Before completing the following application, carefully review the 'Guidelines and Information' and 'Application Checklist' documents at www.horsesandhumans.org.

Proposals should be designed to convince reviewers that the applicant clearly understands the topic to be studied, has the expertise to conduct the study, has devised a logical scientific approach and is proposing a study that is relevant to HHRF.

The 2023 HHRF Grant will be awarded for up to $75,000 with the focus on the impact of EAS on social, physical, cognitive, mental, emotional and/or spiritual aspects of participants.

HHRF endorses the concept of One Health defined by the CDC as "…the goal of achieving optimal health outcomes recognizing the interconnection between people, animals, plants, and their shared environment." HHRF recognizes the depth and breadth of the field of Equine Assisted Services. With this in mind, the grant applications should include rigorous research proposals measuring the impact of the horse human interaction on the wellbeing of the human participant including but not limited to the social, physical, cognitive, mental, and/or spiritual elements of the whole person.

As there are few Standard definitions for Equine Assisted Services, please begin with a glossary of definitions for all your Abbreviations, Acronyms and technical terminology. Thereafter they may be used throughout the application.

APPLICATIONS MUST BE SUBMITTED IN ELECTRONIC FORMAT.

IMPORTANT: PROPOSAL FORMAT: The proposal should be in Word format on 8.5 X 11 inch paper with pages numbered, double-spaced, 1 inch margins and 12-point font size (Times New Roman, Arial or Calibri preferred) and is page or word limited where noted. The order of the written proposal should follow the outline described below, including use of the outline numbering and headings. Answer the questions individually, and if any of the questions is not applicable, indicate with "N/A".

A complete application packet includes:

I. Cover Page
II. Scientific Abstract
VIII. Biographical Sketch of Principal Investigator

III. Need/Justification
IV. Research Narrative
V. Literature Review
VI. Proposed Budget
VII. Proposed Time Line
IX. Safety and Quality Standards
X. Evidence of Compliance with Government Requirements
XI. Plan to Publish
XII. Attachments

Incomplete applications will not be considered. Applications lacking any of the required materials are considered incomplete.

Do not include extra information not requested in these guidelines. Anything extra will not be reviewed.

Adherence to these guidelines is mandatory and failure to do so will result in disqualification (note: word and page limits are strictly enforced.)

Email the completed application to info@horsesandhumans.org **with the subject line "HHRF 2023 Grant Proposal – Principal Investigator last name**."

Horses and Humans Research Foundation (HHRF) must receive the completed electronic application by the end of the business day on the established deadline (Should the deadline fall on a weekend or holiday; the due date is the closest **preceding** business day). All submissions must be **received** by the due date or will not be accepted. The main contact listed on the application will be sent a notice by email of receipt of their application within two weeks of the HHRF office receiving it. If the applicant does not receive such a confirmation, inquire at info@horsesandhumans.org .

HHRF Research Grant Application

I. Cover Page

Title of Project:

Neurological rehabilitation through hippotherapy on the neurofunctional sequels of a brain stroke:

(I) Effect on the functional independence, sensorimotor and cognitive capacities, and quality of life of the patients

(II) Effect on quality of life of the caregivers.

Submission Date:

Principal Investigator Name and Title: *Manuel GAVIRIA, MD, PhD*

Contact Name and Title: *Hélène Viruega, ESMHL*

(NOTE: The contact person is the only person with whom HHRF will have direct contact. The contact person receives all letters and notification from the HHRF office.)

Institute: *Equiphoria*

Address (provide physical AND mailing addresses, if different):

Combo Besso, lieu-dit Rouges Parets, 48500 La Canourgue, France

Telephone Number: *+33 466 32 10 46*

Web Site: *www.equiphoria.com*

Email Address:

contact@equiphoria.com

helene.viruega@equiphoria.com

Other Social media accounts (ResearchGate, LinkedIn, etc.) *https://www.linkedin.com/company/institut-equiphoria/?originalSubdomain=fr*

Years, Titles and any awards of past HHRF Funding Applications: N/A

Attach a Glossary of definitions for all your Abbreviations, Acronyms and technical terminology. Thereafter they may be used throughout the application.

Primary focus area of the investigation:

Brief Description of project in lay language (200 words or less), understandable to 8th grade education level and suitable for use in HHRF Publications as determined by HHRF. This should include information on the purpose or research question, the need for the research, and general explanation of the methodology, procedures, analysis and any other applicable information.

The objective of the study is to analyze the effect on the functional and global impact of a 22-week hippotherapy treatment on patients who have suffered a stroke resulting in moderate to severe disability. A second purpose is to measure the impact of the intervention on the quality of life of their caregivers. The main evaluation criterion is the patient's functional independence measured by a validated clinical score. Secondary

evaluation criteria include the patient's degree of functional disability, motor status, postural balance, gait performance, and quality of life. Quality of life and caregiver's burden are also assessed. The type of study proposed is a prospective randomized clinical trial on the effectiveness of hippotherapy (treatment group) versus conventional outpatient rehabilitation alone (control group). The program will be implemented during the first year after the stroke and will last one year for each patient.

