Improving the Identification and Management of Adult Growth Hormone Deficiency (AGHD)

A. Cover Page

Title: Development and Validation of a Novel Self-assessment System based on a Mobile App to Manage Adult Growth Hormone Deficiency (MAGHD App): a Single-Centre Model.
Grant ID number: 34515061.

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Abstract:
Background: Adult Growth Hormone Deficiency (AGHD) is a recognized clinical entity but several barriers concerning patient-clinician communication, inadequate patients' awareness of the disease, low perceived benefit of replacement therapy and poor compliance still remains.
Overall goal: to improve AGHD management through a Smartphone app (MAGHD App: Manage Adult Growth Hormone Deficiency) integrated with a software framework able to merge patients daily data on physical activity, quality of life (QoL), and well-being with clinical data collected in institutional databases.
Target population: 100 patients with a previous diagnosis of AGHD, whether in treatment with growth hormone or not.
Methods: In a prospective 24 months study, MAGHD App will be developed, connected to MAGHD Framework and validated on 100 AGHD patients. This system will allow to integrate: 1) Physical Activity Data collected by wearable devices, 2) Patient Related Outcomes Data, periodically inserted by the patients through MAGHD App in response to questions extrapolated from validated questionnaires, 3) HCP Data registered in clinical databases and including medical history, biochemical and radiological examination. Data will converge in MAGHD Framework where they will be analyzed and used to create reports visible to patients (in MAGHD App) and clinicians (by a monitoring dashboard).
Assessment: The primary outcomes will be evaluated by determining the impact of MAGHD App/Framework on: 1) patients' QoL, well-being, physical activity, 2) patient-clinician communication, 3) patients' compliance to replacement therapy. The results are expected to positively influence AGHD management by involving patients in care process and giving clinicians a useful tool for clinical practice.

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C. Reviewer Comments

Available Reviewer Comments: It was felt that the aims of the programme as a purely app based activity may be considered a little lofty and there was a lack of an obviously described educational component to improve HCP competence and confidence. Although apps have the potential to bean excellent adjunct and aid to patient care, it was felt that as described, the proposal was putting too much expectation on the delivery of the app alone. Please also note that though you described your proposal as quality improvement, the LOI suggested it may involve research elements. As such, we have changed the proposal type to dissemination and implementation research.

Authors Reply: the flux of information derived from the use of the Manage Adult Growth Hormone Deficiency (MAGHD) App (by the patient) is of importance only if coupled with clinical data derived from clinical evaluation and both biochemical and radiological examinations. As the development and the use of the MAGHD App represents the main innovative aspect of this project we gave it major emphasis in the LOI leaving Health Care Provider (HCP) issues in the background (the clinical management of GHD is well standardized). This choice was made in consideration of the scarce space within the LOI. It was not our intention to only develop the MAGHD App as the sole tool useful to improve the management of adult patients with growth hormone deficiency (GHD).

The development and validation of the MAGHD App represents, however, the prerequisite to conduct and finalize the whole project, but the latter is mainly based on the integration of the flux of data provided by the MAGHD App with the outcomes coming from all the clinical examinations (included in the Institutional Databases) through an integrated framework (MAGHD Framework). The integrated results will be useful to build adequate feedback for the HCP (more complex information) and for the patient (more simple information). In this way the management of GHD patients will benefit from the improvement of the awareness about the patient clinical status for both the clinician and the patient.

D. Main Section of the proposal

1. *Overall Goal & Objectives:*

The main goal of this study is to evaluate the impact of recording patient's daily activities and self-reported feeling concerning quality of life (QoL) and well-being on the management of Adult Growth Hormone Deficiency (AGHD). Patients daily related outcomes will be recorded thanks to the development, implementation and validation of a Smartphone app (MAGHD App: Manage Adult Growth Hormone Deficiency) integrated with a software framework able to merge patient's daily activities data on well-being status, physical activities, and QoL with clinical data collected in their record chart (extrapolated from already available Institutional Databases). The final aim is to improve AGHD management by providing both a flux of data to the clinician interface and simple reports concerning patient's daily activities to the patient. The results coming from the integration of clinical data with information on patient daily activities will allow to provide a comprehensive feedback to the clinician as well as a more simple feedback to the patient. The integration of patient data with clinical data represents an innovative perspective in the management of AGHD. This approach could be easily disseminated by sharing the App if effective in improving the management of these patients.

