CRANFIELD UNIVERSITY

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Improving Treatment Outcomes Through Personalised Medicine – Assessment of Disease Activity in Acromegaly

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ABSTRACT

Purpose

Personalised Medicine (PM), also known as stratified medicine has been known to improve treatment outcomes in a wide variety of disease area settings. Individualising treatment based on patient needs may also offer cost benefits to healthcare spend. Despite availability of multimodal treatment options for acromegaly, achievement of long-term disease control is suboptimal in a significant number of patients. Furthermore, disease control as defined by biochemical normalization may not always show concordance with disease related symptoms or patient's perceived quality of life.

Methods

An assessment to gauge the need to have an easy and helpful tool which may support acromegaly management was elucidated through a multinational qualitative survey. Subsequently, a validated a tool was developed to measure disease activity in acromegaly to support decision-making in clinical practice through a 2 step-approach. Firstly, an international expert panel (n = 10) convened to define the most critical indicators of disease activity. Patient scenarios were constructed based on these chosen parameters. Secondly, a panel of 21 renowned endocrinologists at pituitary centers (Europe and Canada) categorized each scenario as stable, mild, or significant disease activity in an online validation study.

Results

The international qualitative survey revealed that current treatment practice does have shortcomings in fully achieving disease control as well as identifying the need for a helpful solution to guide acromegaly care. As part of elucidating the most important disease activity indicators, from expert opinion, five parameters emerged as the best overall indicators to evaluate disease activity: insulin-like growth factor I (IGF-I) level, tumour status, presence of comorbidities (cardiovascular disease, diabetes, sleep apnea), symptoms, and health-related quality of life. In the validation study, IGF-I and tumour status became the predominant parameters selected for classification of patients with moderate or severe disease activity. If IGF-I level was

≤1.2x upper limit of normal and tumour size not significantly increased, the remaining three parameters contributed to the decision in a compensatory manner.

Conclusion

The validation study underlined the importance of IGF-I and tumour status for routine clinical decision-making, whereas patient-oriented outcome measures received less medical attention. A disease specific tool named Acromegaly Disease Activity Tool (ACRODAT) is in its final stages of development that will support clinicians in reviewing the disease activity in a holistic manner.

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TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

ACRODAT	Acromegaly Disease Activity Tool
AcroQoL	Acromegaly Quality of Life
AACE	American Association of Clinical Endocrinologists
DA	Dopamine Agonists
GH	Growth Hormone
GHRA	Growth Hormone Receptor Antagonist
GHRH	Growth Hormone Releasing Hormone
HbA1c	Haemoglobin Albumin 1c
IGF-I	Insulin like Growth Factor I
IT	Individualised Treatment
LAR	Long Acting Release
LLN	Lower Limit of Normal
MRI	Magnetic Resonance Imaging
OGTT	Oral Glucose Tolerance Test
PASQ	Patient-Assessed Acromegaly Symptoms Questionnaire
PEGV	Pegvisomant
PM	Personalised Medicine
QoL	Quality of Life
RT	Radiotherapy
SMD	Software Medical Device
SPC	Summary of Product Characteristics
SSAs	Somatostatin Analogues
SSTR	Somatostatin receptor subtype
ULN	Upper Limit of Normal
VF	Verterbral Fractures

CHAPTER 1

Section 1: Introduction

The term personalised medicine (PM) or more recently known as stratified medicine is the broad term used to describe a medical model enabling customisation of healthcare tailored to the individual patients need (Kumar, 2011). At the point of completion of the human genome project, there were high hopes on what this could contribute towards PM in assessing effectiveness of current therapies available to discovery of new medicine. While the journey towards perfecting utilisation of PM has been slower than anticipated, there is much progress towards new areas of applicability which reinforces the importance of individualised medicine.

PM may be considered an extension of traditional approaches to understanding and treating disease, but with greater precision. A profile of a patient's genetic variation can guide the selection of drugs or treatment protocols that minimize harmful side effects or ensure a more successful outcome. It can also indicate susceptibility to certain diseases before they become manifest, allowing the physician and patient to set out a plan for monitoring and prevention. Physicians can now go beyond the "one size fits all" model of medicine to make the most effective clinical decisions for individual patients.

In the last 20 years, substantial progress has been made towards the implementation of PM. When all of the pieces of infrastructure fall into place; when we begin to classify and treat diseases not just by their most obvious signs and symptoms, but also by their molecular profiles; when physicians combine their knowledge and judgment with a network of linked databases that help them interpret and act upon a patient's genomic information; when insurance companies pay for tests and treatments that anticipate the needs of the patient as much as react to them; and when regulators insist on using all information available to the physician, including genetic tests, to ensure the safety and efficacy of an approved drug, then "PM" will be integrated into clinical practice and medicine. The exploration has begun with good examples of where PM can really contribute but the concerted effort of pulling together best practices and leveraging what methodology may work across disease areas is yet to happen.

Some examples of where PM research is currently evolving:

1.1 *Pharmacogenetics*

A number of genes, gene polymorphisms and genomic sequences of unknown functions govern the internal metabolic environment. Thus essentially, one could argue that almost all human disorders or diseases will have some form of direct or indirect genomic bases. Evidence is also mounting on genetic variation correlation with treatment effects (Paik, 2006) which again strongly supports the notion of Individualised Treatment (IT) and PM.

1.2 *Warfarin use as an example of need for IT*

Some examples of the need to IT in order to improve treatment outcomes in warfarin use (Klein, 2009) include cardiovascular disease where there is an increased bleeding risk for patients carrying either the *CYP2C9*2* or *CYP2C9*3* alleles. In addition, certain single nucleotide polymorphisms in the *VKORC1* gene (especially the -1639G>A allele) have been associated with lower dose requirements for warfarin. These genotypes hence could predict likelihood of adverse events with warfarin therapy. Hereditary or acquired deficiencies of protein C or its cofactor, protein S, has also been associated with tissue necrosis following warfarin administration.

1.3 *Treating short stature in children*

In the field of endocrinology and growth disorders, newly emerging prediction algorithms in comparison to other more conventional approaches for the planning and evaluation of response to growth hormone (GH) in treating short stature in children (Ranke, 2013) illustrates clearly the value of PM in having a crucial role in optimising efficacy, in particular, utilisation of growth prediction models, based on large datasets of GH treated patient cohorts to choose the right dose for the individual patient. For a process as complex as the treatment with GH in a multitude of diagnoses and development phases of childhood and adolescence, these algorithms may not consider all relevant aspects but they guide the physician towards a more optimal treatment. The

alternative is simply to rely on sound clinical judgement which has its drawbacks when considering differing levels of expertise and dichotomy of patients requiring therapy.

1.4 *'Complex Disorders'*

Disorders such as bronchial asthma, diabetes mellitus, coronary artery diseases and bi-polar depression are commonly resulting from interaction of multiple causative factors and complex environmental factors. The individual genomic profiling, which is now possible with the use of variety of microarrays (Kumar, 2011), can enable identification of individuals who are at higher risk of developing the disease and those who can receive bespoke advice on lifestyle modification, avoidance of contributing environmental factors and institution of short term and long term pharmacotherapy. Foetal / neonatal or childhood screening programs to predict risk factors of likelihood of disease development in later life is part of the solution.

1.5 *Aims and Objectives*

The objective of my thesis was to evaluate the effectiveness of PM in the setting of Endocrinology and specifically 'acromegaly' as a disease area to see to what extend IT approach based on disease activity could be of value in treatment management. There are a variety of ways in which IT could be considered. One potential approach could be identifying an effective model which could be utilised outside its current use. Prior to establishment of PM, epidemiological studies to observe a reference population in assessing incidence, prevalence and outcome of common diseases was seen as the best way to predict treatment outcomes. It has been suggested that PM could be a superior method predicting better treatment outcomes with more focus on genetic variability. Some of the methods currently being investigated such as therapeutic dose optimisation prediction based on patient's disease characteristics, disease severity, gender and genetic factors for example could soon become standard of practice (Franck, 2017) while orienting drug discovery based on genetic variability contributing to drug response may take some time.

A significant area of interest in PM would be to research the field of drug responsiveness to different diseases. Spear et al (2001) reported that the range of responsiveness to drug therapy for anti-depressants (SSRIs) could be as low as 38% while optimising cancer therapies could offer treatment response as high as 75%. This review summarises that on average, a drug on the market is fully effective for only 50% of the people who take it. The consequences in terms of quality and cost of care are significant. Studies have also linked differences in response to the differences in gene that code for the metabolising enzymes, drug transporters or drug targets (Mangravite, 2006; Rieder, 2005; Terra, 2005). In the field of endocrinology, patients who has exon 3 deleted growth hormone receptor are associated with a better response to pegvisomant therapy in acromegaly (Bernabeu, 2010) and thus requiring lower doses of the drug shows clear advantages of the value of careful patient selection through profiling prior to medical therapy.

In clinical practice, three criteria are generally applied for assessing patient status (Downing, 2001):

1. Biomarkers: A biomarker is “a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention” – any substance, structure, or process that can be measured in the body or its product and influence or predict the incidence of outcome or disease”,
2. Clinical: A clinical endpoint is “a characteristic or variable that reflects how a patient feels, functions, or survives”,
3. Surrogate: A endpoint is “a biomarker that is intended to substitute for a clinical endpoint. A surrogate endpoint is expected to predict benefit (or harm or lack of benefit or harm) based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence”.

My thesis will need to explore such disease specific endpoints in order to prioritise the key elements which would then support clinical decision making.

In summary, the specific objectives of my thesis are to:

- explore the utility of PM to date in the context of surgical, radiotherapy and medical treatments which are currently available
- identify which factors may directly or indirectly influence disease activity (both from the treaters' and patient perspectives) and treatment outcome with a view to prioritising these disease markers to be the cornerstone of IT in acromegaly
- design a new and innovative approach to measure disease activity which then allows the clinician to identify the best treatment management approach
- implement an approach which can easily be adopted by the healthcare providers by readily and accessible data which arises from routine clinical practice as well as the resulting tool (to be named 'ACRODAT' – Acromegaly Disease Activity Tool) being user friendly with minimal data entry burden.
- Such a tool should also enable a patient centred consultation

1.6 *Contribution to knowledge*

Taking the concept of PM to apply in a complex disease such as acromegaly will have significant impact and relevance to future drug discovery right through to bedside application and the findings will lead to providing a better guidance on where to channel efforts in individualising treatment. If assessing disease activity is possible based on evaluation of a few disease critical parameters, then this tool could be a powerful source in:

- Identifying patients who are inadequately controlled despite treatment(s)
- Periodic assessment of patients to see improvement
- Review of which therapy(ies) or changes made is enabling a change towards improving disease control
- Helping the physician to assess disease activity and management in a holistic manner combining biochemical, clinical, tumour, co-morbidities and quality of life aspects in an individual.

The research findings will offer significant contribution to knowledge not only in applying the principles of PM to acromegaly as a disease area but if successful, it could pave the way for many such complex, chronic diseases in being able to encapsulate disease activity status by using a few critical disease related parameters which can then be used to optimise treatment management. Such methodology or approach has not been to date tried or tested in the area of acromegaly which makes again the contribution to knowledge innovative and has the potential to be utilised in real clinical practice. While the main objective of the thesis is to find an optimised tool to measure disease activity the exercise may also offer economic benefits either through earlier detection of disease activity and/or enabling earlier assessment of how effective the individual pharmaco-therapies are alone or in combination. Finally such a tool may also enable a more effective patient centred consultation where the tool's output can be used to discuss severity of disease, options available as well as monitoring treatment effect at regular intervals.

In the field of acromegaly, there are several tools aimed at improving patient care. ACROSCORE (Grottoli et al, 2016) is intended once validated, as a clinical screening tool of acromegaly that can be used by general practitioners and non-endocrinology specialists. If successful, ACROSCORE could enable earlier detection of symptoms and signs that are most discriminative for acromegaly with a view to aiding earlier referrals to specialist pituitary centres. Franck et al (2017) identified predictors of the Pegvisomant (PEGV) dose required to normalize IGF-I levels during PEGV monotherapy and in combination with long-acting somatostatin analogues (SSAs). The study concluded that IGF-I levels, weight, height and age can contribute to define the optimal PEGV dose to normalize IGF-I levels in addition to SSA. For PEGV monotherapy, only the patient's weight was associated with the IGF-I normalization PEGV dosage. While such multivariable prediction model is useful for clinical practice it is not yet available in a tool format which clinicians can easily use. Moreover, it does not provide a holistic view which also takes into account the patient's perspective or cater for other treatments utilised for acromegaly.

Such a gap in medical need whereby a simple solution in the way of a disease specific tool could address disease activity measurement and monitoring and could be attractive to both HCPs and patients. If such a solution could then lead to improved treatment outcomes as well as potential cost savings then this would contribute to our current knowledge and add significantly to patient care in acromegaly. Bernabeu et al (2015) demonstrated that the annual direct costs are estimated to be at least 60% greater in patients with uncontrolled acromegaly compared with those with controlled disease. Didoni et al (2004) in a cost of Illness study showed a similar outcome where cost savings with controlled disease was attributed to a lower co-morbidity rate. While it is challenging to observe long term implications and cost burden to managing co-morbidities given the high cost and practicality of such studies, short term disease control could already be a good indicator of long term prognosis and hence a disease specific tool which would enable short term holistic management of acromegaly can be hugely beneficial both for disease monitoring, improved treatment outcomes and reduction of direct and indirect healthcare costs.

CHAPTER 2

Section 2: Acromegaly

2.1 Background

The name acromegaly comes from the Greek words for ‘extremities’ (akron) and ‘great’ (megaly) and reflects one of its most common visible symptoms – the enlargement of hands and feet. Other common symptoms include progressive coarsening of facial features (enlarged lips and skinfolds); exaggerated growth of the jaw and nose, and soft tissue swelling (Melmed, 2003). Acromegaly is often diagnosed long after initial signs and symptoms appear as they are mistaken for many other clinical symptoms and diseases. As a result, it is frequently diagnosed at an average of 3 to 5 years after the onset of symptoms (Beckers, 2017). Uncontrolled acromegaly can have many complications including diabetes and cardiovascular disease (Melmed, 2003).

2.2 Epidemiology

Prevalence of acromegaly is equal in men and women with approximately 70 cases per million people with an incidence rate of 4 cases per million population (Holdaway, 1999; Ben-Shlomo, 2008). However, more recent studies have proposed that the prevalence may be as high as 30 – 140 per million and incidence of 2 – 11 per million per year (Beckers, 2017). The discrepancy may be due to better screening methods to environmental causes including industrial pollution being a risk factor for developing pituitary adenomas (Reddy, 2010; Daly 2009). The mean age of diagnosis is around 44 years and due to delayed diagnosis the prevalence may well be underestimated. Further areas that remain to be clarified in the epidemiology of acromegaly include possible geographical variations and the impact of other factors (e.g. ethnic, sex, type of health care system, availability and access to health care resources), as well as data on early-onset and genetic factors (Lavrentaki, 2017). In addition to the visible clinical features, symptoms and co-morbidities, patient report a significantly lower quality of life when compared to normal healthy population (Biermasz et al, 2004).

2.3 Anatomy of pituitary and the role of growth hormone in acromegaly

The pituitary gland is a pea-sized gland located above and behind the nasal passages, nestled in a groove of the sphenoid bone in the skull (fig.1). It contains 2 main lobes (Melmed, 2006):

- Posterior pituitary: Which is composed of neural tissue and releases neuro-hormones (or neuropeptides) received from the hypothalamus. These hormones affect water balance and play a role in labour and childbirth
- Anterior pituitary: This is composed of glandular tissue and secretes hormones that control growth, milk production in postpartum women, and function of other endocrine glands (the thyroid gland, adrenal glands and gonads)

The hypothalamus is a portion of the brain located above the pituitary gland. The hypothalamus performs both neural and endocrine functions. The hypothalamus uses the posterior pituitary to store some of its hormones. The hypothalamus also regulates the secretion of anterior pituitary hormones by secreting releasing and inhibiting factors.

Growth Hormone Releasing Hormone (GHRH), which is a hypothalamic hormone stimulates release of Growth Hormone (GH). GH is secreted by the somatotroph cells in the lateral anterior pituitary and is responsible for bodily growth. However, GH may not be directly responsible for certain obvious growth-promoting effects, such as the growth of skeletal muscle and bone tissue. Instead, the effects of GH on these tissues are thought to be mediated through Insulin-like Growth Factors (IGFs) released in response to GH stimulation. IGFs are produced in the tissues, particularly in the liver (Melmed 2006).

2.4 Disease Cause and Burden

In more than 90% of cases, acromegaly is caused by a non-malignant pituitary tumour (pituitary adenoma) which causes over secretion of GH (Melmed, 2006). These adenomas are classified as:

- Microadenomas: Which are <10mm in diameter
- Macroadenomas: Which are >10mm in diameter

Pituitary adenomas are common intracranial neoplasms with the vast majority of tumours being sporadic. However, in recent years there has been increasing recognition that pituitary adenomas can occur in a familial setting accounting for up to 5% of the total number of acromegaly patients diagnosed. Over the last decade, these families (~200) have been classified as having Familial Isolated (i.e., no other organs involved in this tumour syndrome) Pituitary Adenomas (FIPA). These patients are often characterised by early onset of disease, often aggressive tumour growth, a predominance of somatrotroph and lactotroph adenomas and in general very difficult to treat (Korbonits, 2011).

The American Association of Clinical Endocrinology (AACE) guidelines 2011 update (Katznelson, 2011) recommend considering a diagnosis of acromegaly in patients with two or more of the following:

- New onset diabetes
- Diffuse arthralgias (joint pain)
- New onset of difficult to control hypertension
- Cardiac Disease, including biventricular hypertrophy and diastolic or systolic dysfunction
- Fatigue
- Headaches
- Carpal Tunnel Syndrome
- Sleep Apnea Syndrome / Obstructive Sleep Apnea
- Excessive sweating
- Loss of vision

- Colon Polyps
- Progressive jaw malocclusion

Figure 1 (Melmed 2003) below illustrates the extent of symptoms and co-morbidities which could be present in patients with acromegaly. Not all patients will display all of the symptoms and co-morbidities and not all of these may be attributed directly to acromegaly. However, direct consequences of GH hypersecretion for example, enlarged extremities are obvious while association of co-morbidities play an important role as they need to be managed because they lead to increased mortality. The number of co-morbidities is influenced by many aspects not least the time of diagnosis and treatment in relation to the disease existence and the degree of disease control achieved by the various treatment modalities.