Will others collaborate or consult with you on this project? YES ~~NO~~

If yes, list Individuals or Organizations collaborating on project:

Boehringer Ingelheim – Animal Health, Paris, France

Deparment of Neurology – Centre Hospitalier Sud Fancilien, Corbeil Essonne, France

Attach letters to you that state collaborating individuals or organizations agreement to do so.

Does your project involve an underserved population? ~~YES~~ NO

If you answered "yes" please describe:

End Date of Project:

Amount Requested from HHRF: $

II. Scientific Abstract: **400** words or less, double spaced, describing the proposed project.

Stroke is a high burden illness and the second leading cause of worldwide disability with generally poor recovery rates. Robust benefits of hippotherapy in functional recovery following various severe neurological disabling conditions has been shown. In the present study, we will analyze the effect of a hippotherapy program on the outcome of post-stroke patients in the first-year post-stroke.

Method: A randomized controlled clinical trial on the effectiveness of hippotherapy (4 weeks hippotherapy/18 weeks conventional neurorehabilitation) versus conventional neurorehabilitation alone (22 weeks) will be conducted. In the treated group, one-hour daily hippotherapy sessions will be exclusively delivered during the hippotherapy's cycles, alternated with periods of conventional neurorehabilitation. A test battery will measure both the functional and psychological outcomes. The primary endpoint will be the patient's functional independence. The secondary endpoints will measure the sensorimotor function, autonomy, and quality of life, as well as the caregivers' quality of life and burden. The time points for

measurement will be: before the beginning of the treatment, at the end of the treatment (week 22), and at week 48 (to analyze the sustainability of functional gains).

Results and conclusion: Individual brain connectome, life history and personality construct influence the brain's functional connectivity and are central to developing optimal tailored neurorehabilitation strategies. According to our current practice, hippotherapy allows the enhancement of substantial neuroplastic changes in the injured brain with significant neurological recovery. The protocol aims to confirm those issues.

Sections III-XII below should total 14 pages or less (**excluding** cited references, copies of IRB and IACUC applications, biographical sketches of the research team (limited to five pages each), and letters of support from Collaborators which should be included as Attachments in Section XIII) typed on one side of the page only, with pages numbered, double spaced, 1" margins and 12-point font size.

III. Need/Justification: Preliminary data that supports the proposal

a. State the purpose or question to be addressed that will be the focus of the project. Include your conceptual framework.

We know that every individual has their own unique brain configuration (connectome) and their own unique life history and personality construct. Stroke patients have multiple confounding factors such as age, gender, biological rhythms, homeostatic mechanisms, and comorbidities, all influencing brain's functional connectivity. How fundamental are these in developing optimal neurorehabilitation strategies remains to be explored. Some points of discussion that can be supplied by hippotherapy appear to be crucial: the intrinsic rhythms of the patient's processes, the right entry point (i.e., the initially targeted sphere by the therapist), the silent barriers linked to insufficient neuroplastic responses (inhibitory pathways), the relevance of therapeutic strategies (as perceived by the patient), their sequencing, and their potential viability with respect to homeostasis considerations. All of them depend on the self-identified priorities of the patient when functional recovery is engaged. In this panorama and taking into account our experience through

more than one decade of practice, we believe that hippotherapy is a key entry point to foster neurological reshaping.

b. Explain the broad significance and implication of the project to the Equine Assisted Services field.

The hippotherapy approach, as we understand it, combines (i) a multidisciplinary cross-sectoral team simultaneously around the patient, (ii) a global approach focused on the individual and his/her potentials rather than on the disabilities, and (iii) strict care protocols that include a program for caregivers. The program provides an innovative disruptive response to the conventional care of diseases of neurological origin. Hippotherapy gradually emerges as a cutting-edge solution for human impairment, activity limitation, and participation restriction as defined by the World Health Organization. The main objective of the clinical trial, which relies on the protocol presented here, will be to validate hippotherapy as a novel approach to stroke neurorehabilitation consisting of a personalized all-inclusive rhythm-adapted patient's empowerment, which constantly re-evaluates and adjusts itself in real time, according to the patient's neurological possibilities, their interaction with their family caregiver(s) and their lifetime goals.

c. What are the results of relevant pilot research, if available.

N/A

IV. CORE RESEARCH NARRATIVE:

a. Describe the research design and methodology in detail, and how they answer the purpose/question of the project.

