1. Title of project

Global Registry For Novel Therapies In Rare Bone & Endocrine Conditions

Short title – GloBE-Reg

2. Scientific background

Patient registries are organised systems that collect uniform data to identify a wide range of outcomes for a population defined by a particular disease, condition or exposure. In the field of endocrinology we have performed a mapping exercise (1) which showed that the majority of current registries collect natural history data on a narrow range of endocrine conditions. Registries can also provide valuable data that can support regulatory decision making on medicinal products by providing evidence on the efficacy/ effectiveness and safety of medicinal products in the frame of non-interventional studies at a post-authorisation level. In endocrinology, most of the existing registries have not been designed for this purpose and even if they are redesigned their scope is guided by the conditions they cover, rather than the drugs that require post-regulatory approval surveillance. The registries that do exist for this specific purpose have been developed by industry for one specific drug and the long-term utility of these industry registries becomes limited as industry loses interest after the period that is required for a post-approval surveillance study. For instance, in paediatrics and, particularly, paediatric endocrinology, the combination of outcome and safety can only be judged after a follow-up period of three to four decades as a minimum. Thus, there is an increasing realisation that registries that are developed in partnership between industry, academic organisations, health care professionals and patients are more likely to succeed in the long-term as effective tools for non-interventional studies of medical therapies that have already been approved. These issues were discussed in detail at an EMA workshop in 2016 (2, 3). More recently in 2020, the agency performed a survey of existing registries in its database and although the full results are yet to be published, the survey showed that only a small percentage of the surveyed registries collect systematic information on adverse events and those that do collect these data, do not have standardised processes for sharing data. GloBE-Reg is developing a platform that can support post-regulatory approval studies for several novel therapies. The Steering Committee of GloBE-Reg met for the first time in late 2021 and consists of members of industry as well as representatives from a wide range of endocrine organisations across the globe. This committee agreed to focus first on one class of drugs, recombinant human GH (rhGH) as a model of how GloBE-Reg could work and if this model is successful then it could be applied to other classes of drugs too.

Although several industry led registries have existed for rhGH and have been effective in quantifying efficacy, identifying predictors of response and identifying common and rare side effects of rhGH therapy and the incidence of those events, these registries have also suffered from incomplete data entry and a lack of patient- or parent-reported outcomes. Another major weakness of these registries is the focus of each registry on a single rhGH product making comparisons between products difficult. With the strong link to industry, cessation of monitoring individuals receiving rhGH on completion of therapy prevented assessment of long-term safety events. Previous rhGH registries have also lacked comparator groups to explore comparison of long-term efficacy and safety outcomes. Very importantly, the use of rhGH has now extended to new indications and may extend to other conditions in the future that are different to those for which rhGH was used previously. And lastly, the next few years will see the increasing use of a long acting form of rhGH (LAGH) which may be the same class of drug as daily rhGH but has different pharmacokinetics. In summary, although rhGH has been in clinical use for several decades, with the introduction of novel forms of rhGH therapies such as long acting rhGH (LAGH) and the extension of rhGH therapy to new clinical indications the need for long-term monitoring of clinical and safety outcomes has never been greater (3-5).

3. Scientific plan of the project

The GloBE-Reg GH project can be divided into the following packages.

A. **The development of the GloBE-Reg systems and its core data platform.**

This work package will be led from Glasgow and responsible for coordination, management of the budget, publicity and dissemination, engagement with stakeholders including the Steering Committee, development of the GloBE-Reg platform as well as obtaining all the appropriate approvals. It is anticipated that ethics approval for the use of the platform will be obtained Q2 2022. The governance of the project, including procedures for data access, shall be managed from Glasgow and will follow similar procedures to other projects developed in Glasgow including SDMregistries and the EuRRECa Registries. This WP will also oversee the development of the Data Access Committee (DAC) which will meet remotely 6-monthly but will review applications on an ad hoc basis, following similar procedures to those adopted in other registry projects mentioned above. The platform that will be developed will be similar to the one that has been developed for the EuRRECa Core Registry, a centralized registry which was initially based at the University of Glasgow. It has been created on a .NET framework and consists of two databases; one for the users and one for the cases and was launched in Q4 2022. Unlike previous registry projects coordinated by the Office for Rare Conditions, quality assurance (QA) against source data will also be available as an option through remote meetings. Centres that participate in entering data will be eligible to apply for collaborative centre grants. The QA will only be performed on the core data and a 'Minimum Dataset' that is identified as the most important dataset in the study specific modules, in this case the GH module of GloBE-Reg. The Core Data Platform consists of about 25 fields with less than 10 mandatory fields that will allow the user to select a study drug and a specific diagnosis which will allow the creation of a customised condition specific set of 5 questionnaires that will comprise, in this case, the GH module. These 5 questionnaires will be under the heading of 'diagnosis', 'therapy', 'adverse events', 'clinician reported outcomes' and 'patient reported outcomes'. In addition to diagnosis and drug customisation, the GloBE-Reg platform will also allow clinicians and patients/parents to choose a language so that the user interface can be customised to be displayed in their preferred language.

