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A European Society of Endocrinology audit and multi-country comparison of Adult Growth Hormone Deficiency (AGHD) treatment in clinical practice in Europe, Australia and New Zealand; how closely are protocols and best practice recommendations followed.

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European Society of Endocrinology

Abstract

ESE will carry out a systematic audit on every-day, real practice of Adult Growth Hormone Deficiency (AGHD) patient diagnosis and treatment from over 50 countries and multiple HCP regionally, to compare and contrast differing practices across pan-European, Australian and New Zealand Health Care Professionals (HCP).

The exact prevalence of AGHD is not known, but estimates vary between 200-300 patients/M approximately 100,000 across Europe and is characterized by a reduction in bone mineral density, lean body mass, exercise capacity, and overall quality of life as well as an increase of body fat and cardiovascular risks. Evidence is nowadays overwhelming that most patients benefit from a daily injection of GH and are willing to continue treatment chronically, if they are severely GH-deficient and symptomatic at baseline.

We will request a targeted population of practicing endocrinologists to complete a questionnaire to establish the pan-European baseline of diagnosis and treatment practice across the region, as well as identifying any country-by-country variances compared to standard recommendations. Our methodology sets out to collect aggregated patient data that represents between 5,000 and 10,000 diagnosed patients, with treated, as well as untreated AGHD, so we can identify gaps and opportunities for improvement to optimizing outcomes for these patients.

The outcome of this audit, which will enable ESE in tailoring education on the topic, will be submitted as an abstract to the European Congress of Endocrinology (ECE 2020) and as a full manuscript for publication in the *European Journal of Endocrinology* in summer 2020.

European Society of Endocrinology AGHD Steering Group. June 2017

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Response to reviewer comments

ESE was delighted to learn that our LOI had been put forward to the RFP stage and that the panel was impressed by the scale and ambition of the planned collaboration. We thank the review team for their reflections and subsequent clarity on a couple of minor points they provided at our request. In reaction to those comments, the ESE project Steering Group has met a number of times by teleconference and held a face-to-face meeting to best convey the clarity and outcomes of the project.

We believe ESE is uniquely positioned to carry out such a large audit and needs assessment with the clear purpose of identifying gaps in practice and paving the way for further education, quality improvement and research activity that will benefit patients in the future. To strengthen the success of the project outcome, our final detailed costs estimates have risen, to provide some small compensation to the centres for their data collection activity and to provide a series of individual country findings reports at the study conclusion.

Overall, we have considered and addressed the panel's concerns to add a greater level of detail around our intervention and evaluation plans in the enclosed RFP and have specifically expanded our explanation by providing more detail on our:

- Methodology for devising a questionnaire to identify variances of AGHD diagnosis and treatment practices
- Approach to disseminate the findings of our audit widely, so its conclusions can be considered for further educational activity.
- Two findings report approaches; one addressing insights across all countries, the other identifying insights at a selective country level.
- Use of Moore's framework for learning and change are being applied to this project

Overall Goal & Objectives:

The *European Society of Endocrinology* (ESE) wishes to carry out a systematic audit on everyday, real practice effectiveness of **Adult Growth Hormone Deficiency** (AGHD) patient diagnosis and treatment across pan-European, Australian and New Zealand Health Care Professionals (HCP). The project will be defined and compiled by various AGHD specialists and by working in collaboration with:

- An ESE panel (HCP) experts and the ESE Clinical Committee
- 47 member countries of the *European Council of Affiliated Societies*
- ESE Members or their respective societies in Australia and New Zealand
- 72 HCP in the European Reference Network for Rare Endocrine Disorders (Endo-ERN)
- An EMEA expert on drug usage data to determine the volume of therapeutic GH use

Developing a better understanding of AGHD treatment practice is integral to ESE's Pituitary and Neuroendocrinology therapy focus area plans until 2021. It also demonstrates our strategic priority to disseminate knowledge and provide support to the endocrine specialist community that ultimately improve patient outcomes.