Background
AGHD is widely recognized as a specific clinical entity and recombinant human growth hormone (r-hGH) therapy has become a standard practice since 90s (Ho 2007) thanks to its beneficial effects on body composition, muscle strength, bone mass, cardiovascular risk and patients' exercise capacity and QoL (Molitch et al. 2011). All the beneficial effects of r-hGH in AGHD patients have been established mainly on selected populations by both few randomized controlled trials (RCTs) and several clinical trials (Woodhouse et al. 2006, van Bunderen et al. 2014, Höybye et al. 2015, Newman et al. 2015). Real life studies are also available, but they are mainly based on data collected through multicenter sponsored studies such as the Pharmacia & Upjohn International Metabolic Database (KIMS) (Bengtsson et al. 1999) and the Hypoptiuitary Control and Complications Study International Advisory Board (HYPOCCS) (Attanasio et al. 2002). All these observational studies suffer from missing data in the original databases and/or lack adequate control group (i.e. untreated GHD patients). Well-conducted real life studies have the advantage to provide information on long-term effects of therapies, as well as on safety, adherence and persistence to therapy (Cohen et al. 2015). Accordingly, in clinical practice it is common to find a disparity between hormonal levels and patients' subjective well-being: some individuals with a full-blown AGHD do not report any symptom and turn out reluctant to start a treatment, while others with slight GH deficiency (GHD) experience a deterioration in their QoL that deeply improves after GH replacement (Murray & Shalet 1999). This is mainly due to the fact that clinical presentation of AGHD is frequently based on nonspecific symptoms (Murray & Shalet 1999). Similarly, individual differences in responsiveness to r-hGH are common findings in the real life (Alexopoulou et al. 2010, Moyes et al. 2010). Moreover, when other hormonal deficits coexist and patients have to face with a polytherapy, it can be difficult both for clinicians and patients to relate symptoms to the sole AGHD and to verify benefits after treatment (Alexopoulou et al. 2010). Finally, there is a lack of tools assessing patients' physical activity, which is an

important factor to consider when evaluating energy levels, exercise performance, and well-being. Thus, a gap still remains in the real life setting concerning how to measure the improvements occurring in r-hGH treated patients (Alexopoulou et al. 2010) and how to make patients and clinicians more aware of these changes (Lazure et al. 2014) (Figure 1). Nowadays, considering the shortage of established predictive factors for the overall therapeutic response, the decision to whether or not continue treatment depends often on the ratio of perceived and expected benefits over cost and risks of treatment, as well as on the persistent motivation of the patient (Alexopoulou et al. 2010, Lazure et al. 2014). These aspects involve also physician's attitude and patient's propensity to start r-hGH replacement therapy. *Vice versa* the lack of information useful to predict patients' individual response to treatment poses some clinical troubles about how to select patients who may beneficiate from r-hGH therapy (Alexopoulou et al. 2010, Lazure et al. 2014). Considering that r-hGH treatment is a chronic therapy requiring a daily self-injection, long-term compliance is still a considerable problem in this setting and is influenced by all the above mentioned issues (Figure 1). It is estimated that about 20 to 30% of patients discontinue the treatment, permanently or for extended periods, making therefore an objective evaluation of the therapeutic effects difficult (Alexopoulou et al. 2010). All these aspects are enhanced by the paucity of tools available to improve patients' education and awareness of AGHD. The widespread use of Smartphone applications (apps) presents an opportunity to overcome these difficulties in the AGHD management. We hypothesize that the use of an app connected to an institutional Information system, which enables a systematic data collection from patients and Healthcare Providers (HCPs), will enhance patients' awareness of their current clinical condition and will improve their QoL (Figure 1). Through MAGHD App patients will take an active part in the process of AGHD management and, in return for entering data on daily basis, they will receive periodical reports and graphs coupling daily, weekly, or monthly (depending on parameter recorded) activities data with the outcomes provided by clinical examination. On the other side, an integrated information system able to combine in real time self-reported patients' outcomes (QoL, well-being, physical activities) with the data obtained from clinical, biochemical and radiological examinations may represent an important tool do guide HCPs in their clinical practice (Figure 1).

We believe that the integrated software framework (MAGHD framework) constituted by the MAGHD App connected with the institutional Information System (Institutional Databases), will help clinicians to better understand patients' needs and the most appropriate way to treat them. In the real life, in fact, the main gap concerning the clinical management of AGHD is represented by the lack of objective tools able to measure patients' well-being, physical performance, and psychological status (Figure 1). This means that the awareness of how AGHD compromises the daily activities remains, at least in part, uncertain for both AGHD patients and their clinicians. This represents the main barrier for r-hGH therapy since it undermines both patients' compliance and the clinicians' opportunity to really register changes from baseline related to r-hGH. All these aspects have also meaningful correlates involving the patient-to-physician relationship and communication (Figure 1).

We plan to achieve the overall goal by pursuing the following key objectives:
1) to merge patient's self-reported data with all the parameters coming from clinical, biochemical and radiological examination. At present patient self-reported data are usually

scarce and comes from questionnaires filled only during visits (once or twice a year) and self-reported information obtained during medical interview.

2) to improve patient-HCP communication by a continuous flux of information through the MAGHD App and the integrated Information System;