The quality of the registry platform will also be checked using quality assessment tools developed by the EuRRECa project (https://eurreca.net/affiliate-registries/) and the EUnetHTA21 project (https://www.eunethta.eu/request-tool-and-its-vision-paper/). As the project develops, specialist statistical support will also be available for projects. For optimal utilisation of the data, the option for complex analysis of the data to be handled internally will also be offered under the guidance of the external investigators. Following an application to the DAC, all industry partners shall also be provided with data that are collected on their specific product. The process of data provision will be specified in the Data Request Form and further outlined in the Data Sharing Agreement. For rhGH, individual companies will have their own internal, time-limited, drug-specific scientific study for which they will obtain data from GloBE-Reg. In addition, the generic GH Scientific Study Group (SSG) will investigate the wider and more longer-term aspects related to outcome.

B. **The development of the GH Module**

This will involve the following stages:

- The technical development of the module as described before is being undertaken in Glasgow
- The fields that will be included in the 5 questionnaires, ie 'diagnosis', 'therapy', 'adverse events', 'clinician reported outcomes' and 'patient reported outcomes' will be recommended by the Expert Working Groups (EWGs). Given the extensive knowledge that the members of the EWG have gained from previous rhGH registries as well as involvement in the field of rhGH, it is likely that there will be a high degree of consensus but there is a need to understand this consensus through a series of remote and

physical meetings. All members will be asked to provide a spreadsheet of fields that will be fitted into the 5 categories and those that have a high level of commonality or scientific rationale will be included in the questionnaires as the Minimum Dataset (MDS).

- The next requirement of the EWG will be to identify the fields within the five questionnaires that need to be the Minimum Dataset and the frequency of the collection of the individual fields within this dataset.
- All the fields in the GH module will also be translated into the languages preferred by the members of the EWG for the clinician and patient/parent interface and the members will be asked for their input
- Following the creation of these datasets, the EWG will be asked to test the module before it is made active.

The GH EWG will also undertake the following actions:

- Develop a plan for a range of studies
- Develop a plan for scientific outputs
- Develop a plan for dissemination

Further information about the EWGs is available on the GloBE-Reg website.

C. **The development of modules for other drug classes**
As the core systems in GloBE-Reg mature and the condition specific modules develop, the GloBE-Reg Steering Committee will consider using the platform for other drug classes that require a similar level of monitoring to rhGH therapy.

4. List of expected and measurable outcomes that can be used to judge the success of the support provided

The first EWG on Childhood GHD was formed in the first quarter of 2022, its members were nominated by the GloBE-Reg Steering Committee and it completed its objectives in 2023. Since then GloBE-Reg has launched three further EWGs, two of which are nearing completion. The meetings of the EWGs are organised by the Project Management Group and led by SFA as administrative lead of the EWGs. It is expected that in any one year there will be a maximum of two active EWGs. In addition, the activities of the EWGs have led to the development of new studies and it is is expected that further studies will develop over time. Outputs of the project include publications, dissemination at meetings and newsletters, details of which are available on the GloBE-Reg website.

5. Involvement of stakeholders (eg. Patients, public, professional societies, industry)

A. **Patients** – Diana Vitali, President of SOD Italia and a member of Endo-ERN ePAG has kindly agreed to join the GH Scientific Studies Committee and will also be welcome to join as many meetings of the GloBE-Reg GH SSG. She will also join the face-to-face meeting of the group in Rome in September 2022. Mrs Vitali also has links with ICOSEP (International Coalition of Organisations Supporting Endocrine Patients) and other patient organisations in the field of GHD. Jamie Harvey from the MAGIC Foundation and ICOSEP has also offered her support to the project.
B. **Public** – The GloBE-Reg project has a website with a dedicated area for its committees and it has a X presence too. These will be used to engage with the public.
C. **Professional societies** – The project is partnering with major international endocrine societies. including the GH Research Society. Through its steering committee the GloBE-Reg project will continue to work with these societies.
D. **Industry** - The GloBE-Reg project has already been supported by GenSci, Novo Nordisk and Pfizer as well as the University of Glasgow and it has also reached out to other pharmaceutical companies including Ascendis, Ipsen, LGScience and MerckSerono. In time, GloBE-Reg will also explore involvement in other novel endocrine or bone therapies in children. Novo Nordisk have their own