Our main objectives are to:

- Comprehensively record and aggregate current AGHD best practice treatment in clinical practice conditions
- Gather data from over 50 countries and multiple HCP regionally, to compare and contrast differing practices.
- Work with specialist clinical practitioners, other stakeholders and the current evidence, to reflect current practice with substitution therapy in AGHD
- To identify gaps and opportunities for improvement, with the final aim of optimizing outcome for these patients.
- Identify, country to country, how each relates to the overall pan-European picture, and to the recommended guidelines
- Prepare two reports of our findings including making recommendations on how to provide educational support to countries who wish to establish best practice
- Highlight identified circumstances preventing best practice being established

SMART Element	Summary of how the objective reflects this element?
Specific	We are focussing on AGHD patients, childhood and adult onset, in a targeted geographical area, analysing diagnostic and treatment practices compared to guidelines.
Measurable	We aim to include 5,000-10,000 patients from up to 50 countries.
Achievable	5-10% of target population to be recruited via a limited number of centres
Realistic	We have a strategy in place to mitigate shortfalls in recruitment. We have the support of the ESE endocrine leadership community. We have proven engagement with Society members. We have experience in multi-country, multi-centre projects (http://www.lb.de/ercusyn/)
Timely	Our identified milestones are defined throughout the project

Current Assessment of need in target area

We estimate AGHD affects between 200-300 patients/M, approximately 100,000 across Europe. The condition is characterized by a reduction in bone mineral density, lean body mass, exercise capacity, and overall quality of life as well as an increase of body fat and cardiovascular risks. The concept of AGHD was established more than 20 years ago, and the accumulated evidence is nowadays overwhelming that most patients benefit from a daily injection of GH and are willing to continue treatment chronically, if they are severely GH-deficient and symptomatic at baseline. However, it is also evident that a small percentage of patients do well without substitution therapy, and are therefore not interested in pursuing daily treatment; the reason for this is still unclear and probably multi-factorial^{1,2}.

Our target audience to take part in the study will be practicing endocrinologists in centres around Europe, Australia and New Zealand who care for AGHD patients or are considering what gaps and opportunities there are for improvement, with the final aim of optimizing outcome for these individuals. Our goal will be to collect aggregated patient data from regional centres that represents between 5,000 and 10,000 individuals with either treated or untreated AGHD³⁻⁶.

Once a baseline is established, we can then assess how GH treatment compares to most recently updated treatment recommendations across the pan European region and country by country. Any resultant gap analysis of treatment approaches or reasons for lack of adoption of the published guidance will help ESE better tailor education on the topic and we anticipate that this will lead to learning and change where needed⁷⁻¹¹.

Apart from providing practical education and training opportunities to assist HCPs diagnosis and treatment of AGHD patients, one potential adaptation could be to the on-going development of the ESE pan-European curriculum for Endocrinology, Metabolism and Diabetes (<http://www.es-hormones.org/education/rcclinendodm.aspx>). In combination, the increase in education will ultimately improve AGHD patient long-term outcomes and quality of life, and by doing so is beneficial for the health system, since after improvement, health care costs fall^{12,13}.

Target Audiences.

Our Primary target audience for the study will be those senior endocrinologists within the sample of centres we are requesting perform the audit of treatment practices. To gain the collaboration of centres in Europe, Australia and New Zealand to provide their data and experiences, we will deploy a systematic method to identify and recruit qualified individuals within each centre to meet our goals and objectives. Once engaged, we will continually look for ways to support them further to act as ambassadors of the outcome findings, so that together we can reach and influence our Secondary target audiences – the wider endocrine communities beyond the participating centres.