3) to improve clinicians' competence and confidence in AGHD management, giving them more tools and information for evaluating the effect of GHD on patient's clinical status in terms of QoL, well-being and physical activities and to measure the overall therapeutic response;
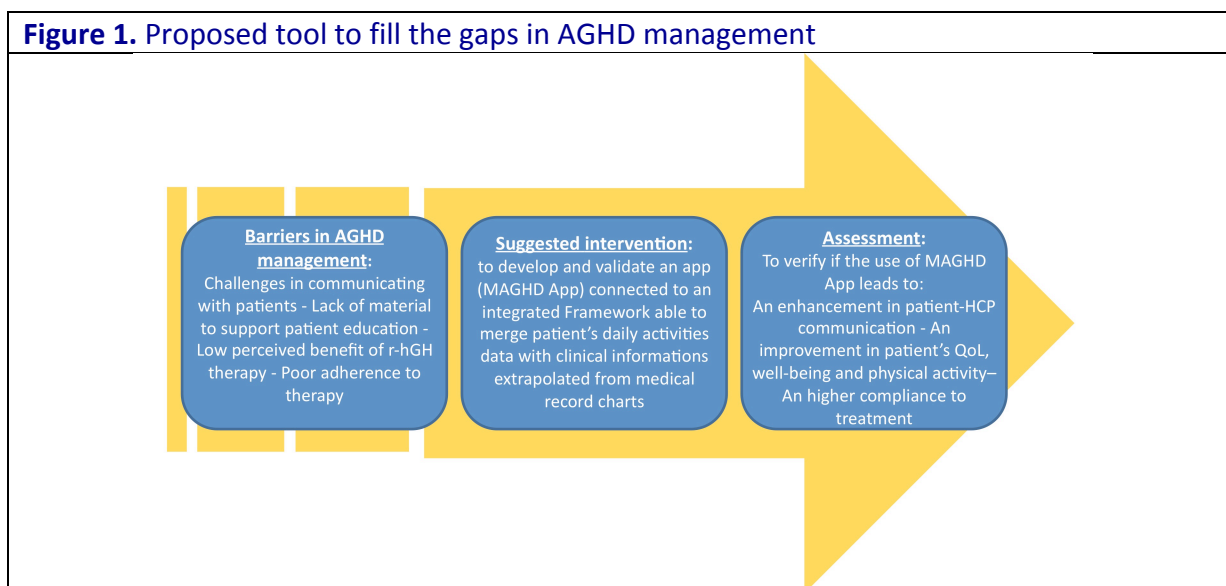
4) to improve patients' self-awareness of their clinical status thanks to the multidimensional integration of several MAGHD data (on well-being, QoL, physical performance, biochemical parameters, etc...) and periodic feedback returned to the patients summarizing in a simple way the main changes in their daily activities and of the parameters monitorized by the MAGHD App;

5) to improve and monitor patient satisfaction and QoL related to r-hGH therapy (awareness of r-hGH effects);

6) to test whether this intervention program improves patient care management and adherence to r-hGH therapy (improvement of patients' motivation and awareness in deciding if the therapy should be continued or stopped);

This project aligns with the focus of the Request for Proposal (RFP) because it: 1) takes advantage of mobile Apps and wearable devices technology to engage patients in monitoring their condition, 2) facilitates communication between patients and HCPs through the integrated MAGHD framework, 3) helps clinicians giving them a more complete picture of their patients (thanks to available data on patients's daily activities and well-being that are shared and matched with classic clinical data) and providing Clinical Decision Support tools useful to guide AGHD management, 4) constitutes a valuable tool for improving patient's self-education, 5) implements self-perceived benefits of r-hGH therapy, and 6) employs validated outcome measures to assess if the connection of the MAGHD App with the Institutional Information System (the latter including all clinical, biochemical, and radiological patient's parameters) actually leads to an improvement in the AGHD management (Figure 1).

Figure 1. Proposed tool to fill the gaps in AGHD management

Barriers in AGHD management:
Challenges in communicating with patients - Lack of material to support patient education - Low perceived benefit of r-hGH therapy - Poor adherence to therapy

Suggested intervention:
to develop and validate an app (MAGHD App) connected to an integrated Framework able to merge patient's daily activities data with clinical informations extrapolated from medical record charts

Assessment:
To verify if the use of MAGHD App leads to:
An enhancement in patient-HCP communication - An improvement in patient's QoL, well-being and physical activity– An higher compliance to treatment

2. Current Assessment of need in target area

In a physiological perspective, the lack of a hormone needs an adequate replacement, thus r-hGH therapy should be guaranteed to all AGHD patients. At present, data available in literature suggest that some clinical and biochemical factors, such as 1) lower serum IGF-1, 2) higher serum total cholesterol, 3) higher waist circumference and 4) worst QoL score, might predict the response to r-hGH (Schneider et al. 2015). In particular, the worse these factors are at baseline, the better is the expected response to r-hGH therapy. In clinical practice, the shortage of tools useful to objectify the improvements induced by r-hGH makes harder for the clinician to decide the better strategy to face AGHD and leaves the patient doubtful about the real need of treatment, with repercussion on patients' compliance. The latter is high and ranges from 30 to 60% of cases in different setting (Woodhouse et al. 2006, Rosenfels & Bakker 2008, Zaninelli et al. 2008).

