Dr. Andrada Mirea

Obviously, this option for establishing the group/ control group/ control represents an objective limitation of our research (and more so within this group/ control group/ control of 89 patients with CP, who only performed physiotherapy during hospitalization, only 13 patients were teenagers); on the other hand, as I have shown above, this group/batch was the only possibility of comparison between the effects of the complex therapeutic-recuperative program including interventions based on RV/augmented and the classic program that only included physical therapy, at the same time the overall size of this group/lot (89 patients with PC) being adequate for its size as statistical power.

We reiterate the fact that the inclusion in our doctoral study was made only after completing the Informed Consent, in which all the information related to the study was found, regarding: the description of the stages, patient safety, benefits, risks, volunteering, the immediate possibility of withdrawing from the study - without negative consequences for the patient -, confidentiality, the right to continuous information by providing the contact data - personal phone number and email address of the undersigned, as a doctoral researcher.

Tabel 5.1. Prezentarea sinoptică a programelor terapeutico-recuperatorii: clasic (doar kinetoterapie) și respectiv de RV/ augumentată, în

LOT	KINETOTERAPIE CLASICĂ	ANTRENAREA STABILITĂȚII ȘI ECHILIBRULUI – MODALITĂȚI APARATUALE MODERNE: PRO-KIN 252	MYRO	NIRVANA	G-EO	TIMP
LOT	30' * 2/ ZI L-V	-	-	*	-	60'/ Z
MARTOR/ CONTROL	30' * 1/ ZI S-D	-	-	-	2	301/Z
LOT STUDIU I	20'	15'	10'	10'	20'	75'/21
LOT STUDIU II	20'	15'	10'	15'	30'	90'/ZI

METODE OBIECTIV		EXERCITII		
CONVENTIONALE				
ENP	CREȘTERLA AMPLITUDINII ARTICULARE	RELAXARE-OPUNERE (R.O.)/"time-relaxenza"— <u>Varianta</u> 1- <u>nentru musculatura</u> antassnista/ hipertona si Varianta II- pentru musculatura hipetona. Isometria se face in punctul de limitare a missairi, dupa ce se menine timp de 5-8 secundo la intensisi maxima. si se sere appi islasarea. RELAXARE-ODITRACTIE (R.C.)/ se isalizeara hipetria nusculaturii hipetrone. La punctul de limitare a missairii se isalizeara himetria ne muschiul hipetron. si consconitent hipetria ne tonta amplitudiona de missaire de intatis din acticulatia. pespectiva.		
KABAT	INTINDEREA MUSCULARĂ	Pacientul din decubii dorsal cu membrul superior deasurra capului cu abductie 30° aumbranul monat, brand hometais externa deastele extines si abduse; «« Beriesra deastele si mina a aumbrand «» supinsarà abductia brandui cu matatis interna unu de flexia si opozitia policelui.		
KABAT	DISOCIERE MUSCULARĂ	Din decubit dorsal bratul pacientului descrie o missare diagonali de atuncare a chiect peste unabul opus armátind missarea: kinetoterapeutul opunànd resiste missarius neconitolase.		
KABAT	COORDONARE MUSCULARĂ	Din decubit dorsal pacientul execută miscarea de les în sus-genunchiul este în extensie, gazdat se face gaztenia dergetelor. Dezia dorsală nislor, supmatia nisloru adductia: Dexa-matia internă a connei.		
FRENKEL	MIȘCAREA CONTROLATĂ	Din decubit dorsal pacientul executi, miscăți de flexie/extensie sold-senunchi urmărind cu privirea executia, dânda-se comenzi de pornire și oprire.		
FRENKEL	DOBĀNDIREA ABILITĀŢII	Din decubit dorsal pacientul duce calcăiul pe muioxul tibici opuse apoi este tidicat si asezat alături de gamba opusă urmată de extensie.		
ROBATH	DOBANDIREA/ANTRENAREA ECHILIBRULUI	Pacientul în extostatism pe placă de echilibru, kinetoterapeutul imprimă miscări de lateralitate, poziția arcientului fiiod schimbată după vo repetăți din aprem-posterior A.P în medio-lateral M.L.		
KENNY	REEDUCARE NEUROMOTORIE	Erio miscarca nasixà « membrului afectat/naralitat: miscàri sacadate de flexic/ext 3/4 secunde in sensul In care ac determina contractia muschiolio, nancà ? secundi duga care se reja, no repetato parientul se concentrata si umalesse miscarca.		
MARGARETH ROOD	ANTRENAREA ECHILIBRULUI	Povitia nacientulus, aietat natrupedie astostatism, kinetoterapeutul aplisa nresiuni nivelul cap-umeri: soid in vedersa stabilizati in pozitie, kinetoterapeutul aplisa missari moderate/intense in vedersa dezechilibrarii in APML. DEZECHILIBRARI-c osbii deschiai/inchiai/incheta cu denivelari.		
TEHNICIMODERNE DE ABORDARE ȘI ANTRENAMENT A STABILITĂȚII ȘI ECHILIBRULUI	ANTRENAREA MUSCULATURII ABDOMINALE SUPERIOARE ȘI INFERIOARE OBLICI ABDOMINALI, ERECTORI SPINALI	Parientul in novine ottostatică, ne placa de schilbru, nacientul isi deplasează centru de nosiume ne dieschi simple (medie-lateral/antern posterior) și complexe (diagonal octasonala), mateind mateinile acestora, din novine statică și dinamică		