The ultimate outcomes from the project will help educate a wide variety of healthcare providers caring for AGHD patients in Europe, Australia and New Zealand. We envisage those to include adult endocrinologists, specialist nurses, radiotherapists and psychologists within 6 key ESE endocrine audiences:

1. **ESE membership:** 4000 individuals consisting of basic scientists to practicing clinical experts and nurse practitioners, mainly based in Europe, but also from Australia and New Zealand

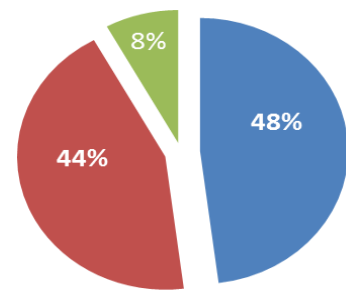
2. **ECE delegates:** The annual European Congress of Endocrinology additionally attracts 1500-2000 non-member delegates from over 90 countries, most within the geographical scope of our audit.

Within these combined audiences, 55% have an interest in the Pituitary and Neuroendocrinology focus area.

3. **ECAS:** In 2013, ESE and our National Affiliated Societies formed the ESE Council of Affiliated Societies (ECAS) with the aim of raising the profile of European Endocrinology. It provides a forum for discussion between ESE and the National Affiliated Societies and an opportunity to identify joint educational gaps on which we can work together for the benefit of endocrinologists throughout Europe. The 47 National Affiliated Societies to ESE provides an opportunity for us to regular engage with a pan-European ECAS endocrine audience of ~ 20-25,000 local specialists.

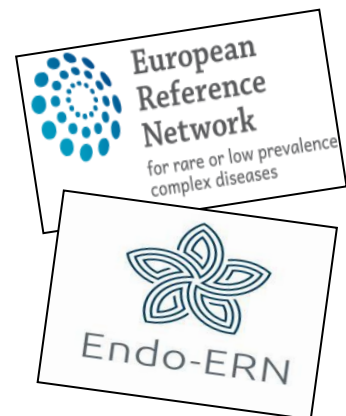
4. **Endo-ERN:** The European Reference Network aims to increase harmonisation of thematic endocrine activity across Europe via 72 centres of excellence who have agreed to work together to improve education and patient outcomes. Professor Gudmundur Johannsson; Adult Chair: Endo ERN Growth and Genetic Obesity Syndrome is collaborating with us during this study. The European Society of Endocrinology and the European Society for Paediatric Endocrinology are key stakeholders in the Endo-ERN and have been integral in the successful set up of this network.

5. **ECE 2020:** We plan to disseminate the AGHD project findings in a multitude of ways, ahead of ultimate publication (see 6.). During the European Congress of Endocrinology 2020 we will present a poster of the main conclusions, and see if it may be possible to also host a workshop or other symposia session within the main programme of the event. Apart from the delegate audiences attending, the presentation material will be available to view globally via the online repository ECE On Demand platform and its associated App.



Research focus

- clinical
- translational
- basic scientists



6. **European Journal of Endocrinology:** Our peer reviewed journal has an impact factor of 4.101 and in 2016 attracted over 1.5M page views. It publishes a number of ESE articles under a common rights licence so they are freely available to all academic and practitioner audiences globally. We will submit the findings of for the AGHD audit for publication in EJE in summer 2020, so those managing clinical decision protocols linked to patient adherence and long-term disease management outcomes will be able to view the recommendations.



Project Design and Methods

Launching the project plan.

In preparation for ESE to carry out the project, we have already established a Steering Group comprising key roles, specifically the appointment of the lead project collaborator, an interim project manager and a provision to hire a research associate at the end of 2017.

We have also established a reporting and governance structure to manage the project from start to end and will launch an associated reporting and communication plan for both internal and external stakeholders as appropriate.