The Endocrinology Unit of Modena is a referral center for hypothalamic-pituitary diseases and actually follows a large cohort of AGHD patients (approximately 120 individuals). Our group participated to the majority of the studies in Italy (KIMS, HypoCCS etc.) for the registration of r-hGH in adults or post-marketing observational studies and is working in this field from more than 20 years. At present, in our Institute r-hGH therapy is offered to patients with documented GHD in the context of an appropriate clinical context (Ho 2007, Molitch et al. 2011). In spite of the consistent number of patients referring to our Unit, we do not follow any specific protocol to manage AGHD and the decision to start or continue the treatment with r-hGH is usually based on patient's clinical condition, on hormonal tests and on the results of the Quality of Life Assessment of Growth Hormone Deficiency in Adults (QoL-AGHDA) questionnaire (McKenna et al. 1999) and of the Questions on Life Satisfaction Hypopituitarism (QLS-H) questionnaire (Herschbach et al. 2001, Blum et al. 2003). However, with the exception of the restoration of a normal serum IGF-1 and an improvement of patient's QoL, no other change is really useful to convince individuals to continue r-hGH therapy if any subjective benefit is perceived. Furthermore, r-hGH treatment leads to little improvements of some clinical parameters, that could not be perceived as clinically relevant by boh the patient and the clinician. As a matter of fact, r-hGH increases bone mineral density (BMD) after 15 years of treatment by 5% and 3% at lumbar and femoral site, respectively (Elbornsson 2012), it increases HDL-cholesterol of 15% while it decreases total and LDL-cholesterol of 8% and 15% (Newman 2011, Elbornsson 2013). Changes in body composition are minimal and seem to be transient (Götherström et al. 2007, Elbornsson et al. 2013).

During this long lasting period we developed a great clinical experience on the 'dark side' of AGHD management in daily practice, which includes patients' reluctance to accept treatment, troubles with compliance to r-hGH therapy and disappointment about the expected results. Moreover, considering that stabilized patients attend scheduled visits in our Center once or twice a year, the data concerning their personal well-being and QoL are limited throughout the whole year. Finally, we don't have neither resources to assess patients' physical activity/exercise performance nor objective measures to evaluate the perceived benefits and advantages deriving from r-hGH outside the context of follow-up visits. There is a need for simple tools able to identify and gather all the little improvements related to r-hGH therapy, in order to find strong markers of efficacy. A system able to continuously record patient's physical activities and data on well-being and QoL is essential to connect and match patient's subjective feeling concerning well-being and daily activities with the clinical data obtained through biochemical and radiological

examination performed in the hospital. Thus, the unification of all these information through the MAGHD Framework may represent a more appropriate clinical tool to monitor changes induced by r-hGH therapy in a real life clinical setting.

We believe this grant would permit us to conduct a focused analysis on our cohort of AGHD patients and to develop a self-assessment system based on an integrated smartphone technology able to fill the gaps in our target area. The use of mobile Apps and wearable devices technology to engage patients in monitoring their condition is highly innovative. Although several apps exist to monitor chronic endocrinological diseases (Buijink et al. 2013, Cui et al. 2016, Chin et al. 2016, Ryan et al. 2017), no specific app has been tested in AGHD till now. The development and validation of a mobile App useful for the continuous monitoring of patient's daily activities will improve patients' and clinicians' awareness on several AGHD items (biochemical, psychological or related to QoL and physical performance) providing integrated information useful to fill the gaps existing on how to merge the perceived (subjective) and objective (coming from clinical examinations) patient's status.

3. *Target Audience:*

The target audience for this proposal includes 100 AGHD patients, whether in treatment with r-hGH or not.

The specific selection criteria will be:

- Inclusion criteria: 1) Having a documented diagnosis of AGHD, according to the latest Endocrine Society clinical practice guidelines (Molitch et al. 2011), 2) Being at least 18 years old, 3) Having a good Italian understanding, 4) Owing smartphones with either an Android or iPhone operating system 5) Patients with other pituitary deficits will be enrolled only if the other hormonal deficiencies are well controlled by replacement treatments since six months in order to avoid the overlap of effects due to different therapies.
- Exclusion criteria: 1) Patients who do not plan to continue follow-up at the Endocrinology Unit of Modena, 2) Patients with a diagnosis of biochemical GHD outside the appropriate clinical context of pituitary disease, 3) Patients with major psychiatric diseases, chronic highly invalidating diseases (these patients will be considered not eligible for being enrolled in the study due to the impact of the underlying disease on well-being and daily activities).

All the subjects will be requested to sign an informed consent and will be enrolled after having obtained the approval by the local ethical committee.

The population of AGHD patients attending to our Endocrinology Unit consists of 120 subjects of both sexes and includes both adult and childhood GHD onset (the latter in a lesser percentage). Approximately 40% of our AGHD patients is not treated with r-hGH, according to age, clinical status, contraindications and lack of patient's consent to treatment. Most of them have a history of previous r-hGH therapy that has been stopped during follow up for various reasons (lack of compliance, aging, occurrence of diseases that contraindicate r-hGH administration, pregnancy, etc.).

We estimate that 98% of AGHD patients (N = 118) own smartphones. Of these 118 subjects, we expect 90% to meet the remaining inclusion criteria, and 85% to agree to participate to the study, for a total enrollment of about 100 patients.

Beyond the primary target, a secondary target audience who may potentially benefit from the dissemination phase of this project consists of AGHD patients referring other Endocrinology Centers and of HCPs external to the Endocrinology Unit of Modena.