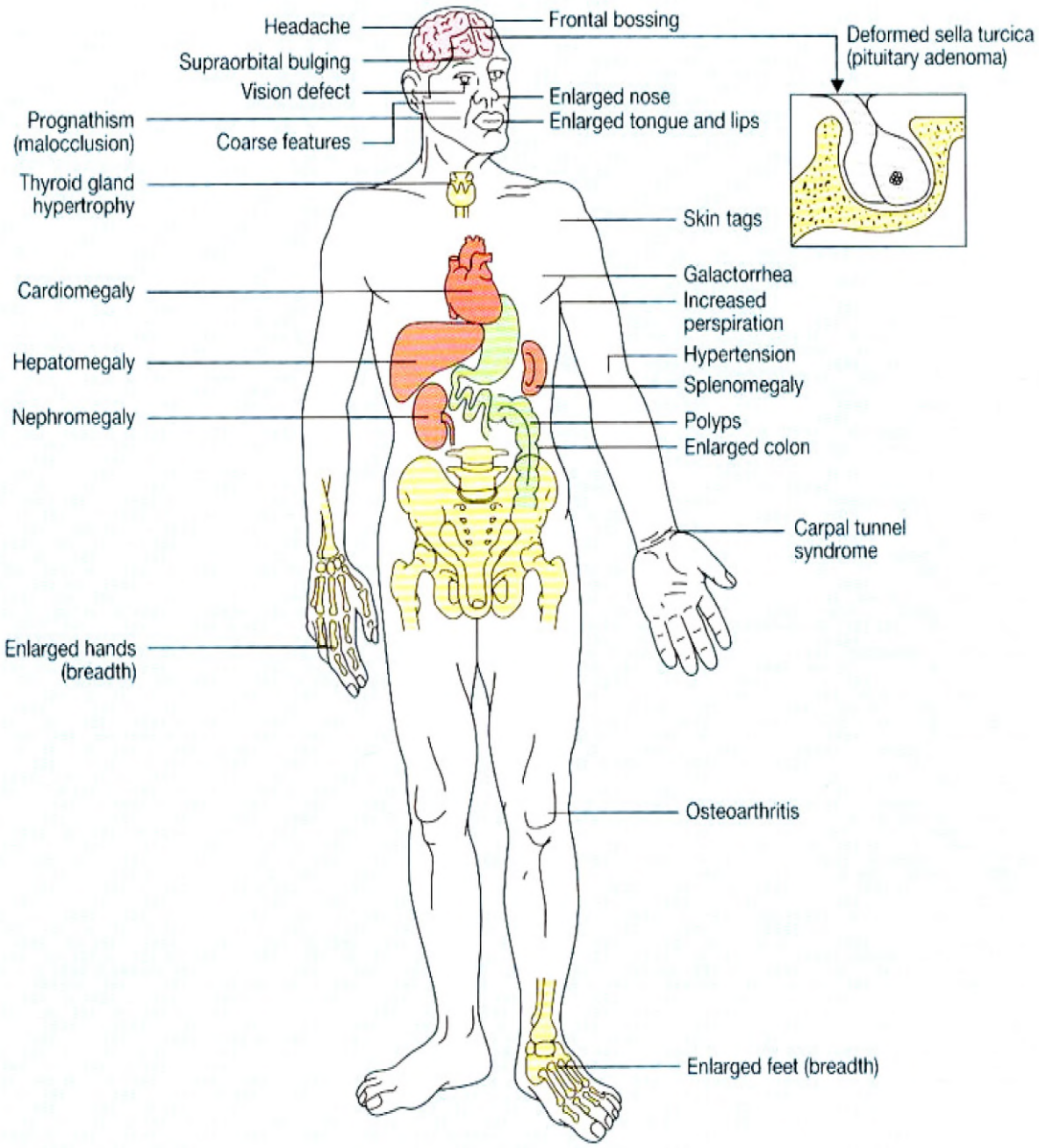

Figure 1: Co-morbidities in association with acromegaly (Adapted from Melmed 2003)

2.5 Diagnosing Acromegaly

Although many patients with acromegaly have changes in their outward appearance, the symptoms of complications are often the reasons for seeking medical care. Clinical signs, symptoms and complications will vary amongst patients due to factors such as age of onset, genetic susceptibility, tumour volume and rate of tumour growth. Once a patient is suspected of having acromegaly, earlier family photos can often be a good way to see for how long

the disease has pre-existed. The suspicion can then be confirmed with biochemical evaluations of GH.

The classic, definitive diagnostic test for acromegaly is the measurement of GH under conditions when it is normally suppressed. In healthy people, ingestion of glucose suppresses blood GH, while in patients with overproduction of GH, this suppression does not occur. The current Oral Glucose Tolerance Test (OGTT) criterion, which uses highly sensitive and specific immunoassays, is the failure of GH to fall (after ingestion of 100g glucose) to 0.3 micrograms/L. This OGTT readout together with elevated Serum IGF-I levels is confirmatory of acromegaly (Freda, 2003).

The following considerations are needed for these tests. OGTT for example, may not be useful in patients with Diabetes Mellitus as they do not demonstrate suppression of GH in response to an oral glucose load (Carmichael, 2009). Hence, serum IGF-I becomes the only remaining available biochemical diagnosis. IGF-I levels on the other hand are influenced by age and gender hence the values need to be interpreted with reference population matched with the age and gender.

Once biochemical evaluation is completed and acromegaly confirmed, then locating the pituitary tumour responsible for the GH overproduction with Magnetic Resonance Imaging (MRI) is the next step (Katznelson, 2011). The information gathered also allows the surgeon to evaluate to what degree tumour tissue has extended into the cavernous sinus and other structures.

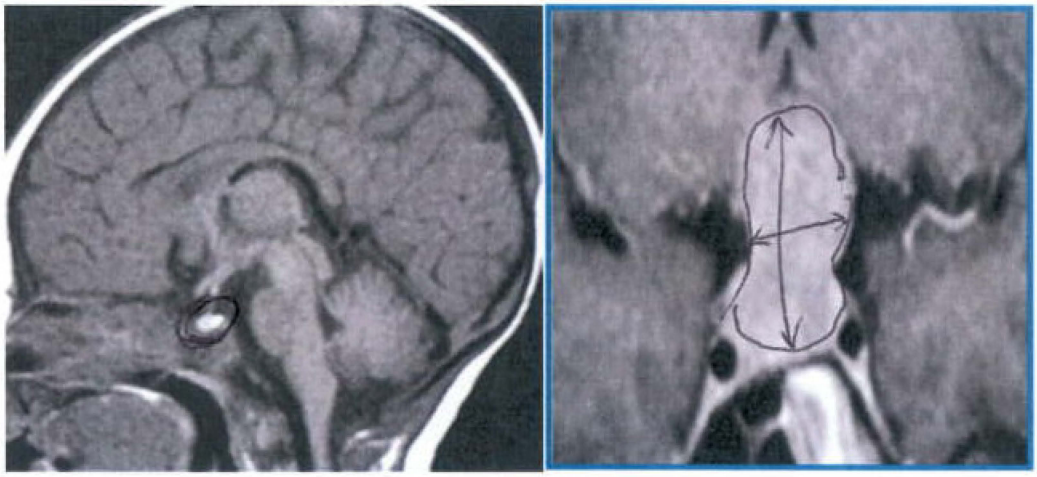

Figure 2: Showing location and appearance of a normal pituitary MRI on the left and a magnified macroadenoma on the right (courtesy of Dr. Evanson, Barts NHS Trust)

Visual field examination and testing for other pituitary functions, echocardiography, colonoscopy and sleep study (to diagnose sleep apnea) would all provide additional value to the confirmation of diagnosis together with severity of co-morbidities and hence an integrated approach to treatment management.

2.6 Managing Acromegaly

There are currently 3 main ways to manage acromegaly and these are used alone or in combination.

2.6.1 *Surgery*

There are two types of surgical approaches used remove the pituitary adenoma. The most common method is 'Transphenoidal' surgery where the sphenoid sinus is reached via incisions made in the nose and behind the lip. The floor of the sella turcica and dura mater are then opened to expose the pituitary. An endoscope may be used to provide a panoramic view of the sphenoid sinus which allows better visibility of resection of adenoma.

‘Craniotomy’ is reserved for patients with pituitary tumours extending far above the sella borders. It involves opening the skull and moving the brain to access the pituitary area. Craniotomy is rarely done as it is traumatic and difficult to perform due to the major ossification of the frontal bone and large frontal sinuses in trying to access the adenoma in addition to longer recovery time as compared to transphenoidal surgery.

There are various factors which can influence surgical success and hence the variability in surgical cure rates at different centres:

- The skill and experience of the surgeon: For example, centres which are known as ‘centres of excellence’ or ‘reference centres’ may perform a high number of pituitary operations increasing the experience of the surgeon, centre and likelihood of positive outcome (Melmed, 2009)
- Type of pituitary adenoma: A much higher remission rate is observed with microadenomas when compared with macroadenomas. In addition, the size, position and invasion into the supersellar space and/or cavernous sinus can also affect the surgical outcome (Melmed, 2009)
- Criteria used to define biochemical cure – the surgical outcome will of course depend on what criteria is applied in regards to GH and IGF-I levels required
- Length of patient follow up – while soon after surgery the patient may show full biochemical cure, the disease can reappear much later either through a recurrent adenoma or due to the incomplete removal of the original adenoma. Therefore post-surgical patients need to be monitored for at least 2 years to confirm full biochemical cure and hence surgical success.

2.6.2 *Radiotherapy*

Radiotherapy (RT) is often used due to failure of surgery and or medical therapy(ies). In recent years, stereotactic radiation (using computer assisted techniques allowing 3D imaging), the most common of which is the Gamma Knife, has been making progress towards replacing the conventional fractionated radiation which has the risk of not targeting with precision the area of interest and hence can affect surrounding areas of the brain. Stereotactic radiation offers the advantage of a focused dose delivered to a limited area in a single session whereas fractionated radiation is delivered through each temple and the frontal area, exposing more areas of the brain to radiation and is given repeatedly over a six week period. Transphenoidal surgery failures account for about 40-50% patients requiring secondary forms of therapy such as RT or medical therapy(ies) (Gonzalez, 2010). RT while being a reasonably efficacious and cost effective intervention, has several drawbacks in relation to the adverse effects it can have including radiation induced hypopituitarism, radiation damage to neural structures and vascular consequences. Hence, RT should be utilised using a tailored approach taking into account benefit vs. risk on a patient by patient basis.

2.6.3 *Medical Therapies*

2.6.3.1 Dopamine Agonists (DAs)

Dopamine receptors are expressed by mixed prolactin / GH-secreting tumours as well as the majority of pure GH secreting tumours (Saveanu, 2008). Until the 1980's, DAs had been the sole medical therapy used to treat acromegaly for several decades. DAs bind to pituitary domain type 2 receptors (D2) and suppress GH action through mechanisms that remain unclear. Use of Bromocriptine which was the first available DA therapy for treatment of acromegaly was relatively ineffective as a monotherapy, normalising IGF-I in only 10% of patients despite some improvement of symptoms including reduced perspiration, decreased soft-tissue swelling and improved fatigue and headache. The newer DA, Cabergoline, has achieved higher response rates in a specific subset of patients with normalisation of IGF-I in 20-33% of patients (Sandret, 2011) although it's product label is not indicated for use in

acromegaly. Both DAs are taken orally which may be appealing for patients preferring or requiring oral medication. Hence DAs can be considered in patients who require treatment in addition to surgery or RTs in select patients with moderate elevations in IGF-I.

2.6.3.2 Somatostatin Analogues (SSAs)

SSAs are synthetic forms of somatostatin, a naturally occurring central (brain) and peripheral hormone which binds to pituitary somatostatin receptors and suppresses GH release. Over 90% of somatotroph (GH-secreting) adenomas express somatostatin receptor subtype-2 (SSTR2) and SSTR5 to which currently approved SSAs, Octreotide and Lanreotide selectively bind. Octreotide Long Acting Release (LAR) (Octreotide SPc), available as an intramuscular injection which can be administered every 4 weeks is a long acting octapeptide which mimics the pharmacological actions of somatostatin and suppresses GH production. Octreotide is indicated for patients who have had inadequate response to or cannot be treated with surgical resection or pituitary radiation of the tumour (Octreotide SPc). Lanreotide autogel (ATG) is given by deep subcutaneous injection every 4, 6 or 8 weeks and follows the same mode of action to that of Octreotide (Lanreotide SPc). These SSAs exert their maximum effect on GH levels after 3–6 months with an efficacy rate of up to 50% and IGF-I levels by 6–12 months to normal ranges in 50-60% of patients. The therapeutic advantage of SSAs is having the dual actions of both biochemical improvement with reduction in both GH and IGF-I and some tumour shrinkage (significant shrinkage categorised as >20% which is achieved in 75% of patients) (Mercado, 2007). The disadvantages of SSAs are the disappointing efficacy rates as mentioned above making it unsuitable for all patients. Side effects include common biliary disorders and GI effects and the deep subcutaneous injections which are painful and require a clinic visit. Although some trials have investigated the possibility of cessation of long term therapy, based on the current available evidence, SSA therapy needs to be continued indefinitely unless patients received irradiation in which case biochemical control may be achieved. A systematic review conducted by

Shanik et al (2016) showed that the efficacy rates of first generation SSAs have been lower than previously thought at approximately 30%.

Since 2016, a newer SSA, Pasireotide (Signifor®) has been available in Europe to treat acromegaly patients who are resistant to either of first generation SSAs (Pasireotide SPc). In a large randomized study in 358 medically naïve acromegalic patients of whom the majority had undergone previous pituitary surgery, patients received either Octreotide LAR or Pasireotide LAR. After 12 months of treatment with either 20 or 30 mg Octreotide LAR and 40 or 60 mg Pasireotide, IGF-I levels were normalized in 23.6 and 38.6% and GH levels in 51.6 and 48.3%, respectively (Colao, 2014). Dose up-titration was used in 50% of the patients on Pasireotide and in 68% of the Octreotide LAR group. When both criteria were used, 31% of the patients on Pasireotide were controlled in contrast to 19.2% of the patients on Octreotide LAR, and the difference was significant. The cure rate in the octreotide arm in this study is clearly lower than that generally reported for patients who had previous surgery. In addition, Pasireotide from trials to date seems to show diabetogenic effects in both diabetic and non-diabetic patients which is a drawback.

2.6.3.3 Growth Hormone Receptor Antagonist (GHRA)

Pegvisomant is the first and currently the only GHRA available indicated for treatment of acromegaly. It is an analogue of human GH that has been structurally altered to act as a GH receptor antagonist. It is given subcutaneously as a daily injection. Pegvisomant binds to GH receptors on cell surfaces where it blocks the binding of endogenous GH. As a result it interferes with GH signal transduction and subsequent IGF-I production. The GH molecule has 2 distinct domains (binding sites 1 and 2) that bind to 2 GH receptors at the cell surface. This interaction, called dimerisation of the receptor, triggers transmission of the GH signal to the cell. With Pegvisomant, this dimerisation does not take place (Pegvisomant SPc). Figure 3 outlines in summary the sites of action for the various treatment modalities discussed so far (Chanson, 2008).

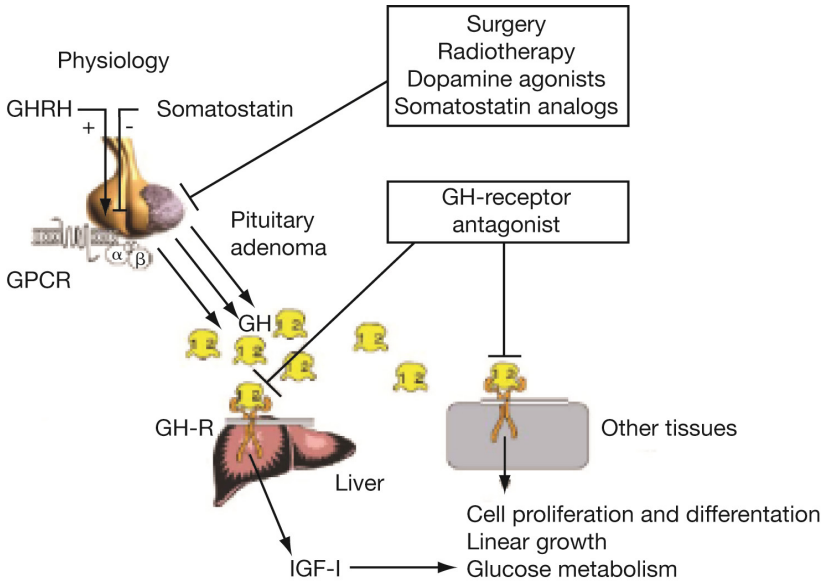

Figure 3: Mechanism of action of acromegaly treatments (Chanson, 2008)

Initial studies with daily Pegvisomant monotherapy reported normalisation of IGF-I in 89–97% of cases (van der Lely, 2001). While the treatment lowers IGF-I, due to its mode of action pegvisomant does not decrease GH levels, IGF-I is the only biochemical marker which can be reliably monitored and used clinically. In addition, because Pegvisomant acts peripherally on GH receptors, it does not have tumour shrinkage effects when compared to SSAs. ACROSTUDY which is a post approval safety surveillance study has reported recently of a tumour volume increase over a 5 year period (defined as an increase of 3mm in diameter or an increase in volume by 20% which is clinically significant) in 3.2% of patients which is comparable to reports in initial clinical trials and when compared with tumour volume increase under SSA therapy (Van der Lely, 2012). Pegvisomant seems to offer improvement in glycaemic control (Parkinson, 2002; Drake, 2003; Rose, 2002) which is a benefit when compared with SSAs. Use of Pegvisomant has shown deterioration of liver function as measured by liver function tests in 2.5% of ACROSTUDY patients. While the mechanism is unknown, it may be associated with genetic polymorphisms of Gilbert's Syndrome which is a genetic liver disorder which may have pre-existed in those patients as opposed to treatment related effect by Pegvisomant (Bernabeu, 2010).

In summary, the last 30 years have seen tremendous advances in surgical cure rates, innovation in delivering radiotherapy and the availability of medical options with dopamine agonists, SSAs and GHRA for the treatment of acromegaly. However, as discussed already, in a significant number of patients the disease remains inadequately controlled. While we await further advances in treatment options, optimising the existing treatment options through a holistic approach in acromegaly care could lead to minimising uncontrolled patients.

CHAPTER 3

Section 3: Addressing the Current Gap in Knowledge

Acromegaly has many disease components (as previously discussed in section 2.4) all of which are interrelated or is associated in context of severity and clinical presentation of acromegaly.

Figure 4 below shows the Melmed (2009) treatment guidelines which has been the most widely referenced although there has been several updates since then (Guistina, 2010; Katznelson, 2011, Guistina, 2013; Melmed 2013; Guistina, 2014). Melmed's 2009 guidelines follow a stepwise approach for achieving disease control however does not specify all the disease parameters which could be utilized.