Design of the study: We will conduct a randomized open, prospective two-arm controlled trial with blinded clinical evaluations on the effectiveness of hippotherapy (plus conventional neurorehabilitation) versus conventional neurorehabilitation alone. In the context of the trial, a double- or single-blind procedure is not possible since participants and some investigators will know which treatment is delivered. To mitigate the placebo and nocebo effects, the patient's functional abilities will be assessed by two independent health actors (i.e., a doctor and a physiotherapist). The study will be carried out at the Equiphoria Institute (La

Canourgue, France: https://www.equiphoria.com/en/) for the hippotherapy program and at the Neurology Service of the Centre Hospitalier Sud Francilien (CHSF Corbeil-Essonnes; https://www.chsf.fr/nos-service/medecine/neurologie/) for the conventional neurorehabilitation.

Study protocol:

Hippotherapy group: The protocol's shape relies on our own clinical experience over the last decade[1–7]. The hippotherapy approach will comprise three cycles. The first one consists of two-week daily sessions at the beginning of the program. This first phase aims to (i) evaluate the patient's neuro-functional capacities, and (ii) build the initial treatment considering the silent barriers that may exist (e.g., PTSD, fatigue, pain, and fear) and that strongly interfere with the individual's functional outcome[8] developing ways to overcome them. After these two weeks, a nine-week "hippotherapy wash out" period follows, during which the patient starts the conventional neurorehabilitation care; then, an intermediate one-week daily hippotherapy cycle follows. Afterwards, a second nine-week "hippotherapy wash out" period, and a final one-week daily hippotherapy cycle will be set up. **The conventional outpatient neurorehabilitation for each patient in the hippotherapy group will be discontinued during the hippotherapy cycles**. Six months after the end of the study protocol, patients will be monitored for sustainability of functional gains. The entire trial will last 48 weeks. The so-called "hippotherapy wash out" period has three main objectives: fix the new schemes; translate them to day-to-day skills; and reveal new unmet needs. Our current clinical practice supports the proposed rhythm for rehabilitation through hippotherapy[1,2,7]. During the remaining 18 weeks, the treatment options are the same than those of the control group (see below).

Control group: Patients of the control group will follow a standard outpatient neurorehabilitation treatment for 22 weeks, consisting of a combination of five half-day physiotherapy, occupational therapy, speech therapy and psychotherapy sessions per week according to the patient's needs. For the patients with a modified ranking scale comprised between 3 and 4, it is likely that the work targeted on gait, balance, and

mobility will focus on gait-oriented physical fitness training, repetitive task training, muscle strength training, and the treadmill training when possible. People with difficulty using their upper limb should be given the opportunity to undertake tailored upper limb training. Interventions, which can be used routinely, involve constraint-induced movement therapy in selected people, repetitive task-specific training, and mechanical-assisted training. One or more of the following interventions can be used in addition to the ones above: mental practice, electrical stimulation, biofeedback in conjunction with conventional therapy, bilateral training, and mirror therapy. Moreover, special attention will be paid to manage mild to moderate spasticity through early comprehensive rehabilitation. Additionally, contractures must be carefully monitored and prevented by conventional motion therapy. Particularly common is the loss of shoulder external rotation, elbow extension, forearm supination, wrist and finger extensions, ankle dorsiflexion, and hip internal rotation. People with severe weakness tend to develop contractures. Any joint or muscle not regularly used can be subjected to soft tissue complications, which will eventually limit movement and may cause pain.

As several techniques are likely to be used, a record of the number of rehabilitation sessions (physiotherapy, occupational therapy, speech therapy, and psychotherapy) and their type will be collected for each patient during the study period and used as a covariate.

b. Describe participant selection and number including inclusion and exclusion criteria.

Participants: Participation in the study will be proposed to every patient hospitalized at the CHSF after a stroke which fulfils the inclusion criteria. Patients will be drawn at random to build the two arms of the study. The study participants will be adult males or females with a moderate to severe disability (Rankin score ≥ 3 and ≤4 at baseline). Each participant will sign written informed consent in accordance with the Declaration of Helsinki. The data will be anonymized and properly stored to respect the confidentiality of sensitive medical data and EU GDPR legislation. A certificate of non-contraindication to hippotherapy will be established by the neurologists of the CHSF for each single patient. In case of a patient's withdrawal, he/she will continue to benefit the planned conventional care with no impact on its quality.

Sample size: From the related data[9], the sample-size calculation was based on a minimum reasonably significant difference in the primary outcome (Functional Independence Measure) of 22 points with a standard deviation of σ = 23.0[10]. To detect that difference with a power of 85% using a two-sample t-test at a two-sided significance level of 5%, a total of 40 patients in the randomized arms, 20 per arm, will be required (moreover, we calculated an extra 30% to prevent a reduction of power due to potential additional dropouts). We will then recruit 52 patients into the study.