4.   Project Design and Methods:

Project Design

Phase 1 – App development and testing; Data Integration
In a prospective 24 months study, an interactive smartphone app (MAGHD App) will be developed, connected to an Integrated Framework (MAGHD Framework) and tested by means of computer simulation. This first phase will require 6 months.
Subsequently it will be validated on an estimated number of 100 AGHD patients (Phase 2 – Clinical Real Data Acquisition); this system will allow to combine patients' information and HCPs clinical outcomes in a single virtual platform and to return easily accessible data to both AGHD patients and clinicians.

The development of the app and the IT tools useful for sharing data in the MAGH Server **are not available** publically at no cost.

Phase 2 – Clinical Real Data Acquisition

Patients with a previous documented AGHD fitting the inclusion/exclusion criteria (see above the Target Audience Section for further details) will be enrolled and grouped as follows (Figure 2):
- Group 1: patients on long-term r-hGH therapy;
- Group 2: patients previously treated with r-hGH, who had stopped the treatment for any reason (age, concomitant adverse reactions, contraindications or personal will);
- Group 3: patients never treated for any reason (according to age, contraindications or lack of patient's consent).

Patients of all groups will be evaluated at baseline (6th month from the start of the protocol), and every 6 months for the following 18 months (visit 1: baseline; visit 2: 12th month; visit 3: 18th month; visit 4 (last visit): 24th month).

Figure 2. Study Design
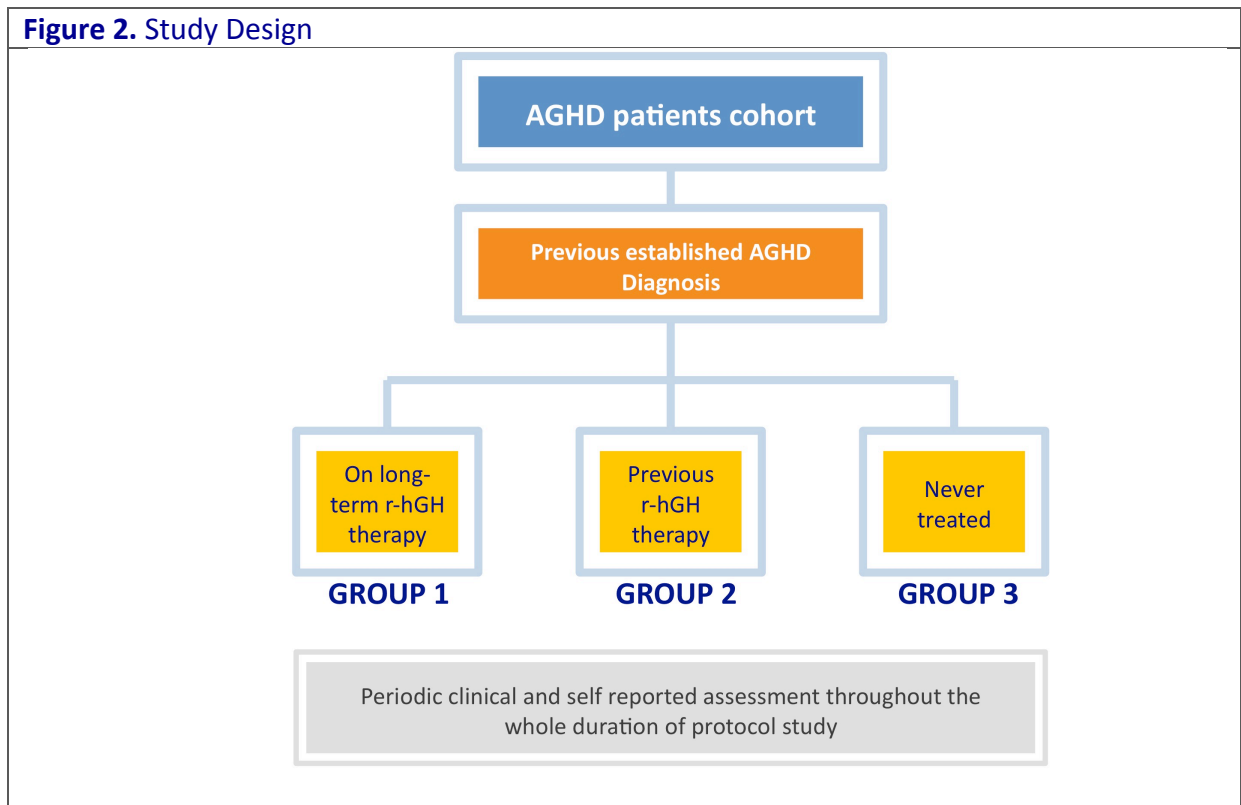
We believe it is important to consider this whole multifaceted AGHD cohort because the connection between MAGHD App and MAGHD Framework will give us different information according to the different groups of study. This integrated system will serve as:

- Group 1: tool to evaluate the overall therapeutic response, to verify the compliance to treatment, to implement patient's self-perceived benefit of r-hGH therapy;
- Groups 2 and 3: tool to improve patients' self awareness of their clinical status thanks to the multidimensional integration of several MAGHD data (on well-being, QoL, physical performance, biochemical parameters, etc...).
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Finally, regardless to the different groups of study, we think that the use of MAGHD App/MAGHD Framework will improve clinicians' confidence in AGHD management and promote patients' self-educational programs based on periodic personal reports. Indeed, both HCPs and AGHD patients will benefit directly from the project outcomes. We expect this intervention program to directly serve AGHD patients by providing them a tool to easily evaluate their symptoms, to enhance their personal well-being and to improve their adherence to r-hGH therapy. On the other hand clinicians following AGHD patients will benefit from the possibility of having new tools for managing AGHD. Finally, the vast collection of data through an integrated system may be useful as an incentive for a more effective patient-HCP communication.