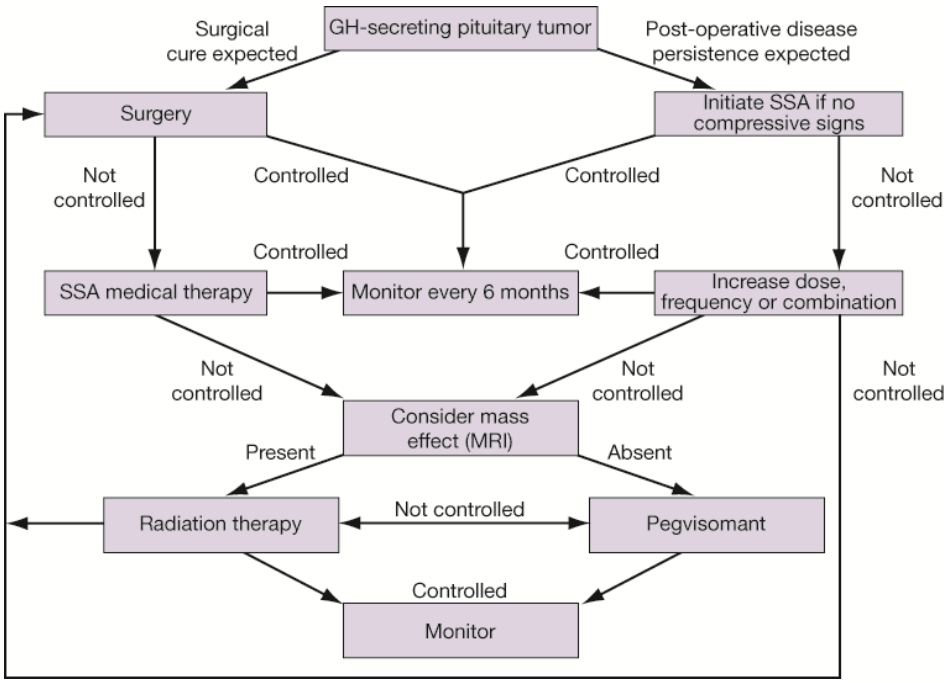

Figure 4: Acromegaly Treatment Guidelines (Melmed, 2009)

Despite variations in annual updates before and since Melmed (2009), surgery remains the first step followed by medical treatments. In addition, radiotherapy is utilized where appropriate or in countries where there are limitations to reimbursement for some medical treatments.

Acromegaly is a complex disease and treatment management of patients' needs to be multifaceted in order to address disease control, effective management of co-morbidities and improvement in quality of life. When reviewing the treatment goals

and guidelines in context of treatment options currently available, individualising treatment plays a big role if therapy(ies) are to be fully effective. Although national and international guidelines are available, there is significant variability in how acromegaly patients are treated across Europe and globally (Schofl, 2013). While other factors come in to play such as access to certain medications or access to good healthcare, patients' understanding of the disease and compliance to medication and time constraints related to evaluating patient status, a reference mechanism which helps the treating physician to take a holistic view of all the key components of disease activity when forming a treatment management plan could revolutionise acromegaly care. This would also help inform the PM and IT approach which could then potentially improve patient treatment outcome, provide cost savings as well as decreasing variability in treating this rare disease.

Burton et al (2013) demonstrated that acromegaly was associated with high rates of hypertension and diabetes along with a number of other comorbidities. They observed that the incidence of comorbidities was highest among patients with acromegaly-related treatment, which may have resulted, in part, from inadequate disease management and/or poor disease control. Unexpectedly, 55% of patients identified with acromegaly received no treatment for acromegaly (i.e., surgery, radiotherapy, and medication) and only 28% received a medication treatment during the observation period. However, some patients may have received a curative surgery prior to the observation period, which may have reduced the use of other acromegaly-related treatments during the study period. Given the high incidence of serious comorbidities associated with active acromegaly, earlier diagnosis and treatment, along with appropriate follow-up care, may potentially avoid the life-long consequences of uncontrolled disease.

A study by Geraedts et al (2015) clearly demonstrated that patients with pituitary adenomas showed decreased quality of life and sleep as well as increased rates of depression when compared to their matched control subjects. The study also showed that in those patients suffering from reduced quality of life, a substantial proportion was due to the incidence of depression and reduced sleep quality. Despite this, there are no current standard protocols or disease specific tool to address such medical need and to integrate this with the earlier discussed parameters of tumour or biochemical activity.

In summary, the gaps in knowledge through the exploration of such a disease activity tool could address:

- Translating international guidelines to disease management for an individual patient
- Provide a standardised approach to clinical management to enable a consistent monitoring and follow up of all patients including assessment of symptoms and QoL which in turn allows for the individualisation of clinical care
- Support monitoring of patient's progress or deterioration at suitable intervals
- Encouraging a patient centred consultation approach
- Offer potential cost savings in making decisions earlier on effective treatment regimens
- And mostly, increase the controlled patients from the current rates to a higher rate

3.1 Impact on Patient Management

The aim of this doctoral thesis was to develop and validate a tool which will follow the personalised medicine concept and enable measurement of disease activity in acromegaly patients within endocrinology departments around the world can utilise to evaluate a patient's clinical status based on a given set of disease parameters. This in turn can be used in making the right treatment decisions for a given patient with a view to improving treatment outcomes and potentially saving costs in treatment management long term.

The thesis has many potential benefits in its clinical application. Taking a complex disease such as acromegaly and building a model which tries to encapsulate all the components without making it cumbersome to use could enable an endocrinologist to make the right decision with regards to effectiveness of the current treatment management plans. This could potentially improve treatment outcomes, save costs and pave the way for other diseases to follow such a PM approach. Improving outcome and value of PM has already been discussed while the economic impact is difficult to estimate mainly because the disease has no clear limits with many

permutations related to its complications. The disease is characterised by insidious, seemingly unrelated symptoms, overlaid with severe hidden complications before diagnosis is established (Knutzen, 2006).

3.2 Treatment Costs

When assessing the economic burden of acromegaly disease, it is important to consider the costs associated with untreated disease, treated but uncontrolled disease and controlled disease. The time to acromegaly diagnosis from initial onset of symptoms is reported as approximately 10 years for many patients. During this time, many patients will have been treated for a number of conditions, perceived as being unrelated to acromegaly. The cost of care and treatment in this period cannot be fully calculated, however they significantly contribute to the financial burden of acromegaly.

A recent literature search identified several studies investigating the costs associated with acromegaly disease and its co-morbidities. No high quality studies were identified that specifically assessed costs of controlled versus uncontrolled disease (Ben-Shlomo, 2011). In addition, not all studies identified included costs of treatment for the co-morbidities related to uncontrolled acromegaly.

The cost of care of patients prior to diagnosis of acromegaly was calculated and published in conjunction with The Pituitary Network (Knutzen, 2006); however the study contained no indication as to how costs were calculated. It was determined that the average annual cost of acromegaly prior to diagnosis (due to treatment for comorbidities) was US$ 28,025 per patient, which, when multiplied over the average time to diagnosis (9.79 years), gives a total average cost before diagnosis of US$ 274,364.75. Therefore, while this estimate may not be accurate, it can be extrapolated that earlier diagnosis and treatment as well as achieving full disease control could lead to significant cost savings.

3.3 Examples of PM approaches in acromegaly to date

There are limited examples when it comes to successfully implemented methodology of PM and IT in acromegaly. Jessica Brzana and co-workers (2013) assessed characteristic features of individual growth hormone (GH)-secreting adenomas at diagnosis, correlated with SSA sensitivity, using defined tumor markers. A retrospective review of 86 consecutive acromegaly surgeries (70 patients) were performed between January 2006 and December 2011. Response to SSA therapy was defined as normalization of IGF-I and random GH of 1.0 ng/ dL and immuno-histochemical staining pattern were categorized as: sparsely granulated or densely granulated adenomas, mixed growth hormone-prolactin (GH / PRL) and SSRT2 positivity were correlated with clinic-pathologic features, adenoma recurrence, and SSA treatment response. Based on pre-surgery adenoma imaging dimensions, 81% were macro-adenomas and average maximum tumor diameter was 18.1 ± 9.9 mm. Patients on SSAs were followed for 13.4 ± 15.8 (mean ± SD) months. Sparsely granulated adenomas were significantly larger at diagnosis, exhibited lower SSTR2 positivity and had a lower rate of biochemical normalization to SSAs. Densely granulated adenomas were highly responsive to SSAs. Overall, patients with SSTR2A+ adenomas responded more favorably to SSA treatment than those with SSTR2A- adenomas. Eighty-one percent of patients with SSTR2A+ adenomas were biochemically controlled (both GH and IGF-I) on SSA treatment, i.e. a much higher normalization rate than that reported in the unselected acromegaly population (20–30%). Detailed knowledge of adenoma GH granularity and the immune-histochemical SSTR2A status is a predictor of SSA response. Fleseriu et al (2013) concluded that these immuno-reactive markers should be assessed routinely on surgical specimens to assess subsequent SSA responsiveness and potential need for adjunctive therapy after surgery. Kiseljak-Vassiliades and co-workers (2015) confirmed these findings 2 years later that densely granulated adenomas showed a higher rate of remission as opposed to sparsely granulated adenomas. Furthermore, where remission was limiting, addition of a second medical treatment, such as pegvisomant, biochemical control could be further improved. While these are well conducted

studies providing encouraging results for PM, there are several limitations. Firstly, the disease control evaluation is limited to the biochemical measurements and not wider to include other parameters. Secondly, the focus is primarily on one class of medical treatment and its response and so may not be applied to all acromegaly patients status of disease.

Cuevas-Ramos et al (2015) conducted a retrospective study using clinical, radiological, and histopathological characteristics to classify three acromegaly types distinguished by 1) tumor aggressiveness and treatment responsiveness, 2) expression profile of somatotroph surface receptors and markers of cell senescence, and 3) disease outcomes. They concluded that after validation, such a classification may be useful to accurately identify acromegaly patients with distinctive patterns of disease aggressiveness and outcome. This classification approach is somewhat helpful but for disease activity monitoring, the concept will need to be explored further for its attractiveness to routine clinical practice. In addition, the patient perspective is excluded in disease stage classification and as a consequence a potential risk in the appeal of the tool in being holistic in its approach.

Guitelman et al (2014) through exploring a case study of an acromegaly patient demonstrated the typical Latin American scenario which is also the case in many developing nations, that patients with active acromegaly who are uncontrolled by surgery and limited by other therapeutic options can suffer a premature, sudden death. For these uncontrolled patients as well as those in remission, attention to QoL issues is highly recommended. Furthermore, the best balance of efficacy, cost and QoL will likely be achieved with an individualized approach to therapy, based on available pharmacological, surgical and radio therapeutic resources. While this is appreciated by the endocrine community, practicalities of implementing a PM approach in acromegaly is a daunting task.

The definition of normal values, that is, criteria for control, remains a challenge, and adequately suppressed GH/IGF-I assessed by biochemical means may not reflect abolished GH excess and true normalization of GH and IGF-I concentrations, for a number of reasons. Firstly, normal growth hormone

values are assay dependent. Secondly, normal IGF-I values are age and sex dependent, and there is probably variation in individual GH receptor sensitivity. Thirdly, serum values may not reflect tissue hormone levels. Fourthly, there are treatment-specific issues, such as altered GH pulsatility during treatment with long-acting SSAs and the limitation that only IGF-I, not GH, can be used as a reliable marker during pegvisomant treatment. Therefore, there is a need for a bioassay that reliably assesses disease activity. To date, it has not been possible to identify a reliable sign/symptom (score)/biochemical marker with good test characteristics that reflects disease activity. A new biochemical parameter that can assess tissue-specific disease activity is necessary, but not available (van der Lely, 2012).

Brzana et al (2013) investigated the utility of a fracture risk assessment tool (FRAX®, World Health Organization Collaborating Centre for Metabolic Bone Diseases, University of Sheffield, UK) to investigate the prevalence of vertebral fractures (VFs) risk in acromegaly patients as well as FRAX's ability predict VF. The study concluded that patients with acromegaly are at greater risk of VFs than the general population and that VFs are underdiagnosed. Despite significant expansion of the use of FRAX in osteoporosis, they demonstrated that the risk of VFs in acromegaly should not be based on a FRAX calculation alone. This study is helpful in showing 2 aspects in regards to PM approaches in acromegaly: Firstly, the limitation of a standard tool which has not been tailored to disease specific needs and secondly such tools when available tend to focus on one aspect of the disease (in this case VFs) rather than taking the holistic approach especially for a complex disease area such as acromegaly.

CHAPTER 4

Section 4: Methodology

The first step in the journey of PM for acromegaly management was to determine whether there was a need in the endocrine clinical practice for measuring disease activity in a holistic manner. Part of that survey would also explore how patients are currently managed in terms of treatment and follow up. Once this was established, assuming there is a need for the PM approach, then summarising the key aspects of the disease and their relative importance to other factors influencing disease activity could help with distilling disease activity through an expert panel. This would then need to be tested through a validation study to see how these key disease indicators would be viewed in its importance with experienced acromegaly treaters.

4.1 Conduct of a survey to identify the need for a disease activity measurement tool and to gauge level of interest and utility of ACRODAT

While diagnosis and treatment of acromegaly presents a challenge for endocrinologists in general, it was necessary to confirm whether providing a software medical device would support them in their clinical practice. Hence the first step of developing ACRODAT was to assess the need for such a tool. A survey was undertaken to gather insights in identifying the current challenges in managing acromegaly patient across Europe. The survey guide can be found in Appendix A. The objectives of the survey were to:

- Understand to what extent lack of control of the disease is perceived as a problem for the clinicians
- Understand how they manage acromegaly patients and level of control
  - How long does it take to achieve control?
  - How difficult is it to achieve control?
- Identify / test the benefits of ACRODAT for the clinicians
- Assess the extent to which ACRODAT is seen to address the challenges and problems faced by physicians

- Evaluate usage of ACRODAT in practice

The 2 main insights anticipated from the survey were:

- Do ‘non-expert endocrinologists’ recognise that a significant proportion of acromegaly patients are not controlled?
- Would ‘non-expert endocrinologists' value the benefits of ACRODAT sufficiently to use this software to help in the management of disease for a significant number of their patients?

The survey was conducted by phone in a 50 minute interview and included endocrinologists from France, Spain and Italy (4 per country). The full survey guide including screening script is included in Appendix B. Ethics committee approval was sought and granted from CHUREC at Cranfield University (submission included in Appendix A).

4.2 Identification of key parameters:

A panel of 10 Key Opinion Leaders (KOLs) in the field of endocrinology, neurosurgery and acromegaly management was convened to determine the appropriate health status parameters and scoring algorithm for ACRODAT development (van der Lely, 2017). The KOLs were selected based on their publication record and their active contribution to acromegaly treatment guidelines and consensus workshops. Given the needs of the exercise whereby additional expertise on both QoL and neurosurgery were needed, 2 individuals were selected to represent these areas (Dr. Buchfelder for Neurosurgery and Dr. Xavier Badia for QoL tool derivation). In order to maximise European representation, one KOL was selected per country. After formation of the expert panel, the members were asked to map all disease parameters associated with acromegaly. The combined list was then refined based on criteria related to their importance in enabling monitoring of disease activity, what would be readily available as part of routine clinical practice, their relevance to health status focusing on the clinical as well as patient's perspective, and the ability of these chosen parameters to be influenced by appropriate clinical action. The additional consideration was that the number of variables selected needed to be easily accessible from routine clinical practice as well as ensuring that the resulting tool would be user friendly and relatively acceptable as far as data entry burden is concerned. The panel members were then asked to define cut-off points and categorize each individual parameter into 3 levels of severity (level 1: the patient is adequately controlled; level 2: the patient shows mild disease activity, further evaluation of the patient's condition is needed; level 3: the patient shows significant disease activity requiring clinical action).

4.3 Validation study:

The next step in the development of ACRODAT was to evaluate the validity of the 5 selected key parameters and their impact on the severity of the disease in a separate cohort of endocrinologists who routinely manage acromegaly patients in their clinical practice (van der Lely, 2017). The validation study had 2 main objectives: 1) to assess the inter-rater agreement of disease activity

status among practicing endocrinologists and 2) to observe the level of agreement between the expert panel and the routinely practicing endocrinologists on the importance of the 5 critical disease parameters and their levels of severity to determine the overall disease activity status, in a set of hypothetical patient scenarios. Both objectives were important to establish how patients are routinely managed in clinics across Europe. A high variability would illustrate a wide spectrum of approach both in terms of acromegaly management as well as how important the validation study participants viewed these key parameters to be. Invitation letter for participants to the validation study and screening questionnaire are shown in Appendix D & E respectively.

For each scenario (hypothetical patient case), the physician was asked whether the patient described by the profile was Stable (S: the patient is adequately controlled); had Mild Disease Activity (M-DA: the patient shows mild disease activity, further evaluation of the patient's condition is needed); or Significant Disease Activity (S-DA: the patient shows significant disease activity requiring clinical action). The 3 disease activity categories were color-coded as Green (S), Yellow (M-DA), or Red (S-DA). Figure 5 shows a sample scenario from the online validation as seen by the participants:

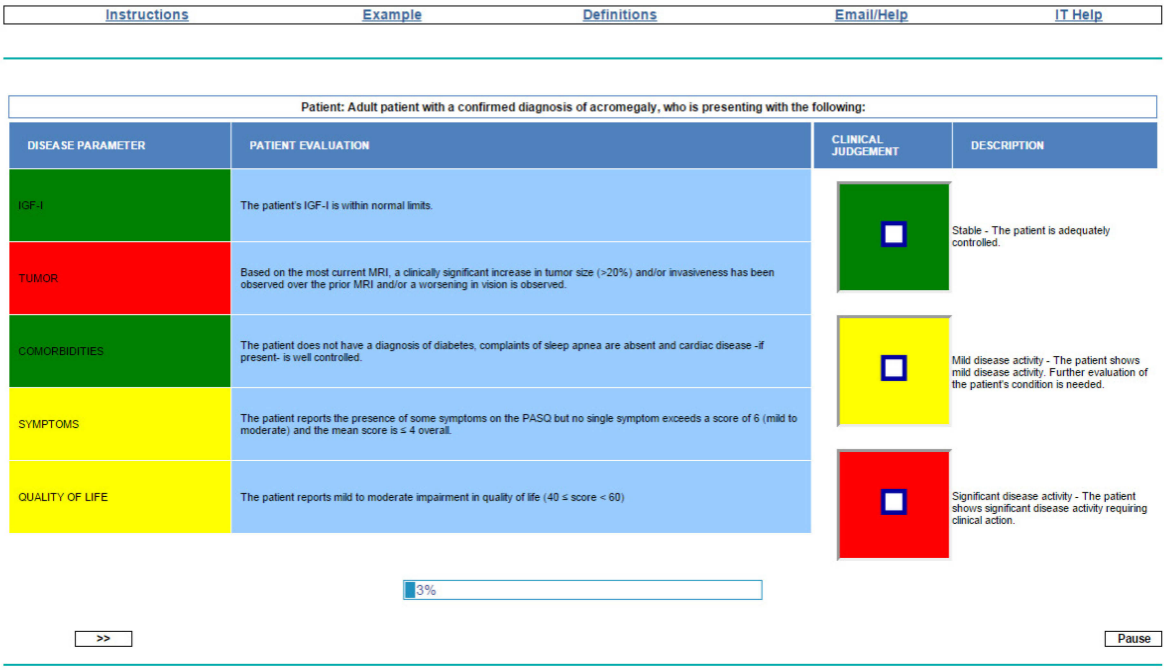

Figure 5: Sample scenario of the validation study

The 5 parameters, and 3 levels within each parameter, produced a total of 243 hypothetical patient profiles or scenarios (Appendix C). Though some scenarios may have reflected a patient profile that would be unlikely to be seen in clinical practice, the expert panel recommended including all possible scenarios for completeness and to avoid making any assumptions about the feasibility of the scenarios. It was estimated by the expert panel that it would take each endocrinologist approximately an hour to rate a total of 52 scenarios, so the number of possible scenarios to be rated was set at 52. The study was designed to ensure sufficient variation and coverage of health parameters in the scenarios by using a random selection approach. In addition, a pre-defined subset of scenarios was presented to all participants to allow for examination of inter-rater agreement. The 10 “common” scenarios were selected by the expert panel and included clinically plausible scenarios representing a wide range of overall health statuses from fairly good health to very poor health. These scenarios were selected by the advisory board and were interspersed in a random order within the first 26 scenarios presented to each physician. The remaining (“non-common”) scenarios were selected

randomly from the pool of remaining scenarios with the constraint that all scenarios would be asked at least once to at least one participating physician.

