

A. Cover Page

Identifying information

1. **Project Title:** The Sicilian and Calabrian Spoke to Hub Interactive Network for the diagnosis and management of Adulthood Growth Hormone Deficiency
2. **Grant ID number:** 34584263
3. **Collaborators:** Salvatore Cannavo', Francesco Ferrau', Maria Antonia Violi, Rosaria Maddalena Ruggeri
4. **Abstract:** The Endocrine Unit of the University Hospital of Messina is seeking support for developing a spoke to hub interactive network designed to improve healthcare professionals' (HCPs) knowledge on growth hormone deficiency (GHD) diagnosis, management and long-term follow-up, aiming to increase GHD cases identification and improve rGH treatment adherence. A network between our tertiary referral center and General Practitioners of GHD patients (GPs) as well as other HCPs (Outpatient Clinic Endocrinologists, Neurosurgeons, Neuroradiologists, Neuro-oncologists) practicing in Sicily and Calabria will be established. All participants will attend "GHD management" training workshops. Moreover, we seek to develop a website/webapp featuring all necessary information on GHD diagnosis, treatment and long term follow-up also including a live-chat allowing prompt contact between spokes and the hub unit. Our goals are to increase GHD diagnosis, improve HCPs GHD patient management skills, aiming to increase medication adherence, patient quality of life and to reduce therapy drop-out.

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C. Reviewer Comments

We kindly thank the Review Panel for their positive feedback. We strongly believe that our initiative can create a communication network between HCPs and to determine a real clinical benefit to our patients. As stated, GHD diagnosis in Italy can only be performed by authorized centers and rGH can be prescribed exclusively by certified expert Endocrinologists, practicing in the authorized centers. Nevertheless, although GPs lack specific skills on GHD management, patients have to refer to them in order to refill their prescription, in case of rGH related adverse events as well as for any other medical advice. Therefore, our project can be of use to any Italian rGH prescribing center as well as to all Italian GPs. Our aim is to reduce the communication gap between tertiary centers, GPs and other HCPs, to improve their GHD management skills.

D. Main Section of the proposal :

1. Overall Goal & Objectives:

The Endocrine Unit of the University Hospital of Messina (Department of Human Pathology of Adulthood and Childhood “G. Barresi” of the University of Messina) is seeking support for developing a spoke to hub interactive network designed to ameliorate healthcare of growth hormone deficiency (GHD) patients. We aim to improve both General Practitioners’ (GPs) as well as Outpatient Clinic Endocrinologists’ (OCEs) awareness on GHD diagnosis, treatment and long term follow-up. Our overall intent is to increase GHD cases identification and encourage GPs and OCEs to recognize low therapy adherence and to motivate patients to better treatment compliance. We therefore seek to improve healthcare professionals’ (HCPs) skills on GHD management in order to be able to better educate their patients regarding their condition, medication and expected outcomes by creating an interactive spoke to hub network between our Endocrinology Unit -which is a referral center for pituitary diseases- and our GHD patients’ GPs and OCEs. Furthermore, we seek to increase GHD related conditions awareness by including other HCPs as Neurosurgeons and Neuroradiologists and Neuro-oncologists.

Key Objectives:

1. Increase in GHD cases identification by incrementing all HCPs awareness on GHD related conditions
2. Improve GPs and EOCs GHD management skills in order to increase medication adherence, quality of life and decrease therapy drop-out rates

2. Current Assessment of need in target area:

In Italy, GHD diagnosis can be performed only in authorized centers and rGH can be prescribed exclusively by certified expert Endocrinologists. The Endocrine Unit of the University Hospital of Messina, is a referral center for pituitary diseases, in particular for GHD diagnosis and rGH prescription and patients refer to us not only from the province of Messina, but from all corners of Sicily as well as Calabria Region. Sicily is composed by 9 provinces, the three largest being Catania, Palermo and Messina, and Calabria Region is composed by 5 provinces, the largest being Reggio Calabria and Cosenza. In this wider area GHD diagnosis can be performed in 6 Sicilian authorized centers (2 in Palermo, 2 in Messina and 2 in Catania) and in 3 centers of Calabria Region (2 in Catanzaro and 1 in Cosenza). GHD prevalence in the provinces of Messina, Catania and Palermo is higher compared to the other Sicilian as well as all Calabrian provinces. This apparent lower GHD prevalence reported outside the three major Sicilian provinces is probably due to the high percentage of under-diagnosis. Our goal is to increase HCPs recognition of potential GHD cases in order to increment GHD diagnosis, especially in the remote areas.