Anexa nr.8. Descrierea și aplicarea kinetoterapiei clasice privind metodele și procedurile folosite

#### Pilot Study I

14 adolescents with PC and consecutive balance disorders were studied, to whom the "intensive" therapeutic-recuperative approach methodology was applied, and the effects on some stabilometric parameters of the application of the complex therapeutic-recuperative program based on the use of physical therapy and RV/augmented, between the specific clinical-functional status of the enrolled patients, from admission vs. the one at discharge. result

There is a correlation between the data obtained for the situation with "C.E." and the one with "O.E."; more precisely, for the areas of the ellipses obtained at admission, the Pearson correlation coefficient is 0.9587, signifying a very strong correlation, and for the areas of the

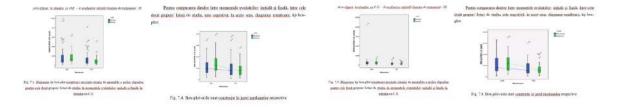
ellipses obtained at discharge, the same type of coefficient had the value of 0.7831, also signifying the correlation. The paired t-test attaches a P-value of 0.0324 to the statement "at discharge the ratio of areas obtained for "C.E." vs. "O.E." is lower than the same ratio at admission". This value is less than the threshold of 0.05, therefore the statement can be considered as statistically significant.

#### Study II

Study II included, as we have shown, 89 patients (of which 14 were added representing adolescents with CP and consecutive balance disorders, from the Pilot study 40 in the "moderate" group/lot, with a methodological dosing algorithm related to a total duration of recovery treatment of 75 minutes and 34 in the "intensive" group/group [of which 14 from the Pilot Study (I)]; we remind you that all patients in the two study groups/groups were teenagers, aged between 13- 18 years (156-216 months).

Working hypothesis: If these modern methods of therapeutic-restorative approach can have a positive and objectified instrumental/statistical influence - the balance function.

#### Result



Statistically significant differences were determined, comparing the primary, related data collected at the initial (before the beginning of the therapeutic-recovery programs) and final (at the end of the therapeutic-recovery programs) evaluations, between the results obtained through the classical therapeutic-recovery approach (in the group/batch control/control) and the complex, diversified and augmented programs, which we used in the two study groups/lots (previously presented), for most of the parameters in the evaluation scales or, respectively, the means/equipment facilities used.

#### **Study III**

Working hypothesis: as we showed in this, the third study, we aimed at the fact that by adding patients recruited in both study groups/groups we would create the possibility of obtaining (using, for evaluations, the same scales and measurements), of additional, propensity data for statistical analysis able to provide further increase in consistency and reliability for the final conclusions of our overall doctoral clinical research. We had a total

of 163 patients, if we exclude the control group/group and 252 if we include it, distributed as follows: "moderate" group/study group: 74 patients (75') "intensive" group/study group: 89 patients (90') control group/ control group (for GMFM-66 only): 89 patients.

#### Results:

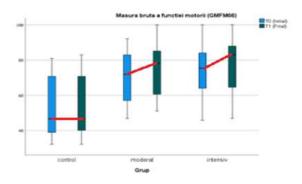


Figura 8.30. Graficul BoxPlot al scalei GMFM-66 per grup/ lot și per moment: filtrând pentru adolescenții din cadrul grupului/ lotului martor/ control

Regarding the comparison between three groups/groups analyzed by the study (the two study groups/groups and the control group/group), comparison made only for the parameter/ on the GMFM-66 scale, we found significant differences between the group/group control and each of the two study groups/lots, in their favor at both T0 and T1.

#### Discussions and partial (sectoral) conclusions

We will present, a little further, synthetically, in table 8.125. the three perspective comparisons, with the most important statistical values (including p-values).

Thus, in the last column, on the right, on a green background, the significant differences are marked (p-value < the 0.05 threshold; see, however, the related nuances of understanding/interpretation, presented on page 8.75.).

For an exhaustive image/representation, we have presented on a light green background those p-values close to the statistical significance threshold of 0.05.