In the survey, each parameter was color coded according to the level of severity (green for level 1; yellow for level 2; red for level 3) as an easy reminder for the rater as to the defined differences in level and to reduce random error. A summary page was included at the end of the survey to allow physicians to review all of their response and go back if they wanted to change an answer.

4.3.1 Selection of participants

Endocrinologists had to meet the following criteria to be eligible for the study: (1) worked in a hospital, hospital outpatient clinic, or private outpatient clinic; (2) saw at least 5 acromegaly patients annually or, if less, supervise others who treat acromegaly patients (3) was not familiar with ACRODAT or has not been involved in extensive development activities for ACRODAT prior to this study (4) was able to read and understand English (5) was willing and able to participate in the study, which involved completing an online survey lasting approximately 60 minutes.

After providing agreement to participate in the study, physicians were emailed a link to complete the online survey. Participants were compensated for their time (2 hours based on national fair market value rates, to include familiarising with the instructions of the online survey and the key parameter and severity definitions) in completing the survey (van der Lely, 2017).

4.3.2 Sample Size

Due to the exploratory nature of this study, formal sample size calculations were not considered appropriate. Nevertheless, in studies where multivariable modelling is expected to be performed, the study should have at least 10 events for each variable included in the model (Hosmer, 2013). In this study, predictor variables comprised the 5 health status parameters, each of which was a 3 -level ordinal variable. For each health status parameter, indicator variables were created for all but one of the levels (the referent level S

(stable) was not coded because it is a linear combination of the other levels). Therefore, the multivariable model would have 10 variables.

Furthermore an “event” can be defined as the physician categorization of a hypothetical patient as S (or having M-DA, or having S-DA). An assumption (based on Van der Lely, 2012) was made that an “event” would occur in roughly 1/3 of the patients (i.e., roughly 1/3 of the hypothetical patients would be categorized into each of the 3 possible outcomes), which meant that the study would require a minimum of 300 independent observations (10 events x 10 variables / (1/3)). Since the same physician was expected to evaluate many different scenarios, observations in the dataset were not independent, causing some statistical power to be lost. As an attempt to adjust for this potential loss in statistical power, the number of observations was doubled, resulting in a dataset with a minimum of 600 observations. Given that 21 physicians were available to evaluate the scenarios, the study required each physician to evaluate roughly 29 scenarios (600/21) at a minimum.

4.3.3 Statistical Analyses

Survey results were analyzed in SAS 9.3. (van der Lely, 2017). The Fleiss’ kappa was calculated to provide a summary statistical measure for assessing the reliability of agreement between endocrinologists in rating the common scenarios. For algorithm development to predict disease activity categorization based on values of the five health status parameters, both Classification And Regression Tree (CART) methods and multivariable logistic regression methods were implemented (Breiman 1984; Hosmer 2013). Full details including the study protocol for the validation exercise is shown in Appendix C.

CHAPTER 5

Section 5: Results

5.1 Summary of survey research findings to gauge level of interest and utility of ACRODAT

There appeared to be no significant differences between the opinions of the 12 participants across the three countries (France, Italy and Spain). Where cure is not possible, physicians aim to control patient's IGF-I / GH to improve symptoms. Key goals in acromegaly were identified as:

- Early diagnosis
  - The earlier the diagnosis the greater the chance of cure or good control through drug therapies
- Complete cure though surgery
  - Reduce tumour mass through surgery
- Control hormone excess (IGF-1 / GH) and thus control symptoms
  - Treat patients to target
  - Manage comorbidities
- Thus improving quality of life

While it was acknowledged that managing acromegaly was challenging, respondents claimed mostly to have succeeded in managing patients satisfactorily. Physicians were aware that some of their patients are uncontrolled but this was explained as good treatment options being in short supply. Being unsure when to intervene, plus a lack of satisfaction with therapy options, were viewed as delaying the next therapeutic step. Few physicians recognised any tendency in themselves to being conservative with acromegaly treatment or think that they delay progressing therapeutic steps. Several reasons were suggested as to why therapeutic progression may stall. These were as follows:

- Slowly evolving disease means it is sometimes difficult to know when to intervene
- Guidelines are flexible and may not be precise enough to indicate when to modify treatment

- Lack of satisfaction with current treatment options
  - Not all patients respond to available therapies
  - Not enough options
- Apprehension about the next step
  - If patient doesn’t respond to ‘last resort' drug, what next?
- Concern about impacting QoL with new therapy
  - Less well tolerated?
  - May not respond?
  - May find regimen less convenient
- Physicians relied on biologic measures (IGF-I and GH) to monitor their patients. Frequency of consultations depended on physicians and how well patients are controlled.
  - On average, consultations occur every 3 - 6 months
  - Uncontrolled patients seen more frequently
  - Symptoms rarely used to monitor because they are seen as too variable

Figure 5 captures the order of priority focus in disease activity in the minds of treaters when it came to deciding on a treatment plan.

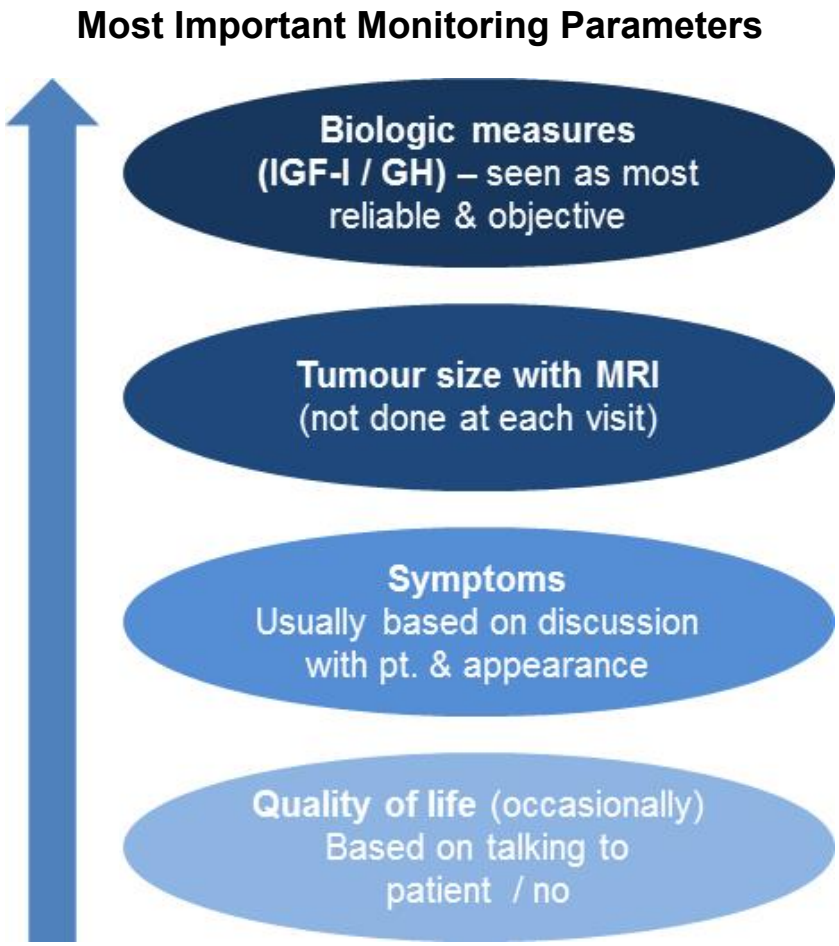

Figure 5: Showing the level of importance to parameters in acromegaly (arrow showing from least to most important)

This illustrates that QoL and symptoms are lower down in priority as compared to achieving biochemical control. Appendix L includes some of the survey response quotes.

Figure 6 Shows the extent of usefulness of ACRODAT as identified by the interviewed acromegaly treaters.

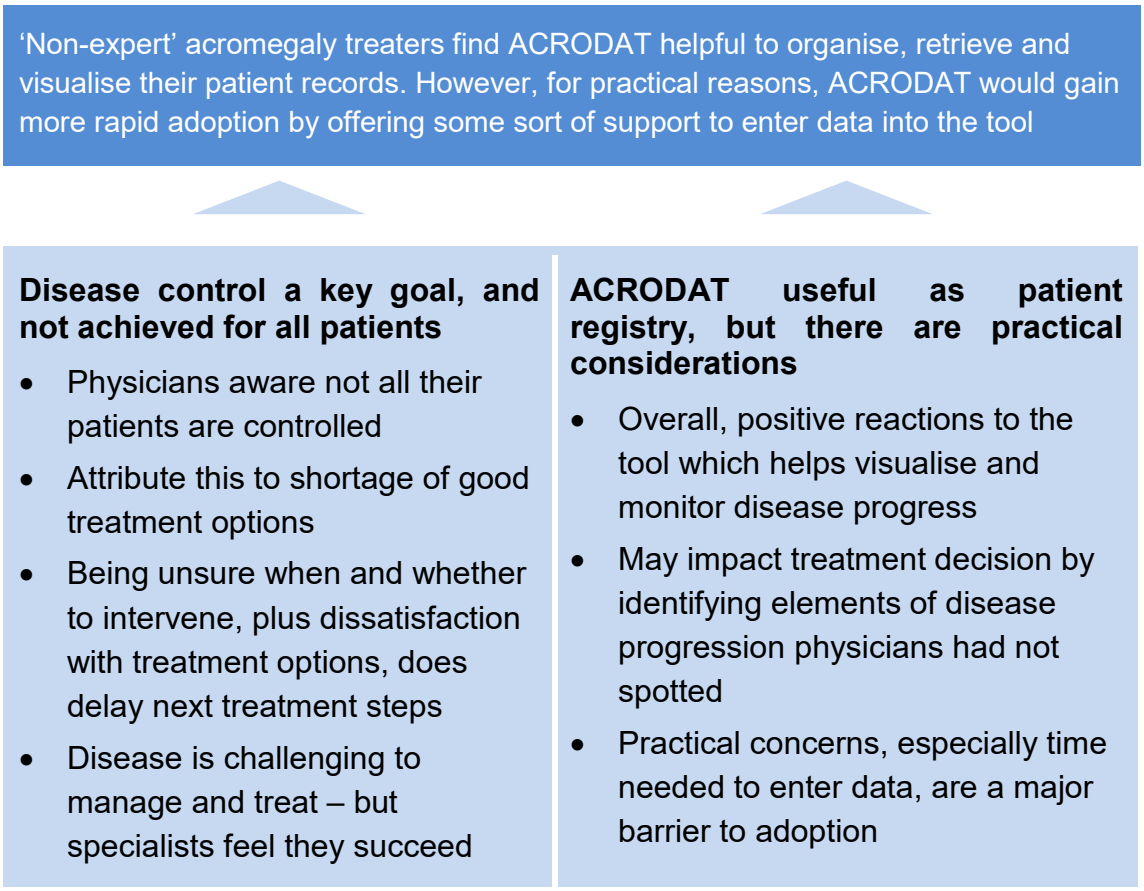

Figure 6: Summarising the qualitative research findings (examples of qualitative interview survey responses verbatim are captured in Appendix L)

When it came to survey questions re: ACRODAT, physicians saw ACRODAT as a means of organising, retrieving and visualising their patients' records. Please note that responses were based on subjective interpretation of ACRODAT prototype screenshots and not based on actual usage of the tool. In particular:

- Most physicians reacted positively to ACRODAT tool
  - On a scale from 1 (not at all) to 10 (very much), physicians gave an overall score of 8 on likelihood to use ACRODAT in practice
- Would be very practical, visual as patient registry
  - Good way to maintain and store patient records
  - Easy to use
  - Enables user to visualise patient details and disease progress

- Highlights all aspects of the patient, incl. QoL
- Standardises consultations: Same parameters for all patients facilitates inter-patient comparisons for disease activity monitoring
- Visual format means it can be useful during patient consultations
- May serve as reminder for certain tests, e.g., MRI scan

Half of the participants felt that ACRODAT will influence their treatment decisions while the remaining half saw the utilisation mainly to keep and manage patient details and acknowledged that it may help monitor patients generally. The findings reflect what physicians think will happen in the future, rather than ACRODAT's true impact on decision-making once launched. Those who felt that ACRODAT has the potential to influence treatment gave the following rationale that it:

- May help physicians catch details which they might otherwise have missed
- Tool gives physicians a more complete picture of each patient's disease stage
- Does not rely only on IGF-I
- Attitudes may well be affected positively by future publications and data showing benefits of ACRODAT

Practical considerations represented the main barrier to ACRODAT's adoption rate; both technical and practical. From a technical standpoint, accessing the internet in a public hospital right through to being a technophobe were rate limiting. On the practical side, data entry burden was feared as the main obstacle with some preferring a paper solution in daily clinic.

5.2 Output to define key parameters and levels of severity:

Five parameters were selected by the panel of acromegaly experts as key aspects of the patient's condition: IGF-I level; tumor status; comorbidities; signs and symptoms and health-related Quality of Life (HRQOL). The funnel approach used to crystallize these key parameters from a large set of disease parameters is illustrated in Table 1. Each parameter was defined and agreed upon by the panel at three levels of severity (see Table 2). The IGF-I levels were assigned using deviations from normal levels. The tumor status parameter was based on MRI results and levels were assigned based on change in size and invasiveness over time. The Comorbidities parameter was assigned levels based on the presence or absence and severity of several acromegaly specific conditions (i.e., diabetes, sleep apnea and cardiac disease). The Symptoms parameter was based on the Signs and Symptoms Score (SSS), a disease-specific tool that consists of five questions scoring 0-8, considering headache, perspiration, joint pain, fatigue, and soft tissue swelling. The maximum score of 40 is indicative of severe signs and symptoms (Rowles 2005). The HRQL Impairment parameter was based on the standardized total score from a validated measure of the AcroQoL. The measure was described in general terms and the interpretation of scores provided was based on three levels of impairment – none or minimal, moderate, and severe. The specific measure was not identified in the validation study to avoid response bias based on the clinician's familiarity with and perceptions of the utility of any single instrument (van der Lely, 2017).

5.3 Validation study:

A total of 21 physicians from Spain, Canada, the United Kingdom, Germany, Italy and France completed the validation study in 2015. The overall characteristics of the participants are summarized in Table 1 below. Fourteen out of 21 worked in a hospital outpatient clinic. On average, they reported having more than 20 years of experience in treating acromegaly and treating 48 patients with acromegaly annually.

Table 1: Characteristics of the participants in the validation study

Physician Characteristic	
Males, n (%)	14 (66.6)
Females, n (%)	7 (33.3)
Age, y	
Median (range)	51 (40–67)
Mean (SD)	51.8 (7.4)
Country of origin, n (%)	
Spain	7 (33.3)
Canada	6 (28.6)
United Kingdom	2 (9.5)
Italy	2 (9.5)
Germany	2 (9.5)
France	2 (9.5)
Unique acromegaly patients seen annually, n	
Median (range)	40 (5–140)
Mean (SD)	48.3 (34.3)
Location of treatment, n (%)	
Hospital outpatient clinic	14 (66.6)
Hospital	5 (23.8)
Private outpatient clinic	2 (9.5)
No. of years treating acromegaly patients	
Median (range)	20 (10–35)
Mean (SD)	21.2 (8.8)

SD standard deviation

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5.3.1 *Inter-Rater Agreement*

For the subset of scenarios that were presented to all participating physicians (common scenarios), inter-rater agreement was assessed. The extent to which physicians agreed on each scenario (represented by Pr in table 2) varied by scenario.

Table 2: Inter-rater agreement of common scenarios

Scenario	S*	M-DA*	S-DA*	Pr**
Scenario 1 [11111]	21	0	0	1.000
Scenario 5 [11122]	17	4	0	0.676
Scenario 11 [11212]	14	7	0	0.533
Scenario 59 [13122]	1	9	11	0.433
Scenario 92 [21212]	4	16	1	0.600
Scenario 122 [22222]	1	17	3	0.662
Scenario 166 [31121]	2	8	11	0.400
Scenario 203 [32222]	1	3	17	0.662
Scenario 230 [33222]	1	0	20	0.905
Scenario 243 [33333]	0	0	21	1.000
Pc* **	**0.295**	**0.305**	**0.400**	**κ = 0.526**

Key:

**S* stable, *M-DA* mild disease activity, *S-DA* significant disease activity.

**Pr denotes the extent to which physicians agree on each scenario (physician pairs in agreement relative to the number of all possible pairs), ranging from 0 to 1 and with 1 representing complete agreement.

***Pc denotes the proportion of all physician assessments that were assigned to each category. For instance, for the outcome "stable," it equals the total number of physician assessments rated as stable (n = 62), divided by the total number of possible physician assessments ($10 \times 21 = 210$).

Fleiss' kappa statistic (κ) provides a summary statistical measure for assessing the reliability of agreement between physicians in rating common scenarios.

[a] Bracketed numbers refer to the level of severity for each of the health status parameters. As an example, scenario 166 [31121] as shown in Table 2 describes a hypothetical patient case with IGF-I at level 3, Tumor status at level 1, Comorbidities at level 1, Symptoms at level 2 and QoL at level 1.