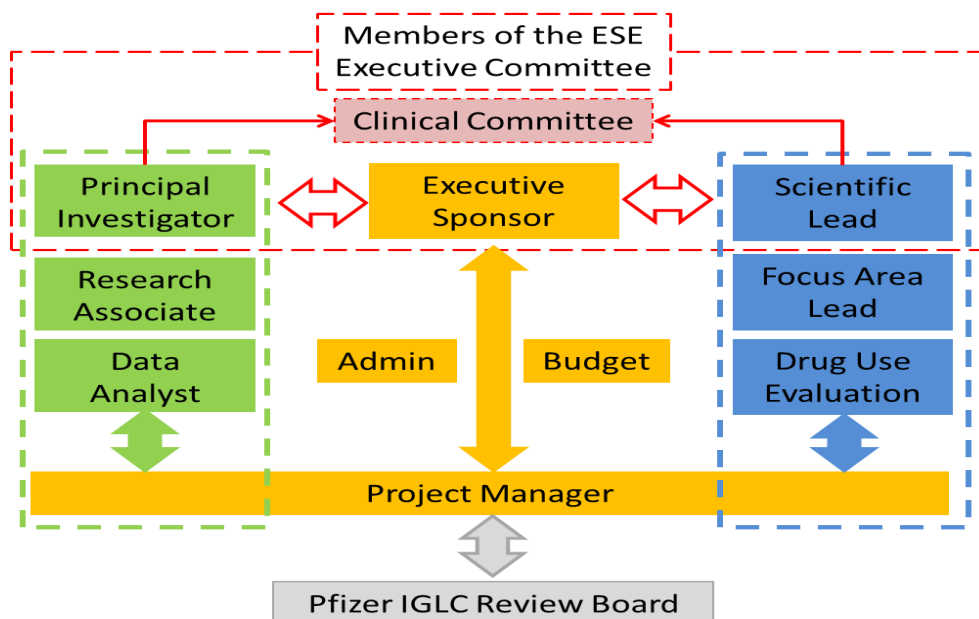


Fig 1. ESE AGHD Project Steering Group organisation.

Within the project Steering Group, of the eight specific roles with regular responsibility for the project, three are members of the ESE Executive Committee, including our Principal Investigator. The informal reporting structure consists of three distinct resource groups; green, blue and orange, working synergistically at all times:

Green group. Led by the Principal Investigator, Professor Susan Webb this group will mainly manage the engagement and management of our questionnaire and gaining responses from collaborating centres.

Blue group. Under Scientific lead, Professor Márta Korbonits, this group will manage the anticipated analytical needs of the audit against the existing treatment guidance, identifying the educational outcomes and supporting our final reporting.

Orange group. The management of the project overall will be led by Helen Gregson, CEO via her overseeing the weekly progress of the AGHD project manager.

The groups will report progress against objectives into the Chair of the ESE Clinical Committee, Professor Jérôme Bertherat and to the ESE Executive Committee quarterly.

Stakeholder identification and engagement.

We plan to audit ESE's 47 National Affiliate Society membership countries, plus Australia and New Zealand, and will need to identify suitable stakeholders within each country to complete the audit. To establish how many centres to ask to collaborate and the total number of patients we want that to represent, we have made the following assumptions:

- A prevalence of hypopituitarism at 200-300/M, approximately 100,000 population
- 70% being GHD
- Total population of all participating countries represents 500 M inhabitants.
- Aim to capture a representative sample of ~ 5-10% of patients from each country.

We estimate this will result in our audit accumulating aggregated data from a range of 5,000 - 10,000 patients. During the analysis phase of the project we will use country population weighted averages to assess the prevalence of responses and findings to compare to other countries. To minimise bias in our sampling method, we will identify centres with AGHD patient experience by approaching this task using four approaches sequentially in a systematic manner until we have enough random centres selected to work with:

1st. Invite ESE members and ECE delegates within the target countries to take part, including asking them to indicate the size of their practice / clinic AGHD population.

2nd. Invite the Endo-ERN to recommend to its members to take part.

3rd. Invite ECAS representatives to identify suitable potential prospects for us to approach them directly.