In table 8.125, at the same time, it is marked (/written in bold) the group/lot "in favor" of which the values of the measured clinical-functional and apparatus parameters have evolved. At the same time, we treated separately the values of the parameter / on the GMFM-66 scale, because in this case the comparison was not only made between the two study groups/lots - but between three groups/ groups of patients with CP (including the group/ control group/ control, in two variants: of 89 cases/ so with good statistical power but with the inconvenience of containing mostly children and not teenagers

– and respectively, a control/control subgroup/subgroup, detached from it and made up exclusively of teenagers, the latter therefore having the advantage of rigor compared to the study groups/groups from the point of view of age but being smaller from the point of view numeral). As such in tables 8.125. and 8,126. comparisons of independent data from one group/batch to another are presented.

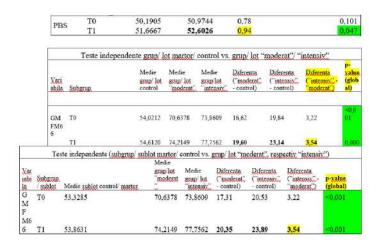
In the tables (8.127. and 8.128.) we present paired comparisons performed on the same patient, but under different test conditions: from one moment (T0) to another (T1) or from the situation with O.E. to the situation with C.E.

Overall, looking from a multi-level approach perspective, both conceptual-methodological of the parameters/variables that were the subject of evaluation and from that of the measurements performed, we found, in general ("global" - see the statistical explanations of earlier) a certain superiority, as a clinical-functional therapeutic-recuperative benefit, of the "intensive" group/batch.

Tabel 8.125. Tabel de sinteză a variabilelor asociate testului Romberg efectuat aparatual pentru determinarea dinamicii, dintre situația cu O.E. și situația cu O.E. (pentru ISG, din motive de siguranță a pacientului, evaluarea se efectuează numai cu O.E.)

Vanabil	Grup/	Medie grup/ lot	Medie grup/ lot	Diferenta ("Intensiv" -	p-
a	lot	"moderat"	"intensiv"	"Moderat")	value
Aria elipsei	O.E. la		Take to the		
	TO	910,449	1134,0313	223,582	0,122
	O.E. la				
	T1	718,6601	664,0543	-54,606	0,421
	C.E.la				
	TO	1731,8183	1785,8288	54,01	0,757
	C.E. la	0000000000		- months	11252012
	T1	1283,8428	1116,4052	-167,44	0,265
2.099	O.E. la		1.0204		0.100
Deviati	T0	2,1479	1.9396	-0,21	0,429
g standar d a trunchiu lui	O.E. la	1,9411	1,4608	-0.48	0.01
	C.E. la	1,7411	1,4008	-0.40	0,02
		2,4308	2.416	-0.01	0,896
	C.E. la	2,4,500	2,410	-0,01	0,030
	TI	2.322	1.8106	-0.51	0.018
	O.E. la			11770	-
Viteza centru presiun g A-P	TO	14,1897	13,3298	-0,86	0,482
	O.E. la				
	T1	12,5164	11,1289	-1,39	0,202
	C.E. la				
	T0	20,6414	18.1672	-2,47	0,386
	C.E. la				
	T1	18,8104	15,3515	-3,46	0,063
Viteza centru presiun e M-L	O.E. la				
	T0	11,285	11,2119	-0,07	0,55
	O.E. la				
	T1	9,3833	8,8619	-0,52	0,546
	C.E. la			W.12	
	TO C.F.	15,374	15,2185	-0,16	0,996
	C.E. In	14205	12.02.47	221	0.22
ISG	T1	14,3415	12,0347	-2,31	0,224
	T0	3,4442	3,2702	-0,17	0,781

Tabel 8.126. Teste independente grup/ lot martor/ (89 cazuri) control vs. grup/ lot "moderat"/ "intensiv"



Tabel 8.127. Testul eșantioanelor pereche (T0 vs. T1)



Tabel 8.128. Teste-pereche (T0 vs. T1)

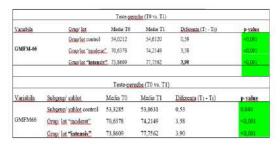
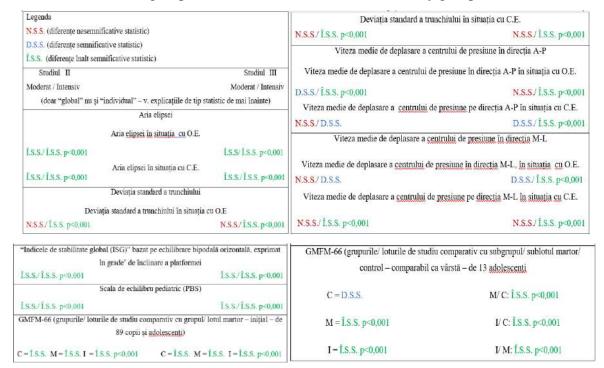