The most extreme scenarios, all parameters at the lowest level of severity (level 1) or all parameters at the highest level of severity (level 3), had complete agreement among physicians, with all physicians rating them as S and S-DA, respectively. The Fleiss' kappa value was 0.526, which indicated a moderate amount of inter-rater agreement. Because of a single physician rating one scenario as S whereas all other physicians rated this scenario as S-DA, a sensitivity analysis on inter-rater agreement was performed excluding this physician. With the outlier removed a Fleiss' kappa value of 0.549 was observed indicating acceptable agreement level.

5.3.2 *Algorithm Development*

Of the 21 physicians, 20 evaluated the maximum number of scenarios each (52 scenarios), while 1 physician evaluated 51 scenarios, yielding a total of 1.091 observations. The outcome variable was an ordinal three-level physician assessment of hypothetical patient condition (disease activity categorization): S, M-DA, or S-DA.

Generally, an IGF-1 >1.2x ULN or the worst Tumor Status (both indicated as level 3) tended to have high scores for S-DA and very low scores for S. Similar patterns for the highest levels of severity were observed for Comorbidities, Symptoms, and HRQL Impairment; however, the distributions were less extreme. Medium levels of severity (level 2) of each health status parameter tended to have higher scores for M-DA and S-DA compared to S. No apparent trend was observed for the lowest levels of severity (level 1) of the health status parameters.

In the CART decision tree model, only two of the health status parameters had any influence in the ultimate disease activity rating: IGF-1 and Tumor Status as shown in Figure 7 below.

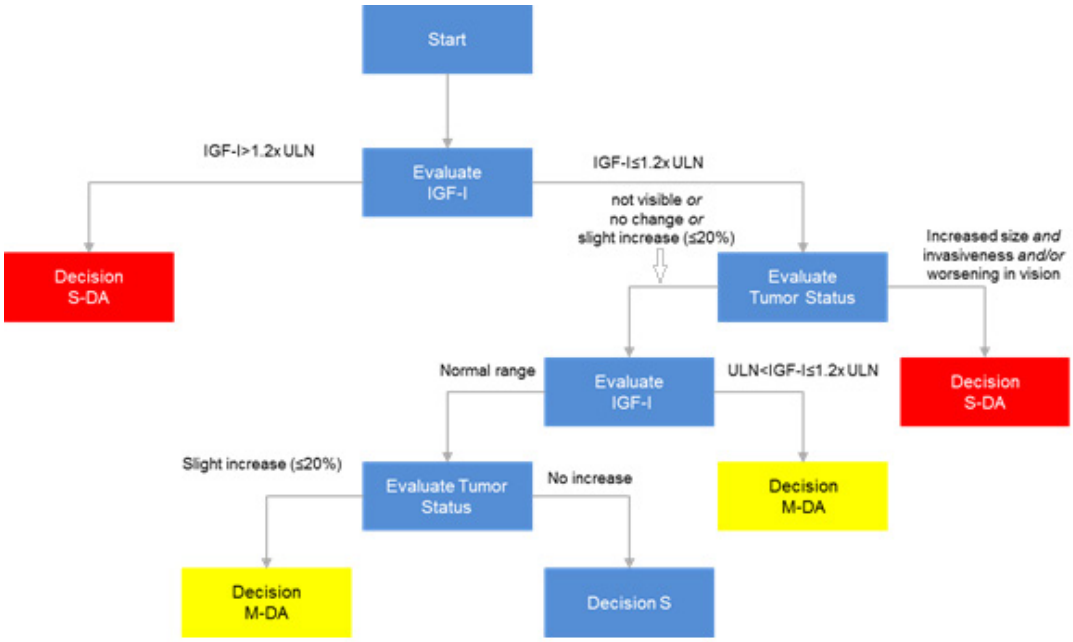

Figure 7: CART decision tree model of validation study

Key:

S = Stable, M-DA = Mild Disease Activity, S-DA = Significant Disease Activity.

If IGF-I was indicated as level 3, then disease activity was immediately rated as S-DA. Otherwise, Tumor Status was evaluated, and if it was indicated as level 3, then disease activity was similarly rated as S-DA. These straight away lead to terminal nodes in the decision tree based on a level 3 indication of either IGF-1 or Tumor Status suggesting a non-compensatory decision-making process. Hence, it was decided that a scenario would be rated S-DA if either IGF-1 or Tumor Status was indicated as level 3 (in a non-compensatory fashion). In addition, results from the CART model also suggested an interaction between IGF-1 and Tumor Status. That is, the effect of either of these health status parameters on the outcome depended on the value of the other health status parameter.

CHAPTER 6

Section 6: Discussion

This thesis focused on assessing the need for PM in the field of acromegaly with a view to finding a solution which may guide and support acromegaly management for treating physicians as well as being useful for engaging and involving patients to improve the understanding of their disease and regular monitoring of improvement with treatment. Such disease activity modelling in a complex disease setting such as acromegaly is feasible and useful, then it could be postulated that a similar approach could be applied to other disease areas especially in the field of rare and complex disorders which by nature is more difficult to treat and manage. The development of ACRODAT used a methodology to explore the need for such a supportive clinical tool with the endocrine community and having established that need, set out to build the tool with elucidation of disease specific parameters and validating through testing with experienced endocrinologists on how patients were scored in their disease status.

Methodological Considerations

6.1 Qualitative Survey

The qualitative survey achieved its aims in identifying the current gaps in acromegaly management. The spectrum of approaches in trying to achieve disease control varied widely and were not always consistent with current treatment guidelines. Furthermore, there was a level of acceptance reflected in a number surveys that complete disease control is only achieved in about 30-40% of patients who were not cured by surgery. The qualitative survey offered a good cross sectional sample of participants from different countries in Europe and hence belonging to diverse clinical settings in Europe. The survey also confirmed what had been published to date on levels of disease control achieved in acromegaly patients. The survey also revealed different treatment goals which the endocrinologists would have as order of priority. There was some commonality in assessment of both symptoms and QoL in that these were not completed in routine consultation but rather addressed through simple questions of ‘how are you feeling’ or ‘how have you been since

the last appointment'. This is one area where ACRODAT could make a significant difference when adopted in ensuring that such assessments can be done and compared over time in a systematic way. It would also ensure the patient's engagement and could support improved adherence to medical treatment(s). A few survey participants reflected on the conflicting results of biochemical normalisation not always resulting in betterment of symptoms or vice versa. This was a useful finding as well as patient choice having an influence on which treatments are finally given which in turn may have an impact on the ability to fully manage the disease (i.e. patient opting for a monthly injection vs. a daily injection which could be more efficacious). Both of these findings highlighted opportunities in the current treatment gaps which ACRODAT could potentially address.

6.2 Identification of critical disease parameters

The expertise of the judging panel added significant value to the purpose of distilling the key parameters of disease activity as the funnelling approach was undertaken. By challenging the addition or omission of a given parameter through evidence based assessment, the consensus was built. The exercise conducted over several meetings to weigh up importance and priorities of each and every parameter while acknowledging that having too many parameters would render the tool unusable due to heavy burden of data entry and resource utilisation not to mention trade off of one important parameter over another. A pragmatic approach taken to choose those parameters which are readily available or can be made available easily in the clinic in the case of questionnaires for PASQ and AcroQoL as well as ensuring that the resulting measured parameters can respond to therapies currently available showing betterment is another key attraction for ACRODAT. This would no doubt also support clinicians who are not experts and not based in specialist pituitary clinics in managing this rare disease on a routine basis by making use of the key disease parameters to assess each patient's status in a methodical, holistic manner. The disadvantage is that there are a several parameters or clinical signs such as arthritis, colonic polyps or facial disfigurement which are important in regards to the patient's acromegaly

status which may not be modified by any of the current therapies available while nevertheless it remains important to the patient. The ACRODAT tool for example in the case of facial disfigurement would report that the patient is adequately controlled in their disease activity although certain domains of AcroQoL would have a lower score due to self-perception and self-esteem. Having said that, ACRODAT's value lies in detecting changes over time in regards to each parameter and if in this scenario, AcroQoL score does not change, then this is useful to know for the treating physician that baseline values have not deteriorated.

6.3 Validation Study

The validation study revealed that the expert centre endocrinologists while placing some value on AcroQoL and symptoms (as measured by PASQ) identified, IGF-I and tumour status to be their main drivers for clinical decision making. This was unexpected in that one would have assumed that in these pituitary specialist centre clinics there would have been a higher focus on managing the disease more actively and holistically due to availability of multidisciplinary teams, experience and resources to make available full and comprehensive care to meet patient needs. This finding may partly be explained by the fact that with hypothetical patient cases, some detail was lacking in the scenarios around medical history and concomitant medications for example which comes into play for clinical decision making. One criticism for the validation study would be that the exercise would have been more meaningful if repeated to have real life clinical cases for the participants to consider with different age groups of patients and having many other co-morbidities as is common in acromegaly. Such a study would also include the element of patient choice around treatment. Study participant decisions may have also been influenced by cost containment measures and resource burden which drove towards prioritising biochemical and tumour status as their main criteria. Having said that, even with such limitations, the study clearly demonstrated, with a good sample size, in an international setting that the IGF-I and tumour status definitions for the highest level of severity (level 3) were generally accepted and validated as representing significant disease

activity requiring clinical action. If neither of those two health parameters were indicated as level 3, then the other three health status parameters (co-morbidities, symptoms and AcroQoL) along with the remaining levels of IGF-I and tumour status appeared to operate in a compensatory manner.

Validation study highlighted on of the weaknesses in current treatment practice even at specialist centres that when the tumour mass is clinically insignificant, biochemical status is mainly guiding decision making. As the qualitative survey showed, biochemical control does not guarantee symptom relief and the general well-being of the patient. Symptoms of acromegaly and reduced QoL may persist despite normal IGF-I levels (Neggers, 2008; Lansang, 2005; Rubeck, 2010). The benefits to patients and their QoL are therefore a relevant consideration in the medical management of acromegaly as also proposed in recent guidelines (Guistina, 2014). The same applies to co-morbidities which requires close monitoring and rigorous management in acromegaly. These aspects once again underscores the importance and usefulness of ACRODAT in routine clinical practice.

6.4 Relation between disease activity parameters, treatment outcomes and cost effectiveness

ACRODAT could have an integral role in disease management of acromegaly patients in the least as a supportive tool for teaching, auditing, enabling, patient centred consultation and engagement. Moreover, when the tool is introduced into clinics, assuming that the tool is user friendly and data entry not cumbersome, it could be systematically used for all patients in acromegaly clinics to see which patients would require further, closer attention. For less experienced hospital clinics, ACRODAT could be informative and encourage faster referral of more severe patients to Pituitary Centres of Excellence.

Apart from surgery and in some cases, radiotherapy as the first line of intervention, medical treatment of acromegaly with SSAs and GHRA, has made it possible to achieve normal serum IGF-I concentrations in a majority of patients with acromegaly. These two compounds, however, impact the GH-IGF-I axis differently, which challenges the traditional biochemical assessment of the therapeutic response. SSAs in certain patients normalizes serum IGF-I

levels in the presence of elevated GH actions in extra-hepatic tissues. This may result in persistent disease activity (the term named as extra-hepatic acromegaly, Neggers, 2011). PEG, on the other hand, blocks systemic GH actions, which are not necessarily reliably reflected by serum IGF-I levels, and this treatment causes a further elevation of serum GH levels. Medical treatment is therefore difficult to monitor with the traditional biomarkers. ACRODAT can play a key part by combining the biochemical assessment with other symptomatology, co-morbidities and QoL to provide a fuller picture of the patient clinical status.

The evidence is still incomplete in regards to whether improvement and attainment of disease control in the short term in acromegaly would lead to a lower morbidity and mortality rate downstream. However, it is anticipated that by lowering risks in those critical parameters especially in regards to IGF-I, tumour volume and co-morbidities, one can expect improvement also in long term health status. One important limitation of the validation study is that other factors not considered in ACRODAT may influence the overall disease activity status of the patient. However, this would be the case in any supportive tool in that the suggestion would not be for ACRODAT to replace much needed clinical judgment which takes into consideration many aspects including patient's motivation and commitment to treatment plan, level of adherence expected to treatment, cost and resource pressures of healthcare, patient's age, safety and efficacy of each treatment intervention and reliability of disease parameter measurements as provided by the local lab (in the case of IGF-I and GH) or the Pituitary MRI gained by the local radiologist. ACRODAT's accuracy also is reliant upon correct information and values feeding into the tool.

6.5 Future Research

Through the qualitative survey, it was established that there is room for improvement in how acromegaly patients are currently managed and that a tool such as ACRODAT has a role to play in routine clinical practice. The development of ACRODAT with the key disease parameters built into measure disease activity of acromegaly could be a way to achieve short and

long term disease control assuming that the treating physicians takes appropriate action in patients where the disease activity is moderate or severe. However this needs to be demonstrated in a prospective, longitudinal study where ACRODAT is evaluated by showing that when patients are monitored by the tool AND with appropriate clinical decisions are made by the treating physicians based on the disease status that patients result in having improved treatment outcomes as compared with patients undergoing routine clinical practice alone. Such a study would not be easy to design and conduct given many challenges including bias introduced by variability in treating centre approaches, level of expertise, assessing longitudinally patient outcomes and savings in healthcare costs as a result of ACRODAT's recommendations.

Since the start of this thesis, 2 key advances has been seen in the field of acromegaly in relation to disease management. The first is Guistina et al (2016) published on a clinician reported outcome instrument currently in development for managing acromegaly known as SAGIT. While there are a few similarities with mapping relevant disease parameters of acromegaly into the tool, there are also several limitations in SAGIT. Firstly, in trying to ensure that most of the disease parameters are present in the tool, the trade-off exercise conducted in ACRODAT (choosing between GH and IGF-I as biochemical parameters to take forward IGF-I as the single most important biochemical marker) is missing in SAGIT making it a very comprehensive reference tool which would consume significant time and resource in completing the tool. Secondly, SAGIT captures symptoms in a simplistic way having headache, sweating, joint symptoms and swelling whereas ACRODAT makes use of PASQ which is more telling both in severity as well as in range of symptoms recorded. For neurosurgeons utilising SAGIT, the tumour grading would be of interest. Therefore, all things considered, the efforts of developing ACRODAT and its unique methodology will not be diluted with SAGIT's eventual introduction. The final degree of uptake of either of these tools or others in this space will be decided by how useful and easy it will be for data entry for endocrinologists and patients entering their symptoms &

QoL data. Furthermore, development of SAGIT also reaffirms the need for such instruments to support acromegaly management.

Medical therapies for acromegaly decreases insulin resistance and increase insulin sensitivity in general. On the contrary, glucose indexes may be differently affected by SSAs and Pegvisomant (Bogazzi, EJE 2013). The second advancement relates to the launch of a 2nd generation SSAs known as Pasireotide, where the impact on glucose homeostasis is even more pronounced. While further work is underway to fully understand the mechanism behind this, a disease activity tool such as ACRODAT which has reflected on the high priority disease markers and the ability of currently available treatments to improve those needs to be adapted to reflect not only the individual co-morbidities component of the tool but also in the overall disease activity status which based on the validation study gives priority to tumour status and IGF-I. This will be a continuing challenge as new interventions are introduced which may fundamentally change how the disease is understood and managed. The same applies to new disease markers which will impact ACRODAT's current set of disease activity markers. As a consequence, ACRODAT will require periodic review to ensure its relevance with a view to updating the tool to keep pace of new information. In terms of operational rollout of ACRODAT, it is planned to be introduced as a software medical device (SMD) and rolled out as a website tool. With the right framework, the potential is significant for ACRODAT to be not only a tool supporting an individual centre but enable with the right permissions and data protection, connectivity between centres and countries whereby treatment patterns can be compared and contrasted in the field of acromegaly. Research studies and patient interfaces could also be created and facilitated through such framework. Finally, by providing a feedback loop for the first generation of ACRODAT users, it could be highly beneficial to implement useful acceptance feedback in order to update the SMD and thereby improving user experience both from clinicians and patients.

Finally, although ACRODAT's development has tried to be inclusive to the needs of the patients (through PASQ AcroQoL), the identification of disease parameters were largely led by the expert panel on behalf of patients. Future

work should accommodate a study whereby an independent exercise is conducted to elucidate the most important parameters as viewed by patients which would meet their treatment expectations. This can then be compared with the existing ACRODAT parameters to see the extent of overlap with the ideal treatment plan taking into account both physician and patient needs. Such an approach would not only improve patient's understanding of the disease and interventions planned as well improving the adherence level and commitment to following the agreed treatment plan long term (Osterberg, 2005).

CHAPTER 7

Section 7: Conclusion

The ACRODAT physician survey revealed that while managing acromegaly is challenging, respondents claimed mostly to succeed with managing their patients. Few physicians recognised any tendency in themselves to being conservative with acromegaly treatment nor did they think that they delay progressing therapeutic steps when warranted. In regards to monitoring the most important parameters, co-morbidities were sometimes disregarded. The research identified a real appetite for the ACRODAT tool at least with half of the audience (based on reviewing screenshots of the pilot tool) in helping them to make better treatment decisions while the other half saw ACRODAT serving the need to keep a good repository of patient details in clinical practice and to support patient monitoring. The barriers for ACRODAT implementation were mainly around the practical consideration of data entry burden together with internet connectivity.

Identification of the key parameters using the funnel approach was a successful model in distilling the most critical parameters which would not only provide a good way of measuring disease activity at various time points but also would theoretically help monitor improvements when therapeutic changes are undertaken.

The validation study using ACRODAT's 5 key parameters revealed that even with endocrinologists experienced in treating acromegaly patients, the main treatment goals and focus were towards the biochemical parameter, namely IGF-I, and tumour status. Where these are stable and patients adequately controlled then co-morbidities, symptoms and QoL seems to act in a compensatory manner exerting some influence. The CART model demonstrated that according to the validation study participants, only IGF-I above 1.2 x ULN and/or tumour volume increase >20% would classify the patient as having significant disease activity requiring a therapeutic change. At best, the other three parameters weighting could move a patient status from S to M-DA assuming both IGF-I and tumour volume is fully controlled.

ACRODAT's development and finalization of the tool as an SMD needs to take into account the need to manage acromegaly patients in a holistic manner as determined by both the expert panel and based on the findings of the validation study. The

success of ACRODAT's acceptance can be ensured by periodic review and appropriate updates to reflect changes in treatment paradigms as well as user acceptance feedback.

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Appendix A: Combined CUHREC Approval form and approvals for the ACRODAT Qualitative Research & Validation Studies

Chapter 2. Cranfield University Health Research Ethics Committee Approval Form

CUHREC Ref:

To be provided by CUHREC administrator

Principal Investigator: Nicola White

Title of Study: Field Survey & Validation of the Acromegaly Disease Activity Tool (ACRODAT)

Before submitting the ethics approval form, please ensure you have completed all sections and provided all supporting documents.