Inclusion criteria: Participating patients will be adults aged 18 and over, with a diagnosis of ischemic or hemorrhagic acute stroke, included during the first year post-stroke, with a Rankin score ≥ 3 and ≤ 4 at inclusion, able to perform 25 degrees of bilateral hip abduction without a history of hip dislocation and/or dysplasia, able to give written informed consent, affiliated to a social security scheme, and who had provided a certificate of no contraindication to hippotherapy issued by their physician.

Exclusion criteria: Patients were excluded if they had a history of major cognitive impairment affecting comprehension (Mini Mental State Examination test < 24 points), a global or sensory aphasia, a neurological or psychiatric co-morbidity (other than mild to moderate post-stroke depression), evidence of uncontrolled seizures, evidence of substance abuse, a history of uncontrolled pain, a history of allergic reactions to dust and/or horsehair, or severe asthma, a body weight ≥ 110 kg, contraindications to physical activity, a history of therapeutic horse riding or hippotherapy during the last 6 months, for women if they are pregnant or lactating, and if they are participating in other biomedical research or in a period of exclusion.

c. Describe data collection and analysis methods.

Data Collection and treatment: The data will be duly anonymized and blindly manipulated in the eCRF. Data management will be performed by a CRO already contracted according to a data management plan. A data monitoring committee composed by a CRA of the CRO and the trial coordinator will oversee the follow-up of data collection accuracy and reporting of adverse events.

Statistical Analysis: Appropriate non-parametric statistics will be used to evaluate the comparability of the intervention and control group at baseline in terms of the clinical characteristics. If, despite the stratified randomization procedure, the groups are not comparable for one or more background variables, those variables will be routinely employed as covariates in the subsequent analyses. The scores for each variable (primary and secondary endpoints) will be calculated according to the published scoring algorithms. Intergroup (effect of the treatment on the measured variable, compared to the control) and intragroup (evolution of the measured variable on the same group) differences in the mean scores over time will be tested using a multilevel analysis. The effect sizes will be calculated using standard statistical procedures. To test the effectiveness of hippotherapy intervention on functional independence (FIM; primary outcome), non-parametric ANOVA measures for non-linear scores (Friedman's test for paired data) will be conducted. In addition, to test the effectiveness of the intervention on the secondary outcome variables, including the caregivers' measurements, non-parametric ANOVA procedures (Friedman's test for paired data) will also be applied. Post hoc analyses (e.g., additional correlation and covariance statistical procedures) will be conducted according to the obtained results. They will fine-tune the initial data analysis by taking into account potential confounding factors. Given the power of the study (80%), the post hoc results will be statistically robust and therefore reliable. The threshold of statistical significance will be $p = 0.05$. Statistical analyses will be implemented by the CRO using SAS® software (version 9.4, SAS Institute, Cary, NC, USA).

d. If an intervention is being studied, describe the intervention in detail and how it will be documented with a goal for manualization.

The hippotherapy exercises will consist of four phases performed sequentially: On the horse simulator (Racewood Ltd., Tarporley, UK): (i) 10 min of warm-up allowing patient's familiarization, muscles' warm-up, and nervous system facilitation (the Therapeutic Equine Simulator System TESS© has been used as valuable complement for hippotherapy in postural balance rehabilitation[1]); in some cases, the simulator can be used for the entire 1 h session depending on the patient's needs. On the horse: (ii) 5 min passive and active

mobilization of the lower limbs, passive and active stretching of the different muscle groups; (iii) 40 min work on global postural balance and fine-tuning of postural responses (eyes open and closed), work on upper limbs' fine motor skills by manipulating objects, strengthening of different muscle groups, reinforcement of the body schema and body image[11] , breathing techniques and visualizations; and (iv) 5 min relaxation with passive mobilizations and passive stretching, especially of the flexor muscles.

The hippotherapy protocol is substantially the same for every patient knowing that a reinforcement of postural balance, symmetry, hip and shoulder dissociation, spinal joint mobility, and muscle tone regularization are needed in both Rankin 3 and 4 patients. These will be obtained through the horse movement at a walk and the simulator movement. During hippotherapy, the postural balance work and the muscle tone regularization are background tasks[1,2]. The physiotherapist will simultaneously work the upper limb through repetitive task-specific training, muscle strength training, bilateral training, and mental practice. The intensity of the exercises will be fully tailored and will depend on the patient's clinical heterogeneity, fatigability, and confounding factors.

e. If outcomes are being measured, list them and describe how and why they will answer the research question.

Primary Efficacy Endpoint:

The Functional Independence Measure (FIM; lasting 30–45 min) (time frame: Changes from baseline to week 22; changes from week 22 to week 48) is an 18-item 7-point Likert scale evaluating physical, psychological, and social function, indicating the amount of assistance required for each task. A final total score is obtained ranging from 18 (complete dependence/total assistance) to 126 (complete independence)[12].