4th. Invite our project Steering Group to recommend centres and colleagues known for their AGHD work academically to complete any sample pool country gaps.

During our approach to centres to collaborate, we will determine the number of AGHD patients they typically see, so we can adjust our audit to achieve the 5-10% representative sample per country we aim to achieve.

Audit questionnaire.

To audit the AGHD treatment practice against existing guidelines we will create a detailed online questionnaire for completion by a senior representative at a range of centres treating AGHD patients. We anticipate examining the evidence and designing and testing the audit questionnaire with key stakeholders in Q1 2018, led by the Principal Investigator and the Steering Group team.

We see a number of sections within the survey, each with their own set of specific sub-questions and in many cases, multiple choice options to complete, for the participants to effectively report their own diagnostic and AGHD treatment practice experiences. This will apply to both childhood onset and adult onset AGHD patients.

- Demographics
- Diagnostic criteria
- Patient selection
- Dosing
- Monitoring
- Treatment goals
- Drug utilization & criteria for therapy access
- HCPs, nursing support and patient engagement

The raw questionnaire will then be sent for external testing with a few select centres, to ensure it works practically. Once this is confirmed we will program the online survey tool to capture responses and provide some top line raw analytical data.

The centres will be asked to assess their own patient data to provide a systematic, comprehensive, but localised analysis of the current treatment practices of AGHD in relation to our structured questions. The data will be collected in an aggregated form by considering all individual patients they have on record within the past 24 months that meet the criteria of our sample population so we can assess each centre's practice reality against the standard guidelines.

ESE asking the centres to aggregate the data mitigates the complexity and expense of needing to construct a custom data management system to manage any large cohorts of individual patient data, and importantly dispenses with any need for each centre to seek ethics committee approval of their engagement with the project. We will issue a letter of collaboration between ESE and the centres for clarity.

As previously indicated, we will evaluate the most recent guidelines to create relevant structured questions around the key measurable qualitative, descriptive parameters we wish to analyse.

To establish variances of in-country drug use, we will attempt to access and evaluate a variety of independent sources (IMS, pharmacy databases, healthcare system provider records) with the support of a specialist researcher. We will also request the centres to identify any circumstances in their local setting that affects the potential of GH being used to treat AGHD patients, such as regulations, access, reimbursement or localised institutional policies. This enables us to look more precisely at these conditions during our analysis phase of selective countries potentially.

A full work schedule and role responsibility description will be defined and allocated to each member of the project Steering Group, before all workflows are constructed and communications prepared, to outline the questionnaire response we wish from each centre, the time by which it should be completed and the actions ESE plans to take from the data collected.

An outline project plan, is indicated in the Work Plan and Schedule section (p16)

Evaluation Design

After aggregating the raw data from the study into crude analysis forms, we will need to refine, analyse and assimilate that large data pool into more condensed and accessible formats. Our goal will be to provide a set of communications for wider dissemination outside ESE as educational officially published outputs. Our evaluation design will comprise four elements:

- Data analysis of the aggregated questionnaire responses
- Report development and recommendations.
- Dissemination of findings
- Devise follow-up activity

At a later date we will also do formal follow-up with ESE members, users and participants when the findings are published, to establish what each centre plans to do in light of the findings. As the study is primarily designed to systematically identify where gaps in treatment practices are occurring across Europe, Australia and New Zealand generally, and uncover reasons why that is the case specifically within certain countries, we cannot quantify at this moment in time what % change in AGHD diagnosis and treatment will occur following the study. Instead, our findings can be utilized by the centres within each country to quantify what change can be achieved and what steps they can take locally to focus efforts to alleviate the issues we uncover.

A measure of success would be to what extent countries with no local guidance adopt the findings as the most up to date recommendations, or the information is integrated into revisions of the national guidance where they exist.

Data analysis

The questionnaire will be designed so that it is as comprehensive as possible in identifying specific variances across centres around Europe, Australia and New Zealand but is not being designed to gather exhaustive levels of data for detailed statistical analysis.