The following list should be checked, completed and submitted with your application:

Document	Enclosed? Select as Appropriate	Version / Date	Checked by CUHREC
Completed Approval Form	Yes	24.10.2014	
Full Study Protocol	Yes	24.10.2014	
Volunteer Information Sheet*	Yes		
Volunteer Consent Form*	N/A		
Patient Information Sheet*	N/A		
Patient Consent Form*	N/A		
Invitation Letters / E-mails*	Yes	24.10.2014	
Investigator Signatures	N/A		

* – must be presented on headed paper.

(Please read the guidance document 'CUHREC Application Process and Requirements for Approval' carefully before completing this form)

Checked by:

CUHREC Administrator

Signature ..... Date .....

Chapter 3. Section 1: Investigator Details and Study Background

Principal Investigator		
Name: Nicola White Department: Health	Staff	
E-mail: n.white@cranfield.ac.uk		
+441234758317		Tel:
Investigator 2	Staff	
Name: Roy Gomez		
Department: Health		
E-mail: r.gomez@cranfield.ac.uk		Tel:
+32496122212		
Investigator 3	Staff	
Name:		
Department: Health		
E-mail:	Tel:	
External Collaborator / Investigator		
Name:		
Address:		
E-mail:		
Tel:		

(Any further information can be submitted on a separate sheet)

What is the proposed start date and duration of this project?

Start date (DD/MM/YY):	01/12/14	
Proposed duration:	0 Years	1 Months

Short Description of Study **[max 200 characters]**

The Validation Study aims to validate the 5 parameters as holistically representing disease activity which then shows concordance across a group of experts in categorising disease activity of patients.

Aim(s) of Project **[max 500 characters]**

The Field Survey intended to guage interest and need for a tool such as ACRODAT given the high medical need in a rare disease setting.

The validation study uses an internet-based survey in which expert endocrinologists will be presented with a series of hypothetical patient profiles based on the five ACRODAT parameters. In each scenario, the survey will ask the endocrinologists whether the patient described in each scenario is well controlled, partially controlled, or not controlled. Due to the high number of possible scenarios, participating endocrinologists will not be asked to rate all scenarios.

The survey will be designed to ensure sufficient variation and coverage of health parameters in the scenarios by using a random selection approach. In addition, a subset of scenarios will be presented to all participants to allow for examination of inter-rater agreement.

Project Background – Scientific Justification **[max 1500 characters]**

The Validation Study aims to validate the 5 parameters as holistically representing disease activity which then shows concordance across a group of experts in categorising disease activity of patients.

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CUHREC Application Form: V6, September 2011 3.

Acromegaly is a rare progressive condition characterized by elevated growth hormone secretion due to a pituitary tumour anomaly. Treatment involves surgical resection of the tumor and often includes pharmacotherapy or radiation to maintain hormone homeostasis. Treatment goals are to reduce / control tumour size, achieve biochemical control through normalization of biochemical parameters (GH & IGF-I) as well as improving signs and symptoms. To enable a holistic evaluation of the disease status necessitated the need to develop ACRODAT, a multi-dimensional support tool that aggregates patient-level outcome data to allow the treating endocrinologist to evaluate the patient's health status.

A panel made up of Key Opinion Leaders in the field of endocrinology, neurosurgery and acromegaly management was convened to develop ACRODAT and determine the appropriate health status parameters and scoring algorithm for this support tool. ACRODAT includes five parameters; 1) IGF-I level; 2) tumour status; 3) comorbidities; 4) symptoms; and 5) health-related quality of life. Each parameter is scored individually, weighted by its importance to overall health status, and aggregated into a composite score. The outcome of the composite score will determine whether the patient's disease

activity score is classified as controlled, partially controlled, or not controlled.

The value of ACRODAT is in its ability to predict what an expert endocrinologist would consider to be a controlled versus (partially) uncontrolled patient with acromegaly. However, the predictive validity of ACRODAT has not yet been established.

Chapter 4 Section 2: Recruitment

NOTE: You must include a copy of invitations (e-mails / letters) to be used for recruiting within this study along with your volunteer information sheet and consent form.

Chapter 5. Volunteer population

Where will volunteers be recruited?	Internally:	Externally:
	☐	☒

Internal

Schools: Health ☐ SAS ☐ SOE ☐ SOM ☐ Shrivenham ☐ Population: Staff ☐

Students ☐ Total number required:

External

NHS ☐ General Public ☐ Other ☒

If other, please specify Adult Endocrinologists across Europe and Canada

Total number required: 30

NRES Approval

Will your study require NRES approval? (e.g., NHS linked projects) No If yes, state which committee:

Will the University be required to act as sponsor for this application? No

Chapter 6. Information and consent

Is written consent required for this duty? No

If no, please state why: The patient scenarios are based on hypothetical cases and therefore no patients are involved in the conduct of this study.

If yes, please answer the questions below.

NRES Approval

Will your study require NRES approval? (e.g., NHS linked projects) No If yes, state which committee:

Will the University be required to act as sponsor for this application? No

How will volunteers find out about the study? (Mark all that apply)

E-mail ☒ Advert ☐ Clinician ☐ Other ☐ Please specify

How will volunteers be informed of the study details? (Mark all that apply)

Information sheet ☒ Personal discussion ☒

Will there be at least 24 hours between invitation and consent? Yes

Who will be responsible for taking consent?

Briefly describe the consent process: The field survey was conducted in 1Q, 2014 across Europe. ICON will be co-ordinating the Validation Study on behalf of the investigators to retain anonymity of sponsor and will reach out to participants initially by letter / email. Those who agree to participate will then be sent a contract and instructions of the online validation survey to complete.

Volunteer recompense

Will volunteers be recompensed for their time? Yes

If yes, how The contract will stipulate the amount paid based on the calculation of 60 mins to complete the validation survey, taking into account Fair Market Value calculations.

Chapter 7. Section 3: Sample / volunteer requirements

Volunteer recompense

Will volunteers be recompensed for their time? Yes

If yes, how The contract will stipulate the amount paid based on the calculation of 60 mins to complete the validation survey, taking into account Fair Market Value calculations.

NOTE: You must include a full study protocol and any other relevant documentation.

Does your study involve: (mark all that apply)

Collection of human samples	Complete section 3A	☐
Intervention	Complete section 3B	☐
Participation in an activity	Complete section 3C	☐
Questionnaire completion	Complete section 3D	☒
Other	Complete section 3E	☐

Volunteer recompense

Will volunteers be recompensed for their time? Yes

If yes, how The contract will stipulate the amount paid based on the calculation of 60 mins to complete the validation survey, taking into account Fair Market Value calculations.

Inclusion / Exclusion criteria

State any specific inclusion or exclusion criteria for this study:

Inclusion criteria: Fully outlined in the protocol

Exclusion criteria:

Blood	Vol	Ml Frequency	Total No.
Urine	Vol	Ml Frequency	Total No.
Saliva	Vol	Ml Frequency	Total No.

Section 3A: Human sample collection, storage and use

For each volunteer:

☐

☐

Other ☐ Give details

Other ☐ Give details

☐

How and where will the samples be collected?

Will the samples be anonymised? Yes

If no please state why:

How and where will the samples be stored?

All samples should be appropriately labelled, including unique CUHREC identifier.

How will the samples be used?

Will remaining samples be destroyed at the end of the study? Yes Who will be responsible for destruction of the samples?

If samples will not be destroyed please explain why:

NOTE: You must include in your study protocol all measurements etc. that will be undertaken on the samples, including any measurements made in external laboratories.

How and where will the samples be collected?

Will the samples be anonymised? Yes If no please state why:

How and where will the samples be stored? *All samples should be appropriately labelled, including unique CUHREC identifier.*

How will the samples be used?

Will remaining samples be destroyed at the end of the study? Yes Who will be responsible for destruction of the samples? If samples will not be destroyed please explain why:

Section 3B: Intervention What will the volunteers be asked to do? Include all measures for minimising risk in this activity: How long will the subject involvement be within the study as a whole?

Section 3C: Activity

What will the volunteers be asked to do? Include all measures for minimising risk in this activity:

How long will the subject involvement be within the study as a whole?

Section 3D: Questionnaire [you must include copies of your questionnaire]

Has the questionnaire been validated?: Yes

If yes, please give details: Details in protocol / survey

How will the questionnaire be administered?: phone interview / online

Section 3E: Other

What will the volunteers be asked to do? Include all measures for minimising risk in this activity: N/A

How long will the subject involvement be within the study as a whole? 60 mins

Chapter 8. Section 4: Data Protection

Section 3C: Activity

What will the volunteers be asked to do? Include all measures for minimising risk in this activity:

How long will the subject involvement be within the study as a whole?

Section 3D: Questionnaire [you must include copies of your questionnaire]

Has the questionnaire been validated?: Yes

If yes, please give details: Details in protocol / survey

How will the questionnaire be administered?: phone interview / online

Section 3E: Other

What will the volunteers be asked to do? Include all measures for minimising risk in this activity: N/A

How long will the subject involvement be within the study as a whole? 60 mins

CUHREC Application Form: V6, September 2011 8.

Will the PI be responsible for the following?:

Anonymisation of subject identifiable data: Yes

Consent form storage: During study Yes

Post study Yes Project data storage: During study Yes Post study Yes

If you answered no to any of the above explain why

How will consent forms be stored? N/A

If non-anonymised data is to be stored electronically where will it be stored?

The data obtained from the study must be stored securely in a password protected file and this should be auditable, so please provide exact locations for data storage ie named computer. If this changes, please inform CUHREC.

For how long will data be stored ? 5 years min.Years If less than 5 years, please state why:

Who will be responsible for data destruction?

Chapter 9. Section 5: Signatures

Principal Investigator …… Date ……

Investigator 2 …… Date …….

Investigator 3 ……... Date …….

External Investigator …….. Date ……..

Will the PI be responsible for the following?: Anonymisation of subject identifiable data: Yes Consent form storage: During study Yes Post study Yes Project data storage: During study Yes Post study Yes If you answered no to any of the above explain why:

How will consent forms be stored? N/A If non-anonymised data is to be stored electronically where will it be stored? The data obtained from the study must be stored securely in a password protected file and this should be auditable, so please provide exact locations for data storage ie named computer. If this changes, please inform CUHREC.

For how long will data be stored? 5 years min. Years If less than 5 years, please state why: Who will be responsible for data destruction?

Cranfield UNIVERSITY

Cranfield UNIVERSITY School of Management

Ethical Approval Form

A Field Survey to gauge level of interest and usefulness of an Acromegaly Disease Activity Tool (ACRODAT)

STATUS: Approved by committee

Lead Researcher Roy Gomez r.gomez@cranfield.ac.uk

Cranfield UNIVERSITY School of Management

Ethical Approval Form

Validation of the Acromegaly Disease Activity Tool (ACRODAT)

STATUS: Approved by committee

Lead Researcher Roy Gomez r.gomez@cranfield.ac.uk

Appendix B: Survey to gauge level of interest and usefulness of ACRODAT

INTRODUCTION (2 Mins)

HOUSEKEEPING

- *Introduce the survey format*
- *Interview to last 50 min.*
- *No right or wrong answers*

Ask participants to approximate their number of acromegaly patients receiving medical treatment, and which types of medication are being used.

Degree of control of acromegaly patients / How challenging is it to get control?

What are the challenges / weaknesses of current system?

- Talk us through the general points of acromegaly,. Surgery, radio therapy and medical therapy.
- What process do 'most doctors' use to manage and treat their patients? (To understand especially the steps and the data inputs doctors use to assess / monitor their patients, also other 'influencers')
  - From literature, we know that approximately 25–60% of the patients are biochemically controlled with first-line medical treatment. What is your clinical experience?
    - How difficult / easy is it to get biochemical control?

Treatment goals and challenges

Moderator say: I would now like to discuss your treatment and management goals in acromegaly.

- Word Association game / Acromegaly – what comes to mind?
- What would you say is your main treatment goal in acromegaly?
  - ***For each goal mentioned ask:***
    - To what extent are you able to achieve this goal?
    - What do you do to achieve this goal?

- Once you have achieved the primary goal, what other goals do you try to achieve?
  - ***For each goal mentioned ask:***
    - To what extent are you able to achieve this?
    - What do you do to achieve this?
    - How would you define "controlled acromegaly disease activity"?
- What do you find most challenging in the treatment and management of acromegaly?
  - What else?
  - What makes it so challenging?

With few patients and high variability is there such a thing as a “typical” patient?

- To what extent do you differentiate between different types of patients? (for instance in terms of patient demographics or disease aggressiveness)
  - **Explore different patient types**
- Do you differentiate based on the level of control of disease activity?
  - Prompt / I am aware that there are Medical Guidelines, could you explain when and when not to use them?
- What steps do you use to assess / monitor acromegaly?
  - What info / data do you use to monitor your patients?
  - IGF-1 readings
  - Tumour size (based on MRI)
  - Comorbidities (e.g., diabetes, hypertension, sleep apnea, etc.)
  - Patient symptoms (e.g., headaches, sweating, joint pain, fatigue, soft tissue swelling)
  - Do you use a formal quality of life instrument? e.g., AcroQoL?
  - Quality of life markers
  - Which ones would you consider as the most critical indicators?
  - Which do you use frequently vs. occasionally?

Indicator 1 to 5:

- How do you monitor it?
- How challenging is this for you?
- Any systematic process you use?

- Do you have the right tools?

If not mentioned, probe on Quality of Life and Signs & Symptoms?

- Which treatments do you use in acromegaly?
  - How do you decide on the treatment options?
  - Do you recognize the differences in between the treatment options – do you use specific treatment options at different stages of the treatment management

Get back to pre-defined Patient Types are discussed earlier:

- What would be the options for these different profiles?
- How do you decide when it is time to change treatment?

Explore “emotional challenges” of area, given challenges is there a tendency for “over conservative” treatment?

Evaluation of the software programme, Software Tool X (ACRODAT)

Presentation / explanation of the programme including understanding its objectives / goals: **You need to explain very clearly that the tool was developed based on input from recognized experts and that the algorithm that defines the degree of disease activity is based on a comprehensive validation study.**

  - Gather first reactions
  - Check each feature in turn to see how physician rates feature, where it would impact treatment decision-making, how it might impact treatment decision-making
- Might this tool be useful to endocrinologists who are not expert in managing the disease activity In terms of:
  - Reassurance
  - Self-challenge
  - Use as internal practice data-base
  - To help teach fellows and residence
  - other

- Are the five measures of disease activity reflected of the key things you look for and monitor with your patients?
- Which of the software features would be most helpful?
  - Why?
- To what extent would it help you achieve the goals we talked about earlier?
- To what extent could it help you make treatment decisions?
  - Where would it impact treatment decision-making?
  - In which situations do you think this tool could be more helpful to you? Why?
  - Any specific patients in mind? Why?
- Who would use it in your team?
- How would you use this software in your practice?
  - Would you use it all the time / at every patient visit / some visits?
  - Who would enter the data into the tool?
- How does this tool fit with your existing procedures and “workflow”?

  (If asked, mention that CE medical device and ideally available from mid 2015)
- How would you describe the benefits of using this software?
  - “reassurance” – that you have systematic access to opinions of acromegaly experts (“Expert in a Box”)
  - “Starting a debate”
    - So that it challenges you to think more critically about the condition?
  - “Improve relationship with patients”?
    - That it formalizes patient feedback which aids doctor – patient relationship?
  - “holistic approach”
    - It reminds me to look at the patient as a person, not just an IGF-1 level
  - Other???

CONCLUSION

- To conclude, how do you rate the usefulness of such a tool in your clinic on a scale from 1 to 10 (1=not useful at all / 10=very useful)?
  - Why this score?
- What would need to happen for this tool to be used widely?
  - What else?

Moderator say: Any final comments or recommendations for the creators of this tool?

Appendix C: Validation Study Protocol for the ACRODAT Health Status Assessment Model

1. Research Plan Synopsis

Research Plan Section	Description
Background and Rationale	Acromegaly is a rare progressive condition characterized by elevated growth hormone secretion due to a pituitary tumour anomaly. Treatment involves surgical resection of the tumor and often includes pharmacotherapy or radiation to maintain hormone homeostasis. Treatment goals are to reduce / control tumour size, achieve biochemical control through normalization of biochemical parameters (GH & IGF-I) as well as improving signs and symptoms. To enable a holistic evaluation of the disease status ACRODAT, a multi-dimensional support tool is being developed that aggregates patient-level outcome data to allow the treating endocrinologist to evaluate the patient's health status. A panel made up of Key Opinion Leaders in the field of endocrinology, neurosurgery and acromegaly management was convened to develop ACRODAT and determine the appropriate health status parameters and scoring algorithm for this support tool. ACRODAT includes five parameters; 1) IGF-I level; 2) tumour status; 3) comorbidities; 4) symptoms; and 5) health-related quality of life. Each parameter is scored individually, weighted by its importance to overall health status, and aggregated into a composite score. The outcome of the composite score will determine whether the patient's disease activity score is classified as stable (S), mild disease activity (M-DA), or significant disease activity (S-DA). The value of ACRODAT is in its ability to predict what an expert endocrinologist would consider to be a controlled

	versus (partially) uncontrolled patient with acromegaly. However, the predictive validity of ACRODAT has not yet been established.
Objectives	The study has two primary objectives: • To assess the inter-rater agreement of disease activity status among expert endocrinologists based on the five health status parameters in a hypothetical set of acromegaly patients • To develop and assess a model that predicts expert endocrinologist judgment of disease activity status (S, M-DA or S-DA), or) based on the set of health status indicators in hypothetical acromegaly patients
Study Design	The study uses an internet-based survey in which expert endocrinologists will be presented with a series of hypothetical patient profiles based on the five ACRODAT parameters. In each scenario, the survey will ask the endocrinologists whether the patient described in each scenario is well controlled, partially controlled, or not controlled. Due to the high number of possible scenarios, participating endocrinologists will not be asked to rate all scenarios. The survey will be designed to ensure sufficient variation and coverage of health parameters in the scenarios by using a random selection approach. In addition, a subset of scenarios will be presented to all participants to allow for examination of inter-rater agreement.
Recruitment	ACRODAT Advisory Board members will provide a list of endocrinologists within Europe (i.e., France, Germany, Italy, Spain, UK) and Canada with expertise in treating acromegaly. From this list, ICON will select the names of the endocrinologists who will be invited by e-mail to participate in the study. Endocrinologists who agree to

	participate will be screened by telephone using a screening form to ensure eligibility in accordance with the approved inclusion criteria.
Sample Size	Approximately 30 to 50 expert endocrinologists from Europe (i.e., France, Germany, Italy, Spain, UK), and Canada will take part in the study with an even distribution of participants from each country.
Eligibility Criteria	*Inclusion Criteria* *Physician will be eligible if:* • Participant is an endocrinologist residing in one of the specified countries who has been identified as having expertise in treating acromegaly and: – Works in a hospital, hospital outpatient clinic, or private outpatient clinic – Sees at least 5 acromegaly patients annually or, if less, supervises others who treat acromegaly patients – Is not familiar with ACRODAT or has not been involved in extensive development activities for ACRODAT prior to this study – Is able to read and understand English Participant is willing and able to participate in the study, which involves completing an online survey approximately 60 minutes in duration.
Outcome Variable	The ranking of disease activity based on the health parameters provided (i.e., S, M-DA or S-DA) will be considered the outcome variable. ACRODAT being a disease specific tool, while it takes into account the general comorbidities status, it is not designed to fully evaluate those and instead aims to focus on the impact of those comorbidities and signs and symptoms for example in

	relation to acromegaly.
Procedures	Participants will be recruited from a list of expert endocrinologists provided by ACRODAT Advisory Board members. Participants will be initially contacted via email by a panel member and ICON will screen them for eligibility via telephone using a screening form. Those identified as eligible and willing to participate will be invited to complete an internet-based survey lasting approximately 60 minutes. All data will be collected online through a secure server. ICON will email eligible and interested endocrinologists a link to the survey with a unique login ID. After completing the survey, endocrinologists will be remunerated for their time and effort in the form of a $350 USD or equivalent honorarium, depending on and in line with the country's local rules and regulations on remuneration of healthcare professionals.
Analysis	All analyses will be detailed in a statistical analysis plan (SAP) with input from Pfizer. This document will define the analysis cohort(s), specify raw and analysis variables (e.g., scoring the ACRODAT algorithm), and detail the statistical methods to be used in the examination of study outcomes. The SAP will include corresponding table / figure shells and an index or sample for any other analysis items (e.g., listings, figures, and replicate tables).