Methods

Phase 1 – App development and testing; Data integration

The MAGHD App and the integrated MAGHD Framework will be provided by DataRiver (www.datariver.it), which is a Contract Research Organization (CRO) certified by AIFA (Italian drug agency), founded in 2009 as a Spin-Off of the University of Modena and Reggio Emilia. DataRiver has experience in the design and development of Web and mobile Apps for the collection, integration and semantic analysis of clinical data. DataRiver provides services and software solutions for the Integration and Management of Clinical Data coming from heterogeneous data sources, clinical data analysis and surveys compliant with sensitive data security and confidentiality requirements.

The MAGHD App will be designed, developed and tested by automatic software testing procedures before the real validation on patients. Then 100 AGHD individuals treated or not with r-hGH will be trained to use the MAGHD App prior to effectively enter in the study.

The MAGHD software framework will allow integrating patient's Physical Activity data (PA-D), constantly collected by wearable devices, with patient related outcomes data (ePRO-D) and HCP data (HCP-D):

- PA-D will be obtained through wearable devices and will guarantee the automatic collection of data regarding patients' daily life activities. PA recorded by the wearable devices will include:
  - physical activity types (e.g. walking, cycling, running etc.),
  - daily steps number,
  - daily walking distance,
  - daily calories burned,
  - sleep duration,
  - sleep quality.
- ePRO-D will be collected via the MAGHD App, which will periodically generate a short question extrapolated from the items of validated questionnaires for QoL (AGHDA questionnaire, QLS-H questionnaire) and the Warwick-Edinburgh Mental Well-Being Scale (WEMWBS) for well-being evaluation (Tennant et al. 2007, Gremigni et al. 2011).

  The App will record the number of the user answers as well as the missing ones and will periodically provide a visual satisfaction analogue scale on the use of MAGHD App usability.

  A simple question asking for adherence to therapy will be sent through the MAGHD App once a week only to patients of group 1 (on r-hGH therapy). The latter will serve to measure patient's compliance to therapy. Patients will be notified by the MAGHD App to promptly answer the periodic surveys. The daily surveys could expire after a predefined time interval to prevent the participants to complete them retrospectively, reducing the risk for recall bias.
- HCP-D will be included in the MAGHD framework integrating several clinical databases. MAGHD framework will integrate patients' records concerning their clinical history and data coming from the biochemical and radiological examination (see below the methods of clinical study for further details).

PA-D, ePRO-D and HCP-D will converge in the MAGHD Framework where they will be integrated, analyzed and used to create graphs and tables visible both to patients (in MAGHD App) and clinicians (by a monitoring dashboard). In this way patients will be able to record data on a real-time basis and to receive periodic reports on their clinical status; we think that this active involvement in the care process and the easy access to relevant clinical information will make patients more aware and confident to face the challenges in AGHD management.

The data collected in the MAGHD Framework database will be exploited for clinical purposes (clinical management of AGHD patients) and for obtaining the final outcome useful for the statistical analysis and the analysis of the study results. The feedback reports will be differentiated according to the user. The reports for patients will be of simple interpretation (e.g. % improvement/impairment of QoL or well-being scores; changes in daily physical activities, etc.) in order to avoid generating anxiety about patient's clinical status. *Vice versa* the report for clinicians will be very detailed and will coincide to the whole integrated database.

The development of the app and the IT tools useful for sharing data in the MAGHD Framework **are not available** publically at no cost.

Phase 2 – Clinical Real Data Acquisition

<u>HCP</u> data will include:

Data obtained from patient's record chard or by interview (for missing information):
- anagraphic data (date of birth, age, sex);
- medical history information (date of diagnosis of AGHD, number of pituitary deficits, duration in term of months of AGHD, cause of AGHD, childhood vs adult onset of GHD);
- symptoms at the time of diagnosis
- test used for diagnosis and serum GH peak at test;
- comorbidities (hypertension, CV diseases, DM, dyslipidemia, overweight, obesity, osteoporosis, etc.);

Data obtained at baseline and at subsequent visits by physical examination:
- anthropometric parameters (weight, height, BMI, waist circumference);
- clinical data (blood pressure, heart rate);
- clinical symptoms
- other therapies (especially other replacement treatments);
- other hormone replacement treatments (and relative dosage) in case of multiple pituitary deficits;