It will instead provide descriptive analysis that can be cross compared to existing guideline data to provide insight into any underlying issues or potential limitations on AGHD treatment adherence. As part of our conclusions, we will suggest ways the data we collect, could be used by individual countries to possibly carry out further evaluation.

We are employing a data analyst to assist the project, so they can apply their specialist knowledge of how to maximise the input criteria we require, to enable the relevant sample data to emerge from the questionnaire responses.

They will analyse and summarise how to present the data in more accessible formats for our report writing, dissemination to our target audiences and ultimate use in our planned publications.

Our analysis will look to maximize finding answers from the data presented, bearing in mind the purpose of the audit is to establish best practice and identify how through ongoing continuous education learning and change can result. We are conscious not to make the questionnaire too extensive, so most sections below will ask 3-5 questions, but with a choice of answer options or an open commentary field to complete:

- Demographics
- Diagnostic criteria
- Patient selection
- Dosing
- Monitoring
- Treatment goals
- Drug utilization & criteria for therapy access
- HCPs, nursing support and patient engagement

Report Development recommendations

Once the data analysis has been completed, the project Steering Group and senior ESE sponsors will meet to hear the overall findings, look at some specific variances together and begin establishing ESE's reaction to the audit.

The task of compiling ESE official response will be led by the Chair of the Clinical Committee and the lead Principal Investigator, who will compile a set of interim, and then final findings into various formats.

Dissemination of findings

The variety of differing formats to disseminate our findings over time will each be designed to serve and influence differing target audiences, with different levels of detail and scientific rigour.

ESE AGHD pan-European, Australia and New Zealand Findings Report

Our initial findings will be prepared into a concise output for all stakeholders and our membership to refer to, under the mentorship of the Principal Investigator.

ESE AGHD Country Findings Report(s)

This sub analysis will look to compare what is happening at a number of specific countries, we believe warrant such an approach and are appropriate to look at further subject to enough data being available to do so comprehensively.

Both types of report will be compiled by coordinating the input from the Research Associate, Data Analyst, and the project Steering Group's commentaries and other Clinical Committee recommended narrative in collaboration with the AGHD project manager.

European Congress of Endocrinology 2020 poster / oral presentation

The collaborator group will prepare a poster or presentation to disclose to delegates attending the congress, either as a printed poster, e-poster or possible oral presentation or part of the main scientific programme. We will also consider offering a workshop for collaborating centres during the study to attend and learn more from the findings and discuss how the ESE can potentially support them in adapting to develop AGHD best practice treatments.

European Journal of Endocrinology article submission

As soon as the Clinical Committee have agreed the official ESE response to the findings, the collaborator group will begin to prepare a scientific original article for publication. It will be

first submitted to the EJE with the recommendation it is considered to be published under a common rights license to ensure it is seen by anyone globally at no charge.

Patient support organisations

We will share our findings with PSGs to potentially identify if there are any additional activities we could consider arranging together to assist the education of patients directly or support HCPs in their engagement with them.

Curriculum recommendations

Our Education Committee will be asked to review the audit and determine if the findings around AGHD best practice treatment practices across Europe merits the updated recommendations being considered part of our on-going development of the pan-European curriculum for Endocrinology, Metabolism and Diabetes (<http://www.ese-hormones.org/education/rcclinendodm.aspx>).

Devise follow-up activity

Once our interim report findings become public, we will begin to identify the specific countries and steps to consider where we feel intervention and support may be required to address significant variances in our study, and implement any adjustments to practice treatment approach. One consideration could be to establish what levels of education exist around AGHD in specific countries and subject to further funding being found to support ESE, potentially developing educational activity to alleviate that issue, such as:

- Publishing an *ESE INSIGHT* supplement on improving AGHD practice adherence.
- Running an *ESE Clinical Update* workshop locally or regionally
- Considering other educational activity as appropriate

An agreed timescale and an individual within an organisation will be identified within each stakeholder country involved in the audit to lead the implementation of these next steps.