Secondary Efficacy Endpoint:

- *For the patient:*

The modified Rankin Scale: (mRS; lasting 5–15 min) (time frame: Changes from baseline to week 22; changes from week 22 to week 48) is a standardized measure that describes the extent of disability after stroke. The mRS is a single-item scale. It ranges from 0 (no symptoms) to 6 (death due to stroke)[13,14].

The Fugl-Meyer Assessment: (FMA; lasting 30–35 min) (time frame: Changes from baseline to week 22) is a stroke-specific, performance-based impairment/recovery index. It is designed to assess motor functioning, balance, sensation, and joint functioning in stroke patients. Assessment items are scored based on the ability to complete the item using a 3-point Likert scale (0 = cannot accomplish; 1 = partially accomplished; and 2 = completely accomplished) where very severe ranges from 0–35, severe 36–55, moderate 56–79, and light > 79 (max. score 226)[15].

The Berg Balance Scale: (BBS; lasting 10–15 min) (time frame: Changes from baseline to week 22) is a 14-item 4-point Likert scale where patients must maintain positions and complete moving tasks of varying difficulty. A global score is calculated out of 56, representing ability to independently complete the test[16,17].

The walking distance in 2 min: (2-MWT; lasting less than 5 min) (time frame: Changes from baseline to week 22) reports the walking distance of the patient after 2 min. The number and duration of rests during the 2 min are also measured[18].

The Short-Form Health Survey: (SF-36; lasting 10 min) (time frame: Changes from baseline to week 22; changes from week 22 to week 48) is a 36-item weighted Likert scale questionnaire, which measures quality of life (QoL) on 8 domains, both physically and emotionally based. The SF-36 is a generic patient-report measure used inter alia in stroke[19].

- *For the caregiver:*

The Short-Form Health Survey: (SF-36) for quality of life (time frame: Changes from baseline to week 22)—see above.

The Zarit Burden Inventory: (ZBI; lasting 30 min) (time frame: Changes from baseline to week 22) is a 22-item 5-point Likert scale. The higher the score, the more extensive the burden. It is one of the most used instruments to assess caregiving burden in clinical and research settings[20,21].

V. Literature Review - A literature Review that identifies a gap that the proposal will address or supports a conceptual framework that supports the design of the project, and is congruent with or improves upon other studies. Include the Investigator's contributions.

State of the art: Current definition of stroke is clinical. It is based on the sudden onset of loss of focal neurological function due to infarction or hemorrhage in the relevant part of the central nervous system (brain, retina, or spinal cord); its definition includes subarachnoid hemorrhage. Stroke is distinguished from transient ischemic attack if the symptoms persist more than 24h. Etiologically, ischemic stroke represents up to 85% of cerebrovascular accidents and is caused by embolism from the heart, artery-to-artery embolism, and in-situ small vessel disease. Hemorrhagic stroke represents the remaining 15% of cerebrovascular accidents and is classified according to its anatomical site or presumed etiology. The most common causes of stroke are hypertension (30–60%), cerebral amyloid angiopathy (10–30%), anticoagulation (1–20%), and vascular structural lesions (3–8%). The cause is undetermined in about 5–20% of cases[22]. Stroke is a high burden disorder worldwide. With 25.7 million stroke survivors worldwide, stroke is the second leading cause of disability after ischemic heart disease. As illustrated by the number of people that remain disabled after a cerebrovascular accident (2 out of 3 according to the US National Stroke Association), the extent of recovery is limited, and novel approaches are urgently needed. It represents a major EU-wide challenge[23] due to its enormous economic burden. It has a major economic impact for Europe, as in 2015 it was estimated to cost the EU €45 billion a year split as follows: ~44% (~ €20 billion) is due to direct health care costs, ~22% (~ €9 billion) to productivity losses and ~35% (~ €16 billion) to the informal care of people with stroke (long-time sequelae management). The societal burden of stroke is also huge: on Mortality, since in Europe, stroke is the second most common single cause of death, accounting

for 405,000 deaths (9%) in men and 583,000 (13%) deaths in women each year; on Morbidity, since stroke can cause permanent damage, including partial paralysis and impairment in speech, comprehension and memory. The severity of the stroke ranges from minimal to catastrophic, and the sequels can be long-lasting. In 2015, stroke was the second cause of lost disability-adjusted life year (DALYs) in Europe, responsible for 17.1 million DALY lost.