Data obtained at baseline and at subsequent visits by clinical (biochemical and radiological) examinations:
- pituitary hormones serum levels (insulin-like growth factor 1 (IGF-1), insulin-like growth factor binding protein 3 (IGFBP-3), adrenocorticotropic hormone (ACTH), cortisol, 24-hour urinary free cortisol (UFC), thyroid-stimulating hormone (TSH), free thyroxine (fT4), free triiodothyronine (fT3), luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol and progesterone (in females), testosterone

and sex hormone-binding globulin (SHBG) (in men), prolactin (PRL) after 30 minutes from the insertion of agocannula;
- biochemical values (haemoglobin, haematocrit, erythrocytes, leukocytes, platelets, renal and hepatic function, electrolytes, glycaemia, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides);
- other hormonal-biochemical data concerning bone metabolism: serum calcium and phosphorous, parathyroid hormone, vitamin D (25-OH vitamin D);
- dual-energy X-ray absorptiometry (DEXA) scan for assessing both body composition as well as both bone mineral content (BMC) and bone mineral density (BMD) on whole skeleton, at lumbar site, and at femoral site;
- r-hGH therapy (weekly dose and duration of therapy in months), if ongoing;

At present, no app-based system for the management of AGHD is available in literature or online. All the biochemical and radiological examinations take part of the clinical work-up of AGHD patients at the Unit of Endocrinology and are all available publically at no cost.

Statistical analysis

Prospective changes analysis
ANOVA for repeated measures will be used.

Groups Comparisons
For continuous variables, the nonparametric Mann-Whitney test will be used for comparisons for variables not normally distributed at the Kolmogorov-Smirnov test. For continuous variables normally distributed will be tested by means of ANOVA (or t-test when apply).
Categorical variables will be compared using the chi-square test and data were expressed as percentages.
A Spearman correlation coefficient test will be used to check for association between variables, in non-parametric variables.

In order to identify possible predictive factors for GH response to treatment a stepwise, linear, multiple regression analysis will be performed based on a previous single regression analysis for each predictor independent variable useful for identifying candidate predictive variables. A univariate analysis will be performed prior to multivariate analysis.

Statistical analysis will be performed using the 'Statistical Package for the Social Sciences' software for Windows (version 16.0; SPSS Inc., Chicago, IL). For all comparisons, p values <0.05 were considered statistically significant.

5. *Evaluation Design*

Phase 1 – evaluation design

All the activities performed during phase 1 will be evaluated by automatic software testing procedures able to check if the data coming from the MAGHD App are correctly recorded and transmitted to the MAGHD Framework. Possible developments errors will be corrected by releasing software updates on the MAGHD App or the information MAGHD Framework.

Phase 2 – evaluation design

The data available in the MAGHD Framework will serve for two different outputs, the first one directed to the user of the App (the patient) and the second one directed to the clinician.

Output for patients:
The patient will receive periodically a feedback concerning i) the results of questionnaires (twice a month); ii) their physical activity (once a week). These reports will provide information on i) %change of their QoL and well-being (questionnaires) and ii) changes in daily physical activities (as reported in the method section).
This kind of report will enhance patient's awareness on day-by-day changes (if present) related to their clinical condition. In particular frequent feedback on QoL and well-being will provide a more objective evaluation of these parameters, thus minimizing possible interference due to life events occurred close to the day in which the questionnaires are filled.

A summary of the patient's clinical outcomes will be provided through the MAGHD App in a simple graphical way in order to communicate changes in serum IGF-1 (the main biochemical marker of r-hGH therapy) and lipid profile. These data will not substitute the official clinical report patients will receive after each scheduled visit.

Output for clinicians:
Through the monitoring dashboard clinicians will be able:

1) to evaluate the relationship among the data coming from MAGHD App and the GH/IGF-1 status of the patient. This will add information on how the GH/IGF-1 status is able to influence daily activities, well-being, and QoL on the basis of continuous monitoring of these parameters. At present, patients with GHD provide this information only during scheduled visits, which are usually performed every six months or annually.

2) to compare the three groups of study differing each other for the exposure to r-hGH therapy (Figure 2) in terms of QoL, well-being, and daily physical activities (MAGHD App).

3) to compare for each patient within the three different groups changes from baseline. This comparison will provide information on how the use of the MAGHD App will influence QoL, well-being, and daily physical activities in each different group.

4) to obtain information on compliance through the question on adherence to r-hGH therapy that will be administered only to patients of Group 1. Clinician will also be able to evaluate how the adherence to therapy is modified overtime (from the start to the end of

the protocol study) only by administering periodically this question through the MAGHD App (patient's awareness on compliance).

5) to evaluate the effects of daily physical activities as recorded by the MAGHD App on lipid profile, weight, BMI, and body composition.

6) to check user's satisfaction about MAGHD App through the number of messages the user has returned and the visual satisfaction analogue scale on the MAGHD App.

7) to perform subgroup analyses (childhood vs adult onset; younger vs older patients; males vs females; isolated GHD vs multiple pituitary deficits; etc.) as secondary endpoints.

Evaluation of outcomes dissemination
If successful, pilot data from this study will be used to sustain the dissemination of the MAGHD App to other Endocrinology Units. The project will be disseminated through publication on indexed international journals and will be evaluated by number of papers/citations received in scientific and academic context.