Table 8.130. Summary synthesis of the results obtained in studies II and III regarding the differences/recuperative clinical-therapeutic evolution between the moments: initial (T0 – before treatment) and final (T1 – after treatment) between the classic recuperative treatment (applied to the group/ control group/ control, respectively to the control

#### subgroup) and the one administered to the study groups



#### Concluzii și contribuții personale

#### Conclusions and personal contributions

- 1. This Doctoral Thesis addresses the problem of balance disorders in adolescents with CP from the modern perspective of the use of apparatus devices with quantified functional evaluation capabilities as well as of some related, physiatry, advanced methodologies.
- 2. It is known that due to the specific posture and motility: orthostatism and walking, biped the static and dynamic balance of the body and, respectively, its positioning in conditions of sequential stability, represents a feature and at the same time a key determinant of human functioning; therefore, attempts to contribute to the correction/recovery in such disorders is a major therapeutic target and unfortunately, still always current given the fact that for lesions, especially severe ones of the CNS, such as those in CP are not at least there is healing for now.
- 3. Under these conditions, I had the opportunity to use and objective the contribution/contributive/evaluative and therapeutic-recovery performances of advanced devices and methodologies in addressing the above-mentioned disorders, taking into account the remarkable level of endowment at international standards of the clinical unit where I carry out my activity.

- 4. I specify, from this point of view, on the one hand the fact that CNCRNC "Dr. N. Robănescu" is the first unit in our country that was equipped with the Pro-kin 252 device and on the other hand, the fact that in the literature to our knowledge (we also mention here that, in preparation for the realization of this doctoral study, we also established a fund of theoretical knowledge, we consider adequate, based on a systematic literature review, related) we did not find any works focused on this population target: adolescents with CP and consecutive balance disorders, with their evaluative and therapeutic-recovery approach, in a physiatry complex multiplanar, including using advanced physical therapy devices and especially in association with RV/augmented procedures.
- 5. Concretely, this doctoral work is the result of my direct experience of about 7 years in the use of apparatus devices and related, physiatry, evaluation and advanced therapeutic-recovery methodologies, including in the approach of balance disorders in standing and walking, consecutive PC; more precisely, in this Doctoral Thesis I used: Pro-KIN 252, G-eo Evolution in association with immersive RV Myro and Nirvana (RA) (interventions associated, within standardized complex programs, of classic kinesitherapy procedures/conventional).
- 6. As it was shown in detail in this doctoral work, we objectified and measured a consistent number of clinical-functional parameters contributing to the assessment of balance disorders in standing and walking, namely five through instrumental determinations and two through clinical-functional quantification scales namely: 1. "Area of the ellipse" (in mm2), 2. "Standard deviation of the trunk" (in degrees), 3. "Average speed of movement of the center of pressure in the A-P direction" in mm/s), 4. "Average displacement speed of the center of pressure in the M-L direction" (in mm/s), 5. "Global stability index" (ISG in degrees of platform inclination), respectively the non-apparatus tests, digitally compatible for processing statistics 6. "Pediatric Balance Scale (PBS)" and 7. "Gross Motor Function Measure (GMFM-66)".
- 7. The determinations listed above also allowed us to objectify/measure the elements of therapeutic-recuperative benefit obtained by applying two dosage schemes, in terms of duration, used by RV/augmented: "moderate" and respectively "intensive" (in an interventional context multiplanar physiatric), which we applied to adolescents with CP and consecutive balance disorders in the groups/groups with the corresponding names ("moderate" group/group vs. the "intensive" group/group).

- 8. Thus based including on a complex analysis/statistical processing methodology, we found that the patients from the two study groups/groups had, post-intervention (T1 vs. T0), significantly statistically superior results compared to both the group/group control/control as well as compared to the control/control subgroup/subgroup and respectively those from the "intensive" group/group had, ("only global" but not "individual" see the detailed explanations in study III of this Thesis Doctorate), statistically significantly better results than those in the "moderate" group/batch.
- 9. We recall for the sake of rigor, the fact that, from the aspect of clinical-functional reasoning, within the measured Romberg-type parameters, the results in the practice of medical-recuperative assistance are quite difficult to observe non-apparatus, but this reality can also be understood as a higher quality element of the use of advanced specific equipment.
- 11. Also, a possible limitation of the present research carried out/ in the elaboration of this Doctoral Thesis, is (in addition to the mixed composition: children plus adolescents of the group/ control group/ control in its entirety and, respectively, the smaller number of cases of the patient component adolescents from the control/control subgroup/subgroup) the options expressed by the respective parents regarding voluntary inclusion in the "moderate" or "intensive" group/group, taking into account aspects of balance (at the same time with subjective elements) between the desire/trust of principle, natural and the psychological "investment" in a procedural complex with a more pronounced profile and, respectively, the concern for a potential risk of additional patient fatigue (by the way, due to the ethical precaution of our research, we chose to carry out the clinical studies related to our work doctoral studies on adolescents (not children) with CP and consecutive balance disorders considering the therapeutic-recuperative component of immersive VR.
- 12. So, the dosage, in the end, between the "moderate" and "intensive" forms has no statistically significant differences (of the "individual" type according to what is explained in the Thesis), which is not unimportant because we allows in the future to adapt to the preferences of teenagers, their relatives and administrative conditions (work schedule/stay period).
- 13. Both the methodology of analysis/statistical processing (rigorous and complex) and the statistical power of the groups/batches of patients evaluated allowed us to draw valid conclusions consolidated even in the conditions of the dynamics of the statistical power of