Current treatment standard care: Improving stroke management for the acute (<1 week after stroke), post-acute (between 8 and 30 days) and chronic phases (>1 month) requires new therapeutic development to achieve a better care and minimize the sequels for stroke survivors[24]. There still exists a need for continued improvements in the delivery of post-acute stroke care. Although initial stabilization and acute management are essential, the early and late rehabilitative phases may be equally critical, if not more so, to patients and their families. As stroke patients advance along the current care continuum, they often encounter fragmented and distinct modules of stroke care, each well-defined with a specific purpose and separate accountability. A stroke care system should provide fluid transitions between each of its key elements, including acute care, subacute care and secondary prevention, rehabilitation, and community care. In particular, understanding the goals of each post-acute rehabilitative phase in various settings and the challenges faced at each level is crucial to the development of an integrated, comprehensive system of stroke care[25]. Patients with acute stroke need assessment for the nature and severity of their neurological deficits and the prognosis, goals, and rehabilitation requirements for recovery. Long-term disability often occurs because of stroke. It stems mainly from cognitive and/or psychomotor impairment. In such cases, dealing with impairment is frequently ineffective, and when it is beneficial, the functional bases for recovery are mainly unclear. Acquired brain injury often produces diffuse damage to the white matter connections leading to disconnection of some areas of the brain, which determines the clinical picture. Current theories emphasize that specific features of brain functioning emerge through the interactions of several regions

rather than through direct action of a specific region[26]. These interactions are possible through a complex brain network organization, and specific impairments would reflect disturbances of such networks.

Hippotherapy: The horse is an excellent support in situations of physical and psychic disability, whether temporary or consolidated[1,2,27–34], providing key elements of stimulation for human impairment, activity limitation, and participation restriction. Rehabilitation through hippotherapy is achieved through the movement of the horse at a walk. It is a dynamic therapy where the amplitude of movement of the patient's body transmitted by the horse is similar to the human walking activity (micro-movements of postural muscles). Moreover, through multimodal inputs (sensory, sensitive, proprioceptive, interoceptive, exteroceptive), hippotherapy has a direct action on the individual's sensorimotor capacities as well as on his cognitive and psychic abilities (attention, memory, emotion, perception, sequencing of complex movements, self-experience, psychic temporality), through the activation of multiple neural networks. A body of scientific evidence has gradually emerged in recent years, reflecting the benefits of hippotherapy in various disabling neurological conditions in humans. Hippotherapy is therefore slowly emerging as a potentially effective method of neurological/neuropsychological rehabilitation. During hippotherapy, specific execution and repetition of a task are key elements of learning/strengthening/promoting a function and central elements of neurological rehabilitation. The acquisition and transfer of skills to other activities is carried out more effectively when the skills are meaningful for the context. In other words, the degree of change associated with neuroplasticity through hippotherapy is linked both to the relevance of the activity and to the intensity and frequency of the elements that constitute it[35–37].

State-of-the-art of hippotherapy intervention in the targeted population: Few studies on the hippotherapy treatment of neurological sequelae of acquired brain injuries have been published but their methodological quality is considerably poor. In general, the studies report beneficial effects on posture, walking, spasticity, gross and fine motor skills but these positive effects are counteracted by the many methodological flaws[38].

In current clinical practice, beyond scientific considerations and methodological evidence, the observed effects are extremely positive in all spheres (motor, cognitive and psychological; unpublished data).

VI. Budget

TOTAL GRANT REQUEST (US Funds): $75.000

1) **PERSONNEL:** *(Principal investigator, co-investigator, statistician, research assistant)* Please provide justification for the scope of their participation and describe salary, fringe benefits, FTE.

   Personnel Total: $ 12.900

   Personnel % of total budget: 17%

   1 research assistant C. Loriette PhD Neuroscience: 212 hours in 2023 ; 240 hours in 2024 : total hourly cost $27 (including social cost paid by the organization $7)

2) **PERMANENT EQUIPMENT:** Itemize and describe purpose, justification of needs, how it will be acquired, etc.

   Permanent Equipment Total: $

   Permanent Equipment % of total budget:

3) **CONSUMABLE SUPPLIES:** Itemize and describe justification of needs, how they will be acquired, etc.

   Consumable Supplies Total: $

   Consumable Supplies % of total budget:

4) **CONSULTANT COSTS**: Describe rate of pay, scope of work, justification of need, etc.

   Consultant Costs Total: $ 53.750

   Consultant Costs % of total budget: 70%

   Consultants :

   - Head of research Dr. M. Gaviria (Workinbio) 175 hours in 2023; 200 hours in 2024 (hourly rate $50); total cost: $18 750

   CRO Axonal-Biostatem: $ 35 000 in 2024

5) **TRAVEL**: *(Will only cover subject travel reimbursement or for meeting of work groups.*)

   Travel Costs Total: $

   Travel % of total Budget:

6) **RESEARCH PARTICIPANTS- RELATED EXPENSES**: Itemize and describe all related costs.

   Participant-Related Expenses Total: $10 500

   Participant-Related Expenses % of total budget: 14%

Participants costs includes lodging and transport

7) **HORSE EXPENSE:** *(Must be directly related to research question and methodology.)* Explain cost basis related to percentage of time used in project.

Horse Expense Total: $

Horse Expenses % of total budget:

Horse expenses including related manpower are self-financed by Equiphoria

8) **BUDGET JUSTIFICATION:** Please provide any further budget justification or explanation here.