Expected Results and Future Directions

This study will provide information useful for scientific advancement in the field of AGHD and its treatment since it will give new insight about the clinical utility of an App in the management of AGHD patients. In case of evidence of clinical effectiveness of the MAGHD App, this clinical tool may be disseminated worldwide and become a useful instrument for monitoring AGHD patients during daily clinical practice or even in the context of clinical studies. In particular, the MAGHD App could be made available on the web and could be downloaded by patients or clinicians who intend to use it for the above-mentioned purposes.
To pave the way for MAGHD App dissemination to AGHD patients referring to other Endocrinology Units , the following steps will be taken:
1) the real usefulness and effectiveness of the App will be verified before the dissemination phase;
2) the App will be made available for other Centers (with adjunctive costs required). In this case, a Support Service will be created, including an e-mail address, to assist clinicians and patients in using MAGHD App and MAGHD Framework. Alternatively, the MAGHD App will be made available on the web for downloading together with informational and educational material.

Moreover, we believe this model is easily applicable to other endocrinological disorders, as it has the potential to enhance the communication between clinicians and patients, to help patients to better understand their symptoms and accept their condition and to improve HCPs competence in chronic diseases management.

The use of the MAGHD App might also apply for:
1) improving AGHD patients management worldwide
2) designing future prospective studies:

2a) comparing patients with a new diagnosis of AGHD before and during r-hGH therapy

2b) tailoring the dose of r-hGH to the patient not only on the basis of IGF-1, but also by using data provided by the App

3b) predicting subgroups of AGHD patients that may beneficiate more from r-hGH.

6. Detailed Workplan and Deliverables Schedule:

If the project will be chosen and supported by Pfizer, the study protocol will be written and submitted to the Local Ethical Committee; the approval constitutes an essential prerequisite for conducting the whole study.

The project will be carried out in 24 months. Months 1-6 will focus on: 1) App development, 2) Integrated Framework development, 3) App testing. After the initial development phase, during the 5th month, the study staff will receive didactic training from DataRiver regarding the use of MAGHD App and of the MAGHD framework.

Patient enrollment and baseline visits will occur between months 1 and 6. The recruited patients, after having signed the informed consent, will be trained to use the MAGHD App prior to effectively enter the study.

Six-month visits (3 visits) will occur between months 12 and 24.

An interim analysis will be performed after the first six months of follow-up to have an indication of the preliminary results obtained, while the final data analysis will occur after completion of the protocol study. After the end of data analysis, manuscript writing and optimization of MAGHD App for public dissemination will be completed. It is expected that the final data analysis, the manuscript preparation and the App dissemination will exceed the protocol duration of 24 months.

The milestones and deliverables are described in Table 1.

Even if the timeline is intense, we are confident that this project is feasible within the 24 months period because: 1) the Endocrinology Unit of Modena and DataRiver have already collaborated to several projects demonstrating a great ability to develop useful tools for clinical studies, 2) the Investigators have a very high experience in recruiting AGHD patients for clinical studies.

Table 1. Workplan and Deliverable Schedules of the Project

Deliverable	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
						Year 1												Year 2						
												Months												
Study Set-Up																								
Full protocol Submission to the Local Ethical Committee and Approval	*The Local Ethical Committee approval constitutes a prerequisite for conducting the whole study. Thus, the onset of the study will coincide with the Approval.*																							
Phase 1	**Smartphone App and Integrated Framework Development**																							
App Development	X	X	X	X																				
Integrated Framework development	X	X	X	X																				
App Testing and Validation					X	X																		
Project Staff Training					X																			
Phase 2	**Clinical Real Data Acquisition**																							
Patients Enrollment and Baseline Study Visits	X	X	X	X	X	X																		
Patients Training						X																		
Follow-up Visits												X						X						X
Phase 3	**Data Analysis and Manuscript Preparation**																							
Data analysis												X^												X*
Manuscript preparation																								X*
Dissemination																								X*

^Interim analysis for the outcome of preliminary results.
*The final data analysis, manuscript preparation and dissemination phase will exceed the protocol duration of 24 months.

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J. Apendix

Abbreviations

ACTH: Adrenocorticotropic Hormone
AGHD: Adult Growth Hormone Deficiency
DEXA: Dual-Energy X-ray Absorptiometry
ePRO-D: Patient Related Outcomes Data
FSH: Follicle-Stimulating Hormone
fT4: Free Thyroxine
GH: Growth Hormone
HCP: Healthcare Provider
HCP-D: HCP Data
HDL-C: High-Density Lipoprotein Cholesterol
IGF-1: Insulin-like Growth Factor 1
LDL-C: Low-Density Lipoprotein Cholesterol
LH: Luteinizing Hormone
MAGHD App: Manage Adult Growth Hormone Deficiency App
PA-D: Active Task Data
QoL: Quality of Life
QoL-AGHDA: Quality of Life Assessment of Growth Hormone Deficiency in Adults
QLS-H: Questions on Life Satisfaction Hypopituitarism
RFP: Request for Proposals
r-hGH: recombinant human Growth Hormone
TC: Total Cholesterol
TSH: Thyroid-Stimulating Hormone
UFC: Urinary Free Cortisol
WEMWBS: Warwick-Edinburgh Mental Well-Being Scale