the groups/batches - and therefore permissive for the practical use of methodological conclusions, of applied dosage for our current profile activity.

- 14. The fact that apart from translational at the level of research and current assistance these technologies should become known to the entire recovery department, provided as a tool in the therapeutic-recovery arsenal, regarding the recovery of balance disorders in PC (and not only ) as a continuation of this research on modern/present multimodal modalities by adding more RV/augmented interventions and treatment/recovery apparatus systems.
- 15. Regarding the technical and economic advantages and disadvantages related to this doctoral scientific research endeavor, I had the beneficial opportunity to be able to use advanced recuperative assessment and treatment devices and technologies a mechatronic stabilometric device entered for the first time in the equipment of a medical-sanitary unit in the country ours adding to this a number of RV/augmented devices and facilities, also modern and not yet very common in our profile units; obviously, any new and especially advanced technology involves the "disadvantage" of some sometimes more substantial costs, on the other hand, obtaining superior therapeutic-recovery results is linked, as a principle, to advances in related interventional devices and technologies and from this point of view, as I have shown in this Thesis, a good part of the postural, dynamic improvements could be objectified with apparatus, but being difficult to observe "with the naked eye" (non-apparatus).
- 16. The results obtained constitute, we consider, a personal contribution to the objectification of the knowledge and interventional, theoretical and practical base thus the objectives of our doctoral clinical study have been achieved.

#### **Bibliography**

- 1. McNulty PA, Mouawad MR, Doust CG, Max MD. Wii-based movement therapy to promote improved upper extremity function post-stroke: A pilot study. J Rehabil Med. 2011;43(6):527–33.
- 2. Ballard C, Shaw F, McKeith I, Kenny R. High prevalence of neurovascular instability in neurodegenerative dementias. Neurology. 1998 Dec 1;51(6):1760–2.
- 3. Morone G, Tramontano M, Iosa M, Shofany J, Iemma A, Musicco M, et al. The Efficacy of Balance Training with Video Game-Based Therapy in Subacute Stroke Patients: A Randomized Controlled Trial. Biomed Res Int. 2014;2014:1–6.
- 4. Li LM, Uehara K, Hanakawa T. The contribution of interindividual factors to variability of response in transcranial direct current stimulation studies. Front Cell Neurosci. 2015 May 12;9.

- 5. Luna-Oliva L, Ortiz-Gutiérrez RM, Cano-de la Cuerda R, Piédrola RM, Alguacil-Diego IM, Sánchez-Camarero C, et al. Kinect Xbox 360 as a therapeutic modality for children with cerebral palsy in a school environment: A preliminary study. NeuroRehabilitation. 2013 Dec 28;33(4):513–21.
- 6. Voinescu A, Sui J, Stanton Fraser D. Virtual Reality in Neurorehabilitation: An Umbrella Review of Meta-Analyses. J Clin Med. 2021 Apr 2;10(7):1478.
- 7. Garcia AP, Ganança MM, Cusin FS, Tomaz A, Ganança FF, Caovilla HH. Vestibular rehabilitation with virtual reality in Ménière's disease. Braz J Otorhinolaryngol. 2013 May;79(3):366–74.
- 8. Byl NN, Pitsch EA, Abrams GM. Functional Outcomes Can Vary by Dose: Learning-Based Sensorimotor Training for Patients Stable Poststroke. Neurorehabil Neural Repair. 2008 Sep 16;22(5):494–504.
- 9. Ghai S, Ghai I. Virtual Reality Enhances Gait in Cerebral Palsy: A Training Dose-Response Meta-Analysis. Front Neurol. 2019 Mar 26;10.
- 10. Kerem M, Kaya O, Ozal C, Turker D. Virtual Reality in Rehabilitation of Children with Cerebral Palsy. In: Cerebral Palsy Challenges for the Future. InTech; 2014.
- 11. Armstrong CM, Reger GM, Edwards J, Rizzo AA, Courtney CG, Parsons TD. Validity of the Virtual Reality Stroop Task (VRST) in active duty military. J Clin Exp Neuropsychol. 2013 Feb;35(2):113–23.
- 12. Riva G, Baños RM, Botella C, Mantovani F, Gaggioli A. Transforming Experience: The Potential of Augmented Reality and Virtual Reality for Enhancing Personal and Clinical Change. Front Psychiatry. 2016 Sep 30;7.
- 13. Freeman D, Reeve S, Robinson A, Ehlers A, Clark D, Spanlang B, et al. Virtual reality in the assessment, understanding, and treatment of mental health disorders. Psychol Med. 2017 Oct 22;47(14):2393–400.
- 14. Lotan M, Yalon-Chamovitz S, Weiss PLT. Virtual reality as means to improve physical fitness of individuals at a severe level of intellectual and developmental disability. Res Dev Disabil. 31(4):869–74.
- 15. Alan B, Craig William R, Sherman Jeffrey D. Developing Virtual Reality Applications. 1st Edition. Foundations of Effective Design, editor. 2009.
- 16. Gonzalez A, Garcia L, Kilby J, McNair P. Robotic devices for paediatric rehabilitation: a review of design features. Biomed Eng Online. 2021 Dec 6;20(1):89.
- 17. Cacau LAP, Oliveira GU, Maynard LG, at all. The use of the virtual reality as intervention tool in the postoperative of cardiac surgery. Revista Brasileira de Cirurgia Cardiovascular. 2013;28(2):281–9.
- 18. Beckers L, Stal RA, Smeets R, Onghena P, Bastiaenen C. Single-case Design Studies in Children with Cerebral Palsy: A Scoping Review. Dev Neurorehabil. 2020 Feb 17;23(2):73–105.
- 19. Saposnik G, Teasell R, Mamdani M, Hall J, McIlroy W, Cheung D, et al. Effectiveness of Virtual Reality Using Wii Gaming Technology in Stroke Rehabilitation. Stroke. 2010 Jul;41(7):1477–84.