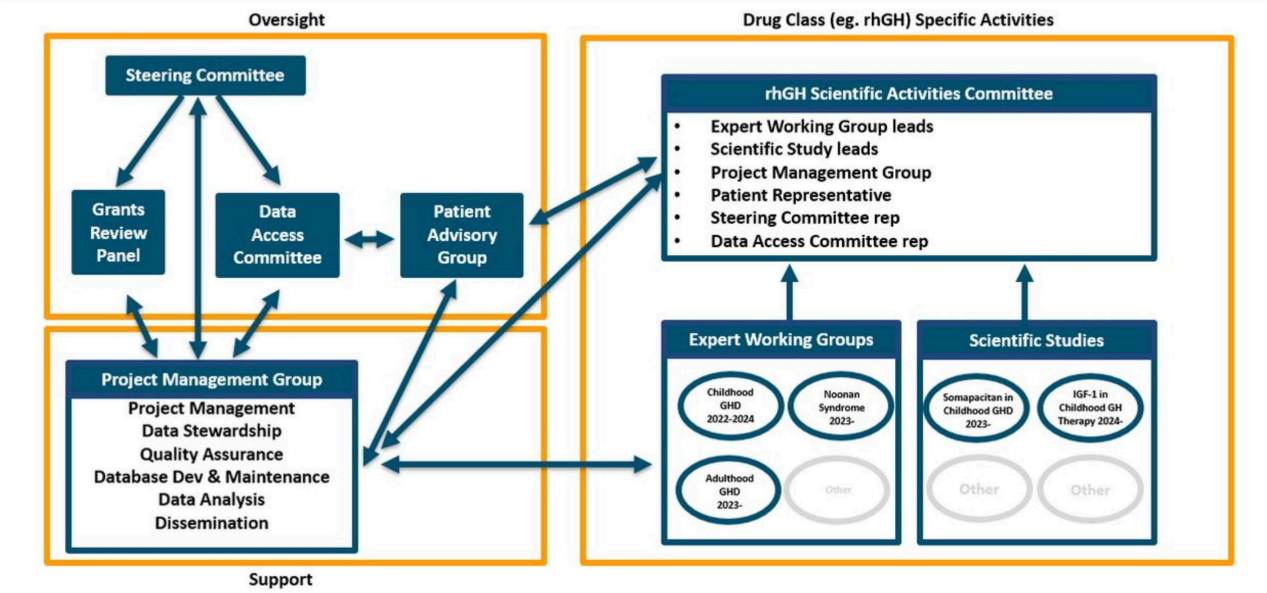
Sompacitan PASS Protocol that that they have submitted to the EMA and this study will be performed through GloBe-Reg. Pfizer intend to perform their own PASS for Somatrogon through GloBE-Reg.

6. Description of Lead Institution

The Office for Rare Conditions (www.officeforrareconditions.org) is part of the University of Glasgow, a charitable, not-for-profit institution. It was launched in January 2017 and it has two broad groups of activities, those that are Glasgow facing and those that have an international direction. The international activities of the Office for Rare Conditions are overseen by Professor Faisal Ahmed who was appointed to the Samson Gemmell Chair of Child Health at the University of Glasgow in 2012. In addition, he was appointed as Professor of Endocrine Registries at the University of Leiden in 2019. For his work he was awarded the ESPE Research Award in 2021. Amongst the international activities, the Office for Rare Conditions has a strong track record in developing web-based registries. Its first international registry was the Euro-DSD Registry launched in 2008 and this was succeeded by the I-DSD Registry in 2011 and joined by I-CAH in 2014 and I-TS in 2021. In addition, the Office has developed registries that support European Reference Networks, Endo-ERN and ERN-BOND through registry projects, EuRRECa which was launched in 2018 and EuRR-Bone, launched in 2020. Whilst the I-DSD/I-CAH/I-TS registries sustain themselves through a wide range of activities, EuRRECa and EuRR-Bone are primarily funded by the EU. The development of these registries has also allowed the Office to develop guidance for core outcomes, patient friendly practice, data governance and quality improvement for existing endocrine registries. The Office for Rare Conditions is closely linked to the Section of Child Health at the University of Glasgow.

7. Project organisation and management

The project will be closely managed and administered by the GloBE-Reg Project Management Group (PMG) which reports to the GloBE-Reg Steering Committee. The PMG will arrange all the meetings of the GloBE-Reg Expert Working Groups and will oversee and manage the group's timelines, milestones and deliverables. All the members of the EWG have been chosen for their expertise in the field of rhGH therapy. The leads of the EWGs, representatives from the companies as well as any other researchers that obtain data from GloBE-Reg for any study related to rhGH will meet regularly in a GH Scientific Activities Committee at which a patient representative will also be present (Fig.1).



8. Project risks and their mitigation

A. The generation of the data fields that are required for GloBE-Reg Core Module and the GloBE-Reg GH Module. The GloBE-Reg Core Module has already been created and work on developing the fields for the GH module has already begun and the risk of this not being done is very low. The impact of this outcome is not greater than moderate rather than

high as Novo Nordisk's Somapacitan Study Group has already provided GloBE-Reg with the fields that it considers important and these are being incorporated into the GH module as the bare minimum. In addition, several fields are also publicly available in published literature in outcome studies.

B. The risk of a delay in reaching a consensus on the data fields is greater but by having regular meetings, it is likely that this risk will be mitigated.
C. The risk of having too many fields that will need to be included in the GH module is moderate based on previous experience but the involvement of the Project Management Group in the development of the list will mitigate this problem. The clinical experts are also aware of the problem of too many fields.
D. The risk of not being able to incorporate any fields in the registry platform are very low. If these fields are very important then they have a potential for high impact and this will be mitigated by a revision of the registry structure.

References

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