OTHER INCOME SOURCES and ANTICIPATED FUNDING SUPPORT:

a. Active/Committed: While not required, HHRF is interested to know if you have any matching funds to support this grant if awarded (federal, institutional and/or private grants or other sources)? Please provide source/institution name, project titles, specified designations and restrictions, starting and ending dates and amounts. Do not include general or overall program support.

Shortfall of funds vs budget will be absorbed by the organization on its own funding

Total Active/Committed: $

b. Pending: Is support for this project being sought elsewhere? Please provide source/institution name, project titles, specified designations and restrictions, starting and ending dates and amounts.

Total Pending: $

c. Related Support: List all other sources of support, pending or current, including federal (NIH, VA, NSF, etc.), foundation, industrial, or other. Give complete titles of all grants as well as total funding, yearly funding, funding for your salary, funding for your research, and inclusive funding dates.

Total Related Support: $

VII. Proposed Time Line

Recruitment will be conducted during a 30-month period. The study will end when the last patient enrolled undergoes a neurological evaluation to determine the durability of functional recovery. The end-of-treatment assessment will be completed within two weeks of the end of 22 weeks of treatment and the end-of-protocol assessment will be completed 26 weeks after the end of treatment. The protocol began in the fourth quarter of 2021 and will run through the first quarter of 2026.

VIII. Biographical Sketch of Principal Investigator (attach)

See attached

IX. Safety and Quality Standards

a. **Safety and quality standards for Equine Assisted Services and Equines**

Hélène Viruega, ESMHL, CTRI, International Instructor - Path Intl., U.S.A.

Amandine Riou, CTRI equivalent French diploma, Psycho-practitioner.

Alexia Laperre, Equine specialist.

Sacha Maurice, Equine specialist, Psychologist.

Manuel Gaviria, MD, PhD.

Corinne Galy, MD.

Romain Boissonnade, Psychologist.

Mélissa Quignon, Physiotherapist.

b. **Site standards for Equine Assisted Services:**

Equiphoria Institute was incorporated in 2011 based on more than 10 years of experience in the USA and on the standards and requirements of PATH Intl. (Professional Association of Therapeutic Horsemanship International). Equiphoria became Path Intl. Premier Accredited Center in 2014 and developed its own standards of quality relying on Path Intl. quality standards and adapted to French regulations.

c. **COVID-19 precautions.**

Measures have been defined by the trial sponsor (Alliance Equiphoria) in the event that it is affected by the coronavirus pandemic (COVID-19) to ensure the integrity of the study and the interpretation of results, while maintaining the safety of trial participants as a priority. This includes: (i) documenting deviations from the study protocol due to COVID-19 and explaining the reasons; (ii) conducting a risk assessment of the impact of COVID-19 on the trial, if necessary by an independent party, and on blinded data; and (iii) through the study coordinator, agreeing with regulatory authorities on any changes to study protocols or statistical analysis plans.

X. Compliance with Government Requirements

YES ~~**NO**~~ ~~**PENDING**~~

The study was approved by the regional Ethics Committee of Saint-Etienne-France (CPP Sud-Est I, CHU de Saint-Etienne-Direction des Affaires Médicales et de la Recherche Hôpital Bellevue-Pavillon 31) that provided ethical approval on 8 September 2021 (authorization n° 2021-087).

XI. Plans to Publish

The project will dedicate considerable efforts for an efficient dissemination strategy aiming to: (i) Implement the communication of the project results at local, national, European and international levels to reach all targeted audiences; (ii) Facilitate the exploitation of project results by explaining the approach to the end users and caregivers; (iii) Identify and develop potential synergies with related nationally and EC funded projects on neurorehabilitation, and potentially carry out joint dissemination activities.

Scientific dissemination will be done through scientific and medical publications providing key results and achievements ensuring coverage of all relevant results and aspects of the project. We will prioritize international high-impact peer-reviewed journals in open access (neurology, clinical and integrative neuroscience, neurorehabilitation).

XII. Attachments

Only cited references including: A glossary of definitions for Abbreviations, Acronyms and technical terminology; letters from collaborators; a copy of IRB and IACUC applications; bibliographic citations.

a. Abbreviations

Term	Description
ANOVA	Analysis Of VAriance
BBS	Berg Balance Scale
CHSF	Centre Hospitalier Sud Francilien
CHU	University Hospital Center
CPP	Committee for Protection of People
eCRF	electronic Case Report Form
CRA	Clinical Research Associate
CRO	Contract Research Organization

DALY	Disability-Adjusted Life Year
EU	European Union
FIM	Functional Independence Measure
FMA	Fulg-Meyer Assessment
GDPR	General Data Protection Regulation
IRB	Institutional Review Board
mRS	modified Rankin Scale
2-MWT	2-Minutes Walking Test
PTSD	Post-Traumatic Stress Disorder
QoL	Quality of Life
SF-36	Short Form health survey
TESS	Therapeutic Equine Simulator System
UK	United Kingdom
USA	United States of America
ZBI	Zarit Burden Inventory

b. **Bibliography**

The publications from the investigators correspond to 1-7.