- 20. Prasertsakul T, Kaimuk P, Chinjenpradit W, Limroongreungrat W, Charoensuk W. The effect of virtual reality-based balance training on motor learning and postural control in healthy adults: a randomized preliminary study. Biomed Eng Online. 2018 Dec 18;17(1):124.
- 21. Ravi DK, Kumar N, Singhi P. Effectiveness of virtual reality rehabilitation for children and adolescents with cerebral palsy: an updated evidence-based systematic review. Physiotherapy. 2017 Sep;103(3):245–58.
- 22. Tatla SK, Sauve K, Virji-Babul N, Holsti L, Butler C, van der Loos HFM. Evidence for outcomes of motivational rehabilitation interventions for children and adolescents with cerebral palsy: an American Academy for Cerebral Palsy and Developmental Medicine systematic review. Dev Med Child Neurol. 2013 Jul;55(7):593–601.
- 23. Carlo O, Callus E, Policlinico SD, at all. Psychological Treatments and Psychotherapies in the Neurorehabilitation of Pain: Evidences and Recommendations from the Italian Consensus Conference on Pain in Neurorehabilitation. Frontiers in Psychology | www.frontiersin.org [Internet]. 2016 [cited 2023 Jan 26];7:115. Available from: www.frontiersin.org
- 24. Allan HR, Samuels MA. Adams and Victor's Principles of neurology, Ninth Edition, Editorial McGraw Hill,; 2009.
- 25. Pro-Kin 252 PHYSIOMED [Internet]. [cited 2022 Oct 24]. Available from: https://www.physiomed.ro/product/pro-kin-252/
- 26. Huizinga J. Homo Ludens. Încercare de determinare a elementului ludic a culturii,. Traducere din olandeză de HR Radian. Kabat H MMP, editor. Bucuresti: Humanitas,; 2017.
- 27. Reha Technology a passion for robot-assisted gait therapy [Internet]. [cited 2022 Nov 7]. Available from: https://www.rehatechnology.com/en/
- 28. Sistem de reabilitare a mobilității mâinii Myro® Tyromotion mobilitatea brațului / virtual / pediatric [Internet]. [cited 2023 Feb 22]. Available from: https://www.medicalexpo.com/prod/tyromotion/product-70389-731854.html
- 29. https://www.physiomed.ro/product/bts-nirvana/.
- 30. Swinden L. NHS. Sexual health Stages of puberty: what happens to boys and girls [Internet]. Design and illustration by Ed Hillyer Corinne Pearlma, editor. England: Newnorth Print Ltd.; 2018 [cited 2022 Oct 7]. Available from: https://www.nhs.uk/live-well/sexual-health/stages-of-puberty-what-happens-to-boys-and-girls/
- 31. Thakur R, Gautam RK. Differential onset of Puberty and Adolescence among girls and boys of a Central Indian Town (Sagar). The Oriental Anthropologist: A Bi-annual International Journal of the Science of Man. 2017 Jun 5;17(1):137–47.
- 32. Pandit S, Panthee B. Awareness and Attitude on Pubertal Changes among Community Adolescents. International Journal of Caring Sciences September-December [Internet]. 2017

  Dec [cited 2022 Oct 7];10(3):1255. Available from: http://www.internationaljournalofcaringsciences.org/docs/16\_bimala\_original\_10\_3.pdf
- 33. Lang CE, Lohse KR, Birkenmeier RL. Dose and timing in neurorehabilitation. Curr Opin Neurol. 2015 Dec;28(6):549–55.