2. Background and Rationale

Acromegaly is a rare progressive condition characterized by elevated growth hormone secretion due to a pituitary tumour anomaly. Treatment primarily involves surgical resection of the tumor and often includes pharmacotherapy or radiation to maintain hormone homeostasis. Endocrinologists typically use insulin-like growth factor 1 (IGF-I) levels and other patient outcomes to monitor treatment effectiveness. Pfizer has developed ACRODAT, a multi-dimensional decision

support tool that aggregates patient-level outcome data to allow the treating endocrinologist to evaluate the patient's health status.

A panel of Key Opinion Leaders (KOLs) in the treatment of acromegaly was convened to develop ACRODAT and determine the appropriate health status parameters and scoring algorithm for the decision tool. ACRODAT includes five parameters:

- IGF-I level
- Tumour status
- Comorbidities
- Symptoms
- Health-related quality of life (HRQoL)

Each parameter is scored individually, weighted by its importance to overall health status, and aggregated into a composite score. The outcome of the composite score will determine whether the patient's disease activity score is classified as controlled, partially controlled, or not controlled.

The value of ACRODAT is in its ability to predict what an expert endocrinologist would consider to be a controlled versus (partially) uncontrolled patient with acromegaly. However, the predictive validity of ACRODAT has not yet been established.

Multivariable regression models are applicable to this type of an assessment (Hosmer, 2013) and form the basis for the methodology applied.

3. Objectives

The purpose of the study is first to examine the inter-rater agreement of disease activity status among expert endocrinologists assessing hypothetical scenarios composed of the five health status parameters and second, to develop and assess a model that predicts expert endocrinologist judgment of disease activity status in acromegaly patients (i.e., S, M-DA, S-DA) on the basis of these scenarios. Various attribute weighting approaches will be tested to ascertain what model provides the best predictive ability. The final model will be incorporated into the ACRODAT tool as the algorithm to provide the outcome (health status) of the individual patient based on the clinicians' input of the parameter levels.

4. Study Methods

4.1 Development of the Physician Survey

4.1.1 Definition of ACRODAT Parameters

Through consultation with a panel of Key Opinion Leaders in the field of acromegaly, Pfizer determined five parameters for inclusion in the ACRODAT model. The selected attributes and their preliminary levels are presented below in Table 5. Definitions and descriptors for the purpose of training endocrinologists how to respond and for scenario building are not finalized for the purposes of this research plan. The IGF-I parameter is assay-based and level is assigned using deviations from normal levels. The tumour status parameter is based on MRI and level is assigned based on change over time. The Comorbidities parameter is assigned a level based on the presence or absence and severity of several specific conditions (i.e., diabetes, sleep apnea and cardiac disease). The symptoms parameter is based on the mean symptom score of the Patient Acromegaly Symptom Questionnaire, which includes headache, excessive sweating, joint pain, fatigue, and soft tissue swelling. Each symptom is scored from 0 (absent) to 8 (severe and incapacitating). The HRQoL Impairment parameter is based on the standardized total score from a validated measure of health related quality of life. The measure will be described in general terms and the interpretation of scores provided based on three levels of impairment – none or minimal, moderate, and severe. The specific measure will not be identified to avoid response bias based on the clinician's familiarity with and perceptions of the utility of any single instrument (such as the AcroQoL).

Table 5: Treatment Attributes and Levels

Health Status Parameter	Parameter Levels
IGF-I	1. = Normal range 2. = From upper limit of normal to 1.2x upper limit of normal 3. = Above 1.2x upper limit of normal
Tumor status	1. = No change in size or invasiveness 2. = Increased size OR increased invasiveness

Health Status Parameter	Parameter Levels
	3. = Increased size AND invasiveness
Comorbidities	1. = No comorbidity is uncontrolled and diabetes is absent 2. = One or more comorbidities is uncontrolled but diabetes is absent OR diabetes is present but controlled, sleep apnea is absent and cardiac disease –if present- is controlled 3. = Diabetes is present and uncontrolled OR diabetes is present but controlled, sleep apnea is present and/or cardiac disease is uncontrolled
Symptoms	1. = Mild: no single symptom above 2 on the PASQ 2. = Moderate: one or more symptoms above 2 but none > 6 3. = severe: one or more symptoms 7 or 8
HRQoL Impairment	1. = None or Mild (total score > 80) 2. = Moderate (60 ≤ total score < 80) 3. = Severe (total score < 60)

4.1.2 Development of Scenarios

Scenarios will be constructed by varying the five ACRODAT parameters to create hypothetical patient profiles. In each scenario, the survey will ask the endocrinologist whether the patient described in each scenario is S (in terms of disease activity), has M-DA (further assessment is necessary), or has S-DA. The format of the survey will be similar to a conjoint analysis. The 5 parameters, and the 3 levels within each parameter, produce a prohibitively large number of hypothetical scenarios. As it will not be possible for each endocrinologist to rate all of the scenarios, they will only be assigned a portion of the overall set. Though there are scenarios that may appear unrealistic, being either clinically remote or impossible, they will be retained in the pool of potential scenarios for completeness. Instructions will be provided to ensure that participants understand this aspect of scenario presentation. In assigning scenarios to endocrinologists, some will be varied across endocrinologists, while a subset (10) will be presented to all endocrinologists to allow for the calculation of inter-rater reliability. Endocrinologists will rate the scenarios for up to approximately 60 minutes.

The panel of KOLs will select 10 clinically plausible scenarios that will be presented to all participating endocrinologists. These 10 “common” scenarios will represent a wide range of overall health status from fairly good health to very poor health and will be used to assess inter-rater reliability. The 10 “common” scenarios will be interspersed in a random order within the first 26 scenarios presented to each endocrinologist. Because participating endocrinologists will be expected to complete a minimum of 26 scenarios (see sample size justification below), each participant will have completed all 10 “common” scenarios before the end of their study participation. The remaining (non-“common”) scenarios will be selected randomly from the pool of remaining scenarios with the constraint that all scenarios will be asked at least once to at least one participating endocrinologist.

4.1.3 Participant Recruitment

The online survey will first be tested by the panel of KOL experts, to check whether the online system is working and whether it is feasible to evaluate 26 scenarios in 60 minutes.

Pfizer will provide ICON with a list of endocrinologists with expertise in treating acromegaly from specified countries in the European Union (i.e., France, Germany, Italy, Spain, United Kingdom) and Canada. The list was compiled based on recommendations from the ACRODAT panel of KOLs that represents experts in the treatment of acromegaly. The panel generated a list of acromegaly experts known to them based on the criteria provided (i.e., works in a hospital, hospital outpatient clinic, or private outpatient clinic, and sees at least 5 acromegaly patients annually or, if less, supervises others who treat acromegaly patients) and through discussion, reached consensus on the sample frame. ICON will identify up to 50 (no less than 5 per country) endocrinologists from the list provided by Pfizer to be contacted initially via email (a template of the solicitation email appears in Appendix A). Solicitation e-mails will be sent with the endorsement of the panel of KOLs, by panel members, representing each of the five EU countries (France, Germany, Italy, United Kingdom, Spain) and Canada. Endocrinologists who agree to participate will then be contacted by ICON via telephone and screened using a screening form (Appendix B). Eligible endocrinologists will be sent a link to the online survey.

4.1.3.1 *Sample Size Justification*

Due to the exploratory nature of this study, formal sample size calculations are not appropriate, as the objective of this study is not to prove or disprove a specific hypothesis.

Nevertheless, in studies where multivariable modelling is expected to be performed, a general rule of thumb is that the study should have at least 10 events for each variable included in the model. The predictor variables will be comprised of 5 health status parameters, each of which is a 3 -level ordinal variable. For each health status parameter, indicator variables will be created for all but one of the levels (the referent level is not coded because it is a linear combination of the other levels). Therefore, the multivariable model will have 10 variables.

An “event” can be defined as the physician categorization of a hypothetical patient as S (or having M-DA, or having S-DA). If we assume that an “event” will occur in roughly 1/3 of the patients (i.e., roughly 1/3 of the hypothetical patients will be categorized into each of the 3 possible outcomes), then the study would require a minimum of 300 independent observations (10 events x 10 variables / (1/3)). Since the same physician will evaluate many different scenarios, observations in the dataset will not be independent, and some statistical power may be lost. As an attempt to adjust for this potential loss in statistical power, the number of observations will be doubled, resulting in a dataset with a minimum of 600 observations. Given that a minimum of 30 physicians will be available to evaluate the scenarios, the study would require each physician to evaluate roughly 20 scenarios (600 / 30) at a minimum. In an attempt to obtain a higher sample size, each physician will be required to evaluate a minimum of 26 scenarios.

4.1.3.2 *Inclusion Criteria*

Interested endocrinologists will be asked to complete a screening form (Appendix B) to ensure that they meet the following criteria:

- Participant is an endocrinologist residing in one of the specified target countries who has been identified as having expertise in treating acromegaly and:
  - Works in a hospital, hospital outpatient clinic, or private outpatient clinic
  - Sees at least 5 acromegaly patients annually or, if less, supervises others who treat acromegaly patients
  - Is not familiar with ACRODAT or has not been involved in extensive development activities for ACRODAT prior to this study
  - Is able to read and understand English
  - Participant is willing and able to participate in the study, which involves completing an online survey approximately 60 minutes in duration

5. Study Procedures

Interested and eligible endocrinologists will be sent an email containing a URL that will lead them to the study website. In the email, endocrinologists will be reminded that their participation is not transferable to another individual and that they themselves must complete the survey in order to be eligible for the honoraria.

5.1 Privacy Statement

Prior to beginning the survey, eligible participants will be prompted to read through an online privacy statement (Appendix C). Participants will be asked to check a box indicating that they have read and understood the statement and that they agree to participate. No participant will proceed to the survey itself without first providing this verification. The sponsor will not know or be able to link any response directly to the respondent and sponsor will only know who responded for those participants who affirm release of their identity for the purpose of participating in future research or publication of results.

5.2 Survey Completion

Those who agree to participate in the study and are eligible will begin by reviewing several screens describing the ACRODAT parameters as well as the levels of each parameter. Pending a review of these descriptions, participants will advance to a set of training scenarios to ensure that they understand the study tasks and the rating categories (i.e., S, M-DA, S-DA) before proceeding to the test scenarios. Once it has been confirmed that the participant understands the study instructions they will be asked to read a set of test scenarios and choose a therapeutic status for each. These hypothetical scenarios will be described using various combinations of the parameter levels described above. In this manner, endocrinologists will be making clinical judgments by considering the levels of the parameters in each scenario.

Whether these decisions are compensatory (i.e., all parameter levels are considered simultaneously and a decision is made by balancing high levels on some parameters and low levels on other parameters) or non-compensatory (i.e., some parameters are considered more important than others and high levels on the key parameter(s) are not considered a trade-off for low levels other parameters) will be investigated and addressed analytically as described below.

Each endocrinologist will be responsible for completing a minimum number of scenarios (26) during the study session to be eligible for the honoraria but may complete additional scenarios up to a maximum number not to exceed 52 until they have used the full 60 minute participation period. Additionally a portion of the scenarios will repeat across endocrinologists to allow for calculating inter-rater agreement, but the remaining scenarios in the set will be randomly assigned. To encourage continued participation, endocrinologists will be periodically reminded that their responses are appreciated and will be given feedback as to their percent of survey completion via a progress bar. At the end of the survey endocrinologists will be asked to confirm that they complied with the rules of the study and completed the survey themselves. In total, the online survey will take approximately 60 minutes to complete. All surveys will be time-stamped to provide a validity check of response time. Endocrinologists who complete the survey will be given a $350 USD or equivalent honorarium for their time depending on and in line with the country's local rules and regulations on remuneration of healthcare professionals (paid directly by ICON Plc).

6. Study Analyses

Survey results will be analysed in SAS 9.2 or higher using the following analytic approaches, which are briefly outlined below. Details of statistical analyses will be documented in a formal statistical analysis plan (SAP).

6.1 Inter-Rater Agreement

For the subset of scenarios that will be asked to all participating endocrinologists (common scenarios), inter-rater agreement will be assessed. An r x c table will be constructed where each row will represent a common scenario, and each column will represent one of the three possible outcomes of endocrinologist assessment (Green, Yellow, or Red). Calculations will include (1) the extent to which endocrinologists agree on each scenario (i.e., how many endocrinologist-endocrinologist pairs are in agreement relative to the number of all possible endocrinologist-endocrinologist pairs), (2) the proportion of all endocrinologist assessments which were assigned to each category, and (3) the Fleiss' kappa statistic. The Fleiss' kappa will provide a summary statistical measure for assessing the reliability of agreement between endocrinologists in rating the common scenarios.

6.2 ACRODAT Model Development and Assessment

The outcome variable is an ordinal three-level endocrinologist assessment of hypothetical patient condition (disease activity categorisation): S, mild M-DA, or S-DA. Due to the categorical nature of the outcome variable, logistic regression is an appropriate method of analysis. Ordinal logistic regression (cumulative logit) may not be a desirable method to employ because it would assume proportional odds in the outcome variable; that is, it would assume that the odds ratios applied to the Yellow versus Green comparison are equal to the odds ratios applied to the Red versus Yellow comparison. Nominal logistic regression (generalized logit) may also not be desirable because inherent ordering in the outcome variable is lost, which may result in an oversimplified model.

The outcome variable will be modelled as two separate binary choices, which may more closely resemble what occurs in clinical practice. The first choice will be whether the patient is considered to be S or M-DA/S-DA. If the endocrinologist fails to rate the scenario as S, the second choice will be whether (a) further assessment(s) is/are needed versus whether the patient is considered to be S-DA. Therefore, although the physician will evaluate hypothetical patients by choosing one out of three possible choices, the analysis will model physician choice as two separate binary choices.

For each binary clinician assessment (i.e., S vs. M-DA/S-DA and M-DA vs. S-DA among M-DA/S-DA), a separate table of frequencies and percentages will be generated displaying the levels of all the health status parameters (rows) for the dichotomization (columns). That is, the frequency and percentage of observations indicating S versus M-DA/S-DA will be tabulated across all levels of parameters, and the table will be repeated for the M-DA versus S-DA choice among scenarios that were not S. These tables will provide a descriptive summary of the data and will be used to investigate the extent to which physicians may be engaging in non-compensatory decision making. For instance, large percentages in any single level of health status parameter (e.g., 80% or greater) may be indicative of non-compensatory decision making. This information will be taken into consideration during the construction of multivariable models.

For each binary choice, binary logistic regression (binary logit) will be performed using the health status parameters as predictor variables. Univariable and multivariable results will be presented. Model building techniques will consider several potential issues, such as interactions, stratifications, multicollinearity, and confounding. These issues in model development will explore the potential issue of non-compensatory decision making, which, if applicable, will be incorporated into the final models. Furthermore, within-endocrinologist correlation will be accounted for in the covariance structure of each model within a generalized procedure in SAS such as PROC GENMOD.

The final models will be used to generate predicted values (ranging from 0 to 1) for each scenario of health status parameter combination. Hence, for each scenario, a predicted value will be generated for the S versus M-DA/S-DA model, and another predicted value will be generated for the M-DA versus S-DA model (among the M-DA/S-DA). Receiver-Operating Characteristic (ROC) analysis will be employed to evaluate the predictive ability of each model as measured by the concordance index, and ROC curves will be generated to evaluate the trade-off between sensitivity and specificity. If applicable, clinician input from the panel members will be solicited to evaluate where to draw potential cut-points or threshold values between colors, while considering potential consequences of false positives versus false negatives. Alternatively, it may be decided to present results on a continuous scale, which ultimately would be transformations of the predicted values from the final models.

7. Protection of Human Subjects

7.1 Confidentiality

All data collected in this study will be kept strictly confidential in accordance with all appropriate legislation and Pfizer Corporate Policy #404. Access to study forms will not be permitted to anyone other than the ICON study team and only ICON will have access to endocrinologist names for the sole purpose of contacting them and providing the participant reimbursement as detailed below. All data housed by ICON will be identifiable only through participant identification numbers. Study staff will be instructed to maintain complete confidentiality of all collected data. Study-related forms and files will be kept on a secure and protected server. Any

reports resulting from the study findings will not contain any identifying information.

7.2 Potential Risks and Benefits

There are no known risks to participants participating in this study.

7.3 Participant Withdrawal from Study

All participants are free to withdraw from the study at any time for any reason—specified or unspecified—and without penalty or loss of benefits to which they are otherwise entitled. It is not necessary for withdrawn participants to complete any additional documentation.

7.4 Compensation

Endocrinologist compensation will be provided and managed by ICON upon confirmation that the endocrinologist has completed the survey. The survey is anticipated to last approximately 60 minutes and each endocrinologist will be compensated according to fair market value with an honorarium of $350 USD or equivalent depending on and in line with the country's local rules and regulations on remuneration of healthcare professionals. No compensation will be provided for (or to) endocrinologists who enroll but do not complete the survey. Only completed surveys will receive the honorarium.

7.5 Adverse Event Reporting

The research website does not allow for participants to add or comment (i.e., no white space) and as such there is no opportunity to provide anecdotes that could be considered adverse events. As all scenarios are contrived and hypothetical, judgements rendered cannot be considered adverse events.