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Research Grant Conditions of Award

1. At least one member of the research team must be fluent in English and published in peer-reviewed English language journals.
2. The grant time line will commence on the day that the grant is awarded or the day that evidence of final IRB approval (if still under consideration) is submitted to HHRF (within 3 months of grant award).
3. No institutional overhead or other indirect costs will be paid and should not be included as part of any grant request. A letter to your institution explaining this condition can be requested if needed. Beware that substantive equipment costs could work against the success of the grant request.
4. All funds awarded shall be used in accordance with the submitted and approved proposal and accompanying budget. Any unused portion thereof shall be returned to the Horses and Humans Research Foundation (HHRF). If an unforeseen problem occurs with the study design, notify HHRF immediately. Potential changes to the study design with additional financial assistance from HHRF may be considered to salvage the study and still lead to a favorable outcome.
5. Grant awards will be made in US dollars. One third of the awarded amount will be paid once the contract is signed by all parties. One third will be awarded after the midpoint report is accepted and the remainder will be awarded when the project is fully completed and approved, unless other arrangements have been specified and agreed to. The value of the grant will not be adjusted for inflation, cost over runs, or foreign exchange rate fluctuations. It is the responsibility of the recipient to manage these potential variables (example: if grant budget deals in euros, a loan could be purchased at the time of award, in US dollars, against the euro).
6. At the midpoint of the grant period a progress report and financial report must be submitted. A final report must be submitted within 60 days of the completion of the project. The final report shall include a scientific abstract, summary data tables, a financial report, and a less-technical lay language article (400 words) to potentially be used in HHRF and related publications as determined by HHRF. Photos, videos, personal stories of the impact of the study and additional marketing materials are requested to be submitted during the grant term and with the final

report. The final report should also include any obstacles the team encountered during the study to be used as a learning tool for future research teams. Any medical changes in participants' medical conditions during the study should be documented in the final report (i.e. less medications required, fewer hospitalizations). Confidential data that could jeopardize formal publication in a peer-reviewed journal should not be disclosed in the lay articles. If a delay in project completion is anticipated, HHRF must be notified promptly with a brief explanation and a request for extension. All investigators are encouraged to communicate and work with HHRF for the best possible outcome of their study. Failure to comply with the above conditions may result in revoking of all award funding.

7. The Principal Investigator must assure HHRF of his or her intended work location. HHRF must be advised at the time of application of all moves, contemplated or real. Changes of address, phone number, fax number and email *within the same institution* must be promptly conveyed to HHRF. Changes in site location during a funded period must be approved by HHRF.

8. All publications (including poster abstracts at medical conferences) resulting from HHRF-funded research must include HHRF in a footnote/credit line/disclosure, and copies of such publications must be provided to HHRF. All publicity and information disseminated about such research must acknowledge HHRF support. This is an essential part of HHRF's conditions of award. Publicity or information about the project is used to keep supporters of HHRF informed about how their donations are being spent. This condition of award does NOT involve disclosure of any information that might jeopardize the applicant's ability to formally publish their findings. HHRF also has permission to share results of this study through publications and outreach materials.

9. The recipient of any research grant awarded must certify that any research, including work involving human and/or animal subjects, will be conducted according to the rules and regulations of the United States National Institute of Health or equivalent National regulations. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3558218/ The recipient must agree to hold HHRF harmless from any and all claims which may arise from any associations/issues related to such research.

10. All studies involving horses must comply with IACUC in the USA or other nationally accepted industry standards for care, treatment, and humane work load. All related program work must comply with accepted industry standards for safety. Please include a reference for those standards.

11. A two year grant period is assumed. Projects that do not comply with the approved timelines will be put into probationary measures and funding will be placed in fiscal holding. (When placed on fiscal hold no further funds can be released without a hearing by HHRF board representatives who will review the entire grant history and determine any further actions).

12. Recipients of HHRF grants will be committed to a serious effort to publish resulting research findings in a peer-reviewed journal. HHRF will be kept informed of publication efforts.

13. All grant applicants must include one signed copy of this "Research Grant Conditions of Award" as a necessary part of their grant application to HHRF.

14. The Foundation reserves the right to terminate an award if the grant holder or staff funded by the grant is in breach of any of the conditions of award or becomes unfit or unable to pursue the work funded by the grant.

I have read and understood HHRF's "Research Grant Conditions of Award" and my signature below signifies that I agree to abide by all conditions specified.

Principal Investigator's signature: _____ Date: _____

Principal Investigator's name and title (please print) _____