- 34. Carvalho I, Pinto SM, Chagas D das V, Praxedes dos Santos JL, de Sousa Oliveira T, Batista LA. Robotic Gait Training for Individuals With Cerebral Palsy: A Systematic Review and Meta-Analysis. Arch Phys Med Rehabil. 2017 Nov;98(11):2332–44.
- 35. Firan FC, Romila A, Onose G. Molecular Sciences Current Synthesis and Systematic Review of Main Effects of Calf Blood Deproteinized Medicine (Actovegin ®) in Ischemic Stroke. [cited 2022 Dec 22]; Available from: www.mdpi.com/journal/ijms
- 36. Avram RM, Onose G, Padure L. Data regarding physiatric advanced approaches of stabilometric and virtual reality for balance assessment and (re)training in cerebral palsy. Romanian JouRnal of medical PRactice. XV(4):2020.
- 37. Mantovani J SD. Historical perspective. In: Dan B, Mayston M, Paneth N, Rosenbloom L. Cerebral Palsy: Science and Clinical Practice. London: Mac Keith Press; 2015. 3–15 p.
- 38. Morris C. Definition and classification of cerebral palsy: a historical perspective. Dev Med Child Neurol. 2007 Feb;49:3–7.
- 39. Lee Y-T, Brennan P, Frontera WR, Silver JK, Rizzo Jr TD. Essentials of physical medicine rehabilitation: Musculoskeletal disorders pain, and rehabilitation. 2nd ed. Elsevier, editor. Philadelphia; 2008. 627–634 p.
- 40. Beaman J, Kalisperis FR, Miller-Skomorucha K. The Infant and Child with Cerebral Palsy. In: Tecklin JS. Pediatric Physical Therapy. . 5th edition. Philadelphia: Lippincott Williams & Wilkins; 2015. 187–247 p.
- 41. Bax MCO. Terminology and classification of cerebral palsy. Dev Med Child Neurol Vol,; 1964. 295–307 p.
- 42. Onose G, Ciobanu V, Pădure L, Morcov C G. Current overview and reappraisal on essays towards systematizing clinical assessment instruments used to evaluate neuro-functional deficits after cerebral palsy including through the ICF(-DH) conceptual framework. bioclima.ro. 2021;
- 43. Sbenghe T. Kinetologie profilactică, terapeutică și de recuperare . București: Editura Medicală; 1987. 111–164 p.
- 44. Carini F, Mazzola M, Fici C, Palmeri S, Messina M, Damiani P, et al. Posture and posturology, anatomical and physiological profiles: overview and current state of art. Acta Biomed [Internet]. 2017;88:11–6. Available from: www.actabiomedica.it
- 45. Data and Statistics for Cerebral Palsy | CDC [Internet]. [cited 2022 Oct 12]. Available from: https://www.cdc.gov/ncbddd/cp/data.html
- 46. Patel DR, Neelakantan M, Pandher K, Merrick J. Cerebral palsy in children: a clinical overview. Transl Pediatr. 2020 Feb;9(S1):S125–35.
- 47. Cerebral Palsy CP National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention https://www.cerebralpalsy.org/about-cerebralpalsy/definition Page last reviewed: May 2, 2022 accesat în 20.09., 2022.
- 48. Hadzagic-Catibusic F, Avdagic E, Zubcevic S, Uzicanin S. Brain Lesions in Children with Unilateral Spastic Cerebral Palsy. Medical Archives [Internet]. 2017 Feb 1 [cited 2022 Oct 13];71(1):7. Available from: /pmc/articles/PMC5364798/