The Regions of Sicily and Calabria together account for the wider Macro region of Sicily and Calabria, an area of over 40,000 km² where live more than 7 million inhabitants, with a mean

population density of over 160 inhabitants/km² (Sicily alone has an area of about 26,000 km², with a population of 5 million inhabitants and a mean population density of 196 inhabitants/km², whereas Calabria Region has an area of 15,000 km², in which live about 2 million inhabitants, with a mean population density of 130 inhabitants/km²). In this wide area there are many connecting issues as transportation between Eastern and Western Sicily as well as all throughout Calabria Region is difficult because of the poor railway and highway networks; moreover, Sicily is connected to the mainland Calabria only by ferry.

The Endocrine Unit of the University Hospital of Messina has a strategic position and places itself exactly in the center of this wide area of the Macro-region of Sicily and Calabria.

We well know that appropriate treatment management has significant impact on patient outcomes, and adherence to daily injections optimizes treatment benefit. Our GHD patients perform semestrial clinical and biochemical control and annual radiological follow-up, while we release rGH prescription every six months. Nevertheless, pharmacies monthly dispense drugs only if the patient exhibits both the Endocrinologist's as well as the GPs prescriptions. Therefore patients have to refer to their GPs monthly in order to have their rGH prescription refilled. GPs often lack specific knowledge on GHD therapy management, and forward patients back to the referral center in case of rGH related non severe adverse effects or even to seek medical advice not related to their GHD condition. This often determines patient demotivation, low therapy compliance and drop-out, especially in patients coming from remote areas.

Indeed, in a recent post-marketing monitoring study involving the rGH prescribing pattern in 6 different Italian regions we demonstrated an over 50% treatment drop-out rate in adult patients undergoing rGH therapy (Ingrasciotta et al., in press). Moreover, by reviewing our patient files we identified a 24% treatment drop-out rate during the last 10 years mainly related to poor therapy adherence, more frequently (63% of cases) in patients coming from remote areas of Sicily. GHD patients often present partial or complete pituitary function impairment and require continuous endocrine follow-up. However, patients from remote Sicilian areas are more likely to refer to local OCEs, with poor experience in pituitary diseases, rather than to distant tertiary centers.

We believe that the great distances, the important transportation issues as well as GPs and OCEs unawareness on GHD management lead to lack of patient motivation which accounts for the elevated GHD patient follow-up drop-outs.

3. Target Audience:

This project is designed for Sicilian and Calabrian General Practitioners of GHD patients as well as Outpatient Clinic Endocrinologists. We aim to include the GPs of GHD patients who refer to our Endocrinology Unit, as well as OCEs (at least 2 OCEs from each province will be invited). Moreover, we also wish to include Neurosurgeons practicing in the 6 Sicilian and 2 Calabrian Neurosurgery Units as well as Neuro-radiologists and Neuro-radiation-oncologists with extensive experience in treating cerebral tumors. Up to 150 HCPs will be invited to take part in this study. GPs will be identified by reviewing our patient files. We expect 80% participation.

We believe that by improving awareness on the probability of GHD diagnosis we will be able to detect and treat 20% more new cases/year. Moreover, we aim to increase the detection of low adherence patients, improve treatment compliance, minimize treatment drop-out by 20%, and therefore improve treatment outcomes, e.g. quality of life (QoL).

4. Project Design and Methods:

We seek to create a spoke to hub interactive network between our Endocrinology Unit and GPs and OCE and the other HCPs dealing with GHD patients.

We plan to organize 1 CME accredited workshop in the beginning of the project. We will furtherly organize a half-way through briefing and one debriefing at the end. The first two meetings will be organized in 3 different locations: one in West Sicily (Palermo), one in East Sicily (Messina) and one in Calabria Region (Catanzaro) in order to ensure better accessibility for all participants.

Proposed Agenda for First Workshop

1. Introduction and Project Presentation
2. GHD Epidemiology, Etiologies, Clinical findings, Diagnosis, Therapy and Long Term Follow-up
3. Web Site/App presentation

We will create a web-based platform containing an “informative/educative” section with general information on GHD etiology, signs and symptoms, diagnosis and treatment, as well as an interactive communication tool. All participants will be invited to register to the web site (proposed URL: www.messinaghnetwork.it) or to download the specific smartphone application. By doing so they will be able to access all GHD regarding information and to directly contact our hub center for further support (live chat active 9-17 Monday to Friday).

We will promptly provide assistance on potential GHD cases as well as advice regarding rGH treatment compliance or related side effects. Participants will be requested to provide feedback in order to evaluate the efficacy of the proposed solution.

We wish to focus not only on pituitary diseases causing GHD, but also to increase awareness on other causes of hypopituitarism as traumatic brain injury, cerebrovascular accidents and infectious diseases (due to the recent migratory waves).