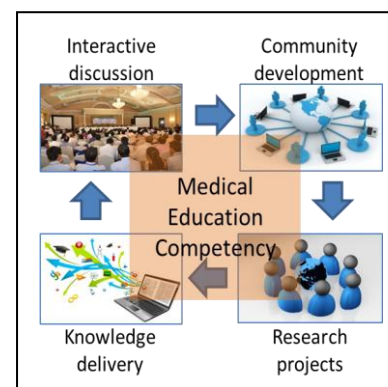
Continual learning and change activity

Throughout the project, we will prepare and distribute regular email update project reports and summary information to keep stakeholders engaged. As part of this process, we will ask that centres provide feedback on the progress of the project periodically and any issues arising from it to help ESE better understand such engagement projects across Europe.

Encouraging educational learning and change behaviours

As a professional educational Society, we are fortunate that our stakeholders trust and rely upon us to satisfy their development of their learning behaviours. We consider, plan, and execute educational activities we undertake based around four ESE core competencies:

- Creating interactive opportunities
- Building community engagement
- Continual research to assess needs
- Defining authoritative knowledge



Throughout the project, we will be actively communicating ongoing findings to encourage wider understanding of many good practice elements of learning and change (L&C) behaviour in a clinical setting:

- Recognizing an opportunity for learning
- Searching for resources for learning
- Engaging in learning to address an opportunity for improvement
- Trying out what was learned
- Incorporating what was learned.

By establishing the need to update and audit the AGHD treatment practices, we have intrinsically built the 7 steps recommended by Moore’s framework¹⁴ into our proposal.

Level	Framework	AGHD audit activity description	Likely AGHD audit source of L&C
1	Participation	Invitation to take part accepted	Email acceptance
2	Satisfaction	Agreement to terms and submission of data on time	Signed letter of agreement
3a	Learning: Declarative Knowledge	Ability to gather the aggregated data into useable form for questionnaire	Completion of questionnaire
3b	Learning: Procedural Knowledge	Agreement to consider findings recommendations and implement necessary changes	Final Report
4	Competence	Feedback on ESE output findings report and suggested next steps	Country to country interventions
5	Performance	Post audit follow-up to establish in-country reactions + any recommended changes to the pan-European curriculum	EJE Article, sample feedback survey to the centres
6 & 7	Patient Health and Community Health	Post-audit identification of patient benefit gaps with specific country stakeholders	Individual country reports

Work plan outline

The project plan will be managed by the appointed project manager, using all regular forms of communication and stakeholder engagement activity, based around these core elements:

- Main project milestones: Timeline of activity and status
- Sub milestones: Detailing all dependent steps to complete
- Resource management: Work schedules and time sheet analysis
- Budget: Monthly costs against estimate and actual, Q1-4 summaries
- Project Communications: All interim (Q1-4) reports
- Marketing: Outbound milestone events, proposed activity and other news

Beyond the use of these project management sections, the project will have five distinct phases, some that overlap between phases:

1. Design and commissioning: November 2017–May 2018
2. Centre engagement and research begins: January–December 2018
3. Communication, collection, aggregation and raw analysis: May 2017–March 2019
4. Detailed analysis, reporting, assessment and recommendations: March–September 2019
5. Detailed country level analysis and post-audit engagement planning: September-Q1 2020

Note: A 6th phase (Publishing) will follow in 2020, but is not part of this grant request.

To monitor and keep stakeholders involved, we plan to have three continuous reporting activities throughout the project:

- An overall AGHD management project report; key status against milestones only
- An ESE update for all stakeholders including external centres against milestones
- A Pfizer IGLC Interim report of progress to date against milestones

Deliverables Schedule:

See page 16 for 2-year detailed work plan

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