- 49. Rose J, Schadl K, Vassar R, Papageorgiou E, de Beukelaer N, Simon-Martinez C, et al. Structural Brain Lesions and Gait Pathology in Children With Spastic Cerebral Palsy. 2020 [cited 2022 Oct 13]; Available from: www.frontiersin.org
- 50. Ogoke CC, Ogoke CC. Clinical Classification of Cerebral Palsy. Cerebral Palsy Clinical and Therapeutic Aspects [Internet]. 2018 Nov 5 [cited 2022 Oct 13]; Available from: https://www.intechopen.com/state.item.id
- 51. Miller G, Cala LA. Ataxic cerebral palsy--clinico-radiologic correlations. Neuropediatrics [Internet]. 1989 [cited 2022 Oct 13];20(2):84–9. Available from: https://pubmed.ncbi.nlm.nih.gov/2739880/
- 52. Cans C. Surveillance of cerebral palsy in Europe: a collaboration of cerebral palsy surveys and registers. Dev Med Child Neurol. 2007 Feb 13;42(12):816–24.
- 53. Wiart L, Rosychuk RJ, Wright FV. Evaluation of the effectiveness of robotic gait training and gait-focused physical therapy programs for children and youth with cerebral palsy: a mixed methods RCT. BMC Neurol [Internet]. 2016 Jun 2 [cited 2022 Oct 13];16(1). Available from: /pmc/articles/PMC4890515/
- 54. Chiari L. Stabilometry. In: Encyclopedia of Neuroscience. Berlin, Heidelberg: Springer Berlin Heidelberg; p. 3830–3.
- 55. El-Shamy SM, Abd El Kafy EM. Effect of balance training on postural balance control and risk of fall in children with diplegic cerebral palsy. Disabil Rehabil. 2014 Jul 13;36(14):1176–83.
- 56. Ma M, Zheng H. Virtual Reality and Serious Games in Healthcare. Adv Comput Intell Paradigms in Healthcare. 6:169–92.
- 57. Martín GJ, Mora CE, Añorbe DB, González MA. Virtual Technologies Trends in Education. EURASIA Journal of Mathematics, Science and Technology Education. 2017 Jan 18;13(2).
- 58. Bonnechère B, Jansen B, Omelina L, Degelaen M, Wermenbol V, Rooze M, et al. Can serious games be incorporated with conventional treatment of children with cerebral palsy? A review. Res Dev Disabil [Internet]. 2014 [cited 2023 Feb 22];35(8):1899–913. Available from: https://pubmed.ncbi.nlm.nih.gov/24794289/
- 59. Michmizos KP, Krebs HI. Serious games for the pediatric anklebot. Proceedings of the IEEE RAS and EMBS International Conference on Biomedical Robotics and Biomechatronics. 2012;1710–4.

#### Listă cu lucrări științifice publicate în reviste de specialitate

1) **Avram RM**, Onose G, Padure L. – ["Modalități de evaluare și kinetoterapie, aparatuale avansate, coordonate metodologic, de abordare a tulburărilor de statică și echilibru la pacienți cu paralizie cerebrală (PC) – rezultate preliminarii", – la Al 13-lea Congres Anual Al "Asociației Medicale Române" și a fost publicat rezumativ în Revista Medicală Româna Vol. LXVI Supliment Special An 2019 <u>AMPH - RMJ.2019.SS(fullissue)</u>, Congres 13 AMR - Page 24-25 (publitas.com)] – (6)(anexa 1).

- 2) **Avram RM**, Onose G, Padure L. ["Data regarding physiiatric advanced approaches of stabilometric and virtual reality for balance assessment and (re)training in cerebral palsy", at The 13th Annual Congress of the "Romanian Medical Association" and was published in summary in the Romanian Medical Journal Vol. LXVI Special Supplement Year 2019 https://rjmp.com.ro/articles/2020.4/RJMP\_2020\_4\_Art-05.pdf ] (7 )(annex 2).
- 3) **Avram RM**, Padure L, Onose G. This study was published in Proceedings of the Romanian Academy; Series B: Chemistry, Life Sciences and Geoscience; [Avram RM, Padure L, Onose G. "Our experience regarding the effects of some advanced physical kinetological recuperative treatment methods in balance disorders in adolescents with cerebral palsy (partial results)"; ("Our experience regarding effects of some advanced physicalkinesiological rehabilitation methods on balance disorders in adolescents with cerebral pals partial results") Proc. Rom. Acad., Series B, 2021, 23(1), pp. 45–75; https://acad.ro/sectii2002/proceedingsChemistry/doc2021-1/Art07.pdf] (annex 3).
- 4) **Avram RM**, Padure L, Onose G. "Study III: "Final data on numerically increased batches and with related optimization of the statistical analysis methodology regarding the effects of some advanced methods of recuperative physical-kinetotherapy treatment in balance disorders, in adolescents with cerebral palsy"(8).











Special thanks go to the PhD supervisor Mr. Prof. Dr. G. ONOSE, for the help provided throughout my professional doctoral training - and who unconditionally supported me in the scientific foundation as well as in the elaboration of this doctoral thesis - which would have been impossible without the help, support and guidance of this entities – who, through high professionalism and dedication, contributed to my formation as a researcher, instilling in me knowledge, perseverance and the courage to move forward!

At the same time and last but not least, I would like to thank Ms. Associate Dr. L. PĂDURE, who inspired my desire to participate in this doctoral endeavor, as well as the acceptance to be able to use the space and the ultra-modern equipment of the CNCRNC Center "Dr. Nicolae Robanescu".

Thank you to all my patients who agreed to participate – and went through all the steps necessary to conduct this doctoral study!