We also seek to include information regarding all rGH injection devices and injection techniques and solutions to common device related technical problems.

Moreover, a calculating tool will indicate, based on the prescription date, device type, drug concentration and dosage, the date of the next prescription renewal. In case the patient doesn't renew the prescription by the due date an alert will be delivered to the GP in order to easily identify low therapy compliant patients. A medical adherence questionnaire (e.g. Morisky Scale, 2) that can easily confirm patient treatment compliance issues will also be included and easily administered to patients. Moreover, reasons for poor treatment adherence will also be listed and solutions for the most common ones proposed (e.g. dosage decrease in case of Carpal tunnel).

During the semestral follow-up in our Endocrinology Unit, all GHD patients will be administered the medication adherence questionnaire as well as the Questions on Life Satisfaction-Hypopituitarism questionnaire to evaluate QoL (3). Results between baseline and end of study will be compared to evaluate medical adherence and QoL improvement as well as drop-out percentage, in order to assess intervention outcome.

To our knowledge, this is the first attempt to create a spoke to hub network between health professionals and a tertiary referral center for pituitary diseases diagnosis and treatment.

5. Evaluation Design:

We will perform GHD diagnostic tests in patients referred to us by the spoke units and we will quantify the number of newly diagnosed GHD cases. Therefore, we will calculate the new prevalence, comparing it to our historical data.

Moreover, we will evaluate all medical adherence and QoL questionnaires administered at baseline and throughout the study to detect changes in treatment adherence and QoL. We expect a 20% decrease in therapy drop-out, as compared to our previous study (1), a 20% increase in therapy adherence and a 20% increase in QoL compared to baseline.

We will then calculate the number of “requests for assistance” received, our proposed solutions and percentage of positive feedback in order to establish intervention efficacy. We will identify specific low medication adherence and drop-out reasons.

We plan to present our study results at national meetings. Specifically, we anticipate presentation of our study results at the annual Italian Endocrine Society Meeting and at the next congress “Incontri Italiani della Malattie Ipotalamo Ipofisarie”.

Our spoke to hub network model can be furtherly applied to any other pituitary diseases referral center.

6. Detailed Workplan and Deliverables Schedule:

Months 1-3 Study set up will be performed: Dr Cotta, and Co-Investigators will identify and invite the 150 study participants. In the same time the web site and smartphone application will be developed in close collaboration with a computer technician. The Training workshop will be held during the 3rd month in three locations as aforementioned.

Months 4-5 Study enrollment will be performed shortly after the workshop.

Months 4-22 Hub center active support (live chat active 9-17 Monday to Friday) will be available. Reported low adherence and/or drop-out cases will be registered as well as the poor therapy adherence reasons. The spokes’ requests for assistance will be registered as well as the provided solutions and feedback. Medication adherence and QoL questionnaires will be administered during the periodic clinical follow-up to all GHD patients of participating GPs. Moreover, we will perform clinical and biochemical evaluation of all potential GHD cases referred by the spoke units.

Month 13th On-going briefing will be performed during the 13th month in the three aforementioned locations.

Months 21-22 During this time data analysis will be performed. We will calculate the overall improvement in treatment adherence and change in QoL as well as the drop-out rate. We will quantify the confirmed new GHD diagnoses referred by the spoke units and will calculate the increase in GHD percentage diagnosis overall.

Month 22nd Final debriefing will take place.

Months 23-24 Abstract/manuscript will be prepared and papers will be submitted. The results will also be presented at national meetings.

Study coordination, monitoring as well as administrative control will be performed all throughout the study.

Gaant Algorithm

	Months																							
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Coordination of the study	█	█	█	█	█	█	█	█	█	█	█	█	█	█	█	█	█	█	█	█	█	█	█	█
Web site/App development	█	█	█																					
Study monitoring	█	█	█	█	█	█	█	█	█	█	█	█	█	█	█	█	█	█	█	█	█	█	█	█
Training Workshop			█																					
Briefings													█										█	
Study Enrollment				█	█																			
Hub Live Support				█	█	█	█	█	█	█	█	█	█	█	█	█	█	█	█	█	█	█	█	
QoL Questionnaire			█						█							█						█		
Morisky Scale			█						█							█						█		
GHD stimulation test				█	█	█	█	█	█	█	█	█	█	█	█	█	█	█	█	█	█	█		
Administrative control	█	█	█	█	█	█	█	█	█	█	█	█	█	█	█	█	█	█	█	█	█	█	█	█
Data analysis																						█	█	
Results evaluation																								█
Meeting Presentations																								█
Manuscript Preparation																								█

E. References:

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