8. References

Chapter 11 David W. Hosmer, Jr., Stanley Lemeshow, Rodney X. Sturdivant. Applied Logistic Regression. John Wiley & Sons, 2013

Appendix D: Solicitation Email to participate in validation study

Dear Dr. _____,

We would like to invite you to participate in a research study to help refine a diagnostic tool that will be used to assess health status in patients with acromegaly. Your colleagues have recommended that you would be ideally qualified for this short study based on your clinical experience and specialty in treating patients with acromegaly.

We are interested in getting your opinion on the clinical status of hypothetical patients and your perspective on their disease activity status across a range of situations. This study will be conducted via the internet and take approximately 60 minutes of your time. The results will be used to provide a better understanding of how experts like yourself evaluate the health status of patients with acromegaly so that less experienced community practitioners can benefit from your knowledge and experience in their own clinical practice.

In the survey, you will be provided with a series of scenarios that describe the current health status of patients previously diagnosed with acromegaly. Each unique scenario will include five separate aspects of their health status. These five aspects will be the only information available to you. Based on your review of the patient's status, you will be asked to make a clinical judgment as to whether you consider the patient's disease activity to be controlled or not.

The study does not require you to provide any information about any of your patients, only to imagine that the patient described in the scenario is your patient.

We understand that this is an imposition on your time, and we will provide an honorarium of [adjust depending on country] for your participation. All of the information you provide will be kept confidential and only anonymous results will be shared with us or the survey research sponsor.

Please reply to this email if you are interested in participating in this very important research project. The survey company, ICON PRO, will then contact you to determine your eligibility for inclusion and provide you with more information about the study. We hope you are able to join us in this effort.

Sincerely,

On behalf of the members of the ACRODAT Advisory Board:

- Xavier Badia, University of Barcelona, Spain
- Thierry Brue, Centre de Recherche Neurobiologie Neurophysiologie Marseille, France
- Michael Buchfelder, Neurochirurgische Klinik, Universitatsklinikum Erlangen, Germany
- Pia Burman, Uppsala University Hospital, Sweden
- Ezio Ghigo, Città Salute e Scienza (San Giovanni Battista Molinette), Italy
- Jens Otto Lunde Jørgensen, Aarhus University, Denmark
- A.J van der Lely, Erasmus Medical Center Rotterdam, Netherlands
- Anton Luger, Medizinische Universität Wien, Austria
- Christian Strasburger, Charitė Universitätsmedizin Berlin, Germany
- Susan Webb, Hospital de la Santa Creu i Sant Pau Barcelona, Spain

Appendix E: Screening Questionnaire

1. Are you able to read and understand English?

   ☐ Yes ☐ No (not eligible - end screening)

2. What is your gender?

   ☐ Male ☐ Female

3. What is your date of birth? _____

4. What year did you complete your residency in endocrinology? _____

5. Where is your practice located?

   ☐ Canada ☐ Italy

   ☐ Spain ☐ Germany

   ☐ France ☐ United Kingdom

   ☐ Other (*not eligible- end screening*)

6. Where do you see the majority of your acromegaly patients?

   ☐ Hospital

   ☐ Hospital outpatient clinic

   ☐ Private outpatient clinic

   ☐ Other (*not eligible- end screening*)

7. How many years have you been treating acromegaly patients? _____

8. How many unique acromegaly patients do you typically see in a year? _____

   a. If less than five: Do you supervise others who treat acromegaly patients?

   ☐ Yes ☐ No

   [eligible if they a) see >= 5 patients per year or b) they see < 5, but supervise others who treat patients]

9. Have you ever heard of ACRODAT?

☐ Yes ☐ No

b. If yes: Have you been involved in development activities for ACRODAT prior to this study?

☐ Yes ☐ No

c. If yes: Please describe your involvement: _____

[eligible if they a) have not heard of ACRODAT or b) have not been extensively involved in development activities for ACRODAT]

Thanks for your time. We will be in touch with you shortly to give you the particulars of your participation.

Appendix F: Parameter List and Levels Definitions

IGF-I

IGF-I, regardless of assay type, can be described based on its value relative to the normal range. In many cases, this is one of the key aspects of the health status of the patient and the effectiveness of treatment. In our patient scenarios, we indicate the IGF-I in terms of its distance from the upper or lower limit of normal.

IGF-I levels

Level 1: The patient's IGF-I is within normal limits

Level 2: The patient's IGF-I exceeds the upper limit of normal but not more than 1.2X the upper limit of normal, or is below the lower limit of normal

Level 3: The patient's IGF-I is significantly elevated, more than 1.2X the upper limit of normal

Tumour

Tumour status is typically assessed using MRI technology. Increases in pituitary tumour size and invasiveness are frequently associated with disease progression at certain levels. The degree of increase may motivate a change in therapy including re-surgery or radiation.

Tumour levels

Level 1: Based on the most current MRI, the tumour is not visible or has not changed since the prior MRI

Level 2: Based on the most current MRI, a slight increase in tumour size has been observed

Level 3: Based on the most current MRI, a clinically significant increase in tumour size and/or invasiveness has been observed over the prior MRI and/or which may include a worsening in vision

Comorbidities

Patients diagnosed with acromegaly frequently have comorbidities related to their acromegaly diagnosis that respond to acromegaly treatment. Often these comorbidities, though present, are effectively treated and controlled requiring no additional intervention in terms of modifications to acromegaly therapy. In other cases, the severity and possible treatment failure of these comorbidities represent a change in acromegaly disease activity requiring further evaluation and/or acromegaly treatment intervention.

Our scenarios consider three comorbidities known to be directly related to acromegaly – diabetes, sleep apnea, and cardiac disease. The combination of these conditions in terms of their presence or absence and the level of disease control are described in each of the scenarios.

Diabetes may be present and well controlled or not well controlled, with “control” defined as having blood glucose levels within normal limits.

Cardiac disease includes hypertension, hyperlipidemia or other cardiac abnormalities. “Control” in this case refers to a status of adequate control through therapy.

Sleep apnea is present based on patient complaints of mild, moderate, or severe experiences.

Comorbidities Levels

Level 1: The patient does not have a diagnosis of diabetes, complaints of sleep apnea are absent and cardiac disease -if present- is well controlled

Level 2: The patient has a diagnosis of diabetes but their glucose status is within normal limits without other comorbidities OR, even in the absence of a diabetes diagnosis, the patient has a cardiac disease diagnosis but currently it is well controlled. A complaint of mild sleep apnea may be present

Level 3: The patient has diabetes that is not well controlled by therapy OR the patient has diabetes which is well controlled, their cardiovascular disease is not well controlled and they may have complaints of moderate to severe sleep apnea

Symptoms

There are five symptoms that may present at varying levels of severity in patients with acromegaly. These are: headache, excessive sweating, joint pain, fatigue, and soft tissue welling.

The severity of these five symptoms is rated on the Patient Acromegaly Symptom Questionnaire (PASQ), a 0-8 point scale ranging from “Absent” (0) to “Severe, incapacitating”(8).

Signs & Symptoms
Patient-assessed Acromegaly Symptom Questionnaire
(PASQ™)

Listed below are symptoms that some patients experience. Read each one carefully. Please let us know how severe each symptom was during the past week including today.

PASQ administration date ☐☐ / ☐☐ / ☐☐☐☐
M M D D Y Y Y Y

	Absent								Severe, incapacitating
1. Headache	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8
2. Excessive sweating	☐	☐	☐	☐	☐	☐	☐	☐	☐

Symptom Levels

Level 1: The patient reports no or only mild symptoms on the PASQ (all symptoms rated ≤ 2)

Level 2: The patient reports the presence of some symptoms on the PASQ but no single symptom exceeds a score of 6 (mild to moderate) and the mean score is ≤ 4 overall

Level 3: The patient reports significant symptoms on the PASQ with the mean score > 4 OR one or more symptoms rated > 6

Quality of Life

For the purposes of this assessment, patient self-reported quality of life includes physical, social, and emotional functioning using a standardized and validated questionnaire. Higher scores are indicative of a better health-related quality of life. The degree of impairment in quality of life is assessed on a 100 point scale with 0 being "death" and 100 being perfect quality of life. Values above 80 can be interpreted as no or minimal impairment, scores between 60 and 80 as moderate impairment and scores below 60 as significant impairment.

The hypothetical patient's quality of life will be reported as follows:

Level 1: The patient reports no or minimal impairment in quality of life (score above 80)

Level 2: The patient reports mild to moderate impairment in quality of life (score between 60 and 80)

Level 3: The patient reports significant impairment in quality of life (score below 60)

Appendix G: Guidance Notes for Validation Study Participants

Introduction

Welcome to the ACRODAT online survey!

Thank you for agreeing to participate in this important study. The primary goal of this survey is to get your medical opinion about the health status and need for treatment modification in a variety of hypothetical patients with acromegaly that you might see in your daily practice. As an expert in the field, your opinion is extremely valuable and important to us. This survey is designed to take approximately 60 minutes to complete. If you do not have time to complete it in one sitting, you may exit the survey at any time and resume later from where you left off.

All your responses will be kept confidential. The survey sponsor will not know your specific answers to any of the scenarios and will only get aggregated data.

What you will be asked to do

You will be presented with a series of hypothetical patient cases (scenarios), each described by five clinical parameters. These parameters and their levels are defined below.

You will be asked to evaluate the patient's current status based only on the given disease activity parameters and determine, based on your clinical knowledge and experience, whether or not the patient's disease is adequately controlled. If you determine that the patient's disease is not adequately controlled, you will be asked to indicate whether you believe that treatment modification is definitely necessary or whether you believe that further evaluation would be needed to make a decision about treatment modification. Below are the definitions that we will use to help categorize the patient's overall health status and the decision of which action to take.

Stable (S)

The patient is adequately controlled.

Mild Disease Activity (M-DA)

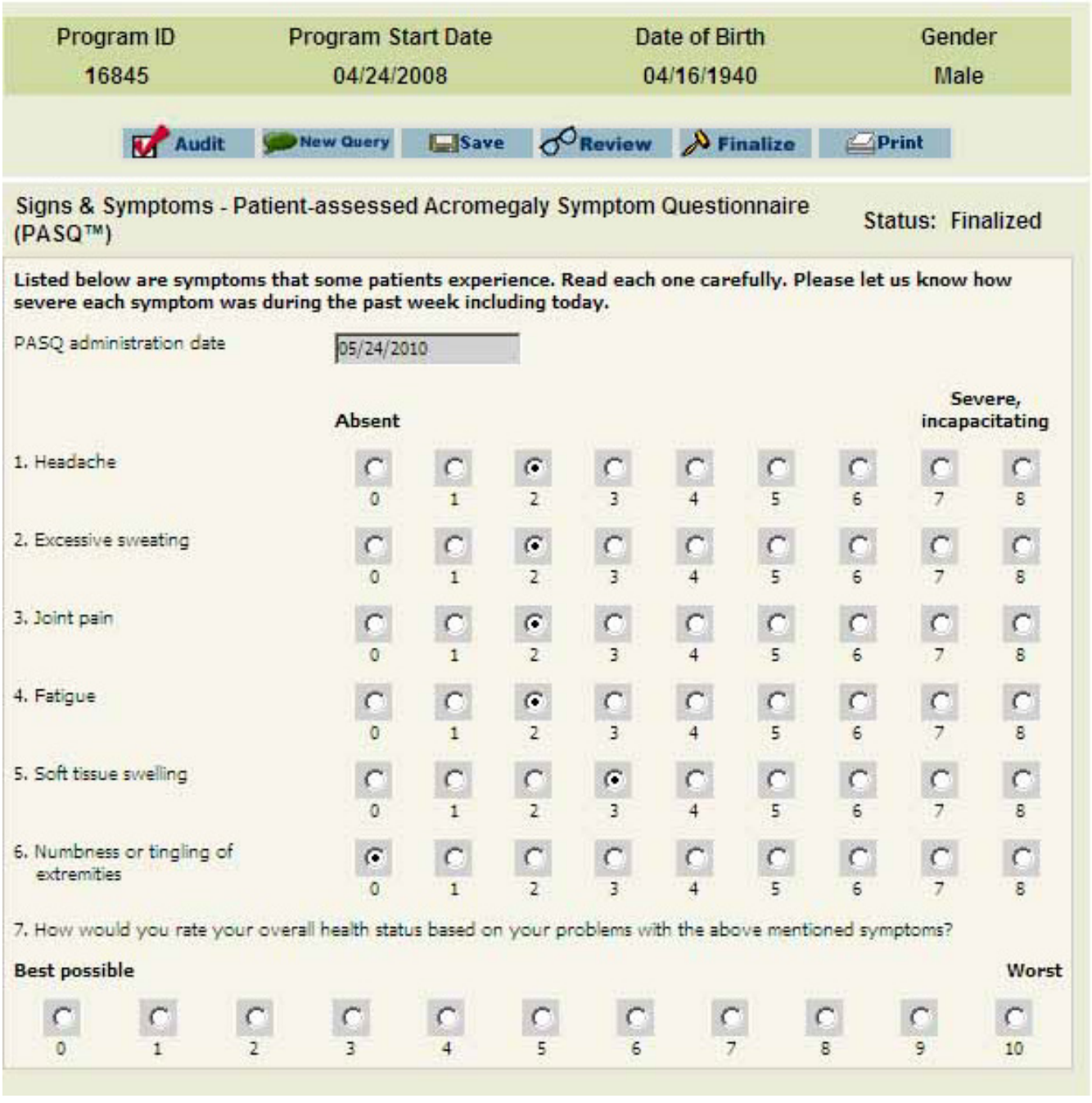
The patient shows mild disease activity. Further evaluation of the patient's condition is needed.

Significant Disease Activity (S-DA)

The patient shows significant disease activity requiring immediate and further evaluation.

Throughout the survey, keep in mind that there is no right or wrong answer to each scenario – it is your clinical opinion that matters. For each scenario, please choose only one of the three available options. Choose the option that best fits the particular scenario, even though it may not be exactly what you would do for every patient like this. Do your best to answer each scenario, even though some scenarios may describe patients you would likely never see in the clinic. Please note, you will not be asked to provide specific treatment recommendations should you indicate that further assessment or treatment change is indicated.

Appendix H: Patient-Assessed Acromegaly Symptom Questionnaire (PASQ)



Program ID	Program Start Date	Date of Birth	Gender
16845	04/24/2008	04/16/1940	Male

Audit | New Query | Save | Review | Finalize | Print

Signs & Symptoms - Patient-assessed Acromegaly Symptom Questionnaire (PASQ™)

Status: Finalized

Listed below are symptoms that some patients experience. Read each one carefully. Please let us know how severe each symptom was during the past week including today.

PASQ administration date: 05/24/2010

	Absent								Severe, incapacitating
1. Headache	0	1	2	3	4	5	6	7	8
2. Excessive sweating	0	1	2	3	4	5	6	7	8
3. Joint pain	0	1	2	3	4	5	6	7	8
4. Fatigue	0	1	2	3	4	5	6	7	8
5. Soft tissue swelling	0	1	2	3	4	5	6	7	8
6. Numbness or tingling of extremities	0	1	2	3	4	5	6	7	8

7. How would you rate your overall health status based on your problems with the above mentioned symptoms?

Best possible										Worst
0	1	2	3	4	5	6	7	8	9	10

Appendix I: ACROQol Disease Specific QoL tool for Acromegaly

1. My legs are weak*
2. I feel ugly**
3. I get depressed*
4. I look awful in photographs**
5. I avoid going out very much with friends because of my appearance***
6. I try to avoid socializing***
7. I look different in the mirror**
8. I feel rejected by people because of my illness***
9. I have problems carrying out my usual activities*
10. People stare at me because of my appearance***
11. Some part of my body (nose, feet, hands,...) are too big**
12. I have problems doing things with my hands, for example. sewing or hand
13. The illness affects my performance at work or in my usual tasks*
14. My joints ache*
15. I am usually tired*
16. I snore at night*
17. It is hard for me to articulate words due to the size of mv tongue**
18. I have problems with sexual relationships***
19. I feel like a sick person*
20. The physical changes produced by my illness govern my life***
21. I have little sexual appetite***

Appendix J: Primary manuscript accepted to the journal 'Pituitary'

Development of ACRODAT®, a new software medical device to assess disease activity in patients with acromegaly

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Abstract:

Purpose Despite availability of multimodal treatment options for acromegaly, achievement of long-term disease control is suboptimal in a significant number of patients. Furthermore, disease control as defined by biochemical normalization may not always show concordance with disease-related symptoms or patient's perceived quality of life. We developed and validated a tool to measure disease activity in acromegaly to support decision-making in clinical practice.

Methods An international expert panel (n = 10) convened to define the most critical indicators of disease activity. Patient scenarios were constructed based on these chosen parameters. Subsequently, a panel of 21 renowned endocrinologists at pituitary centers (Europe and Canada) categorized each scenario as stable, mild, or significant disease activity in an online validation study.

Results From expert opinion, five parameters emerged as the best overall indicators to evaluate disease activity: insulin-like growth factor I (IGF-I) level, tumor status, presence of comorbidities (cardiovascular disease, diabetes, sleep apnea), symptoms, and health-related quality of life. In the validation study, IGF-I and tumor status became the predominant parameters selected for classification of patients with moderate or severe disease activity. If IGF-I level was ≤1.2x upper limit of normal and tumor size not significantly increased, the remaining three parameters contributed to the decision in a compensatory manner.

Conclusion The validation study underlined IGF-I and tumor status for routine clinical decision-making, whereas patient-oriented outcome measures received less medical attention. An Acromegaly Disease Activity Tool (ACRODAT) is in development that might assist clinicians towards a more holistic approach to patient management in acromegaly.

Key terms: Acromegaly, AcroQoL, patient-reported outcomes, ACRODAT

Introduction

Acromegaly is a rare chronic disease associated with metabolic abnormalities, risk of cardiovascular complications, slowly progressive, irreversible disfigurement, and increased mortality [1]. In more than 99% of patients, acromegaly is the result of a growth hormone (GH)-producing pituitary tumor, which causes elevated circulating levels of GH and insulin-like growth factor-I (IGF-I) [2]. Visible signs include enlarged hands and feet, enlarged jaw and facial bones, thickening of the skin, and excessive sweating. Common patient complaints also include headache, joint pain, fatigue and sleep disturbances [1, 2]. Acromegaly has also been associated with reduced quality of life (QoL) [3], which may show improvement with treatment [4-6]. However, patients are frequently not diagnosed until 5–10 years after onset [1] and, if disease control is not achieved, acromegaly is associated with increased mortality and risk of metabolic and cardiac complications [1, 7, 8].

Several guidelines for assessment of disease activity are available [9, 10]. A widely accepted consensus on criteria for cure defines active disease as (1) a random GH >1 µg/L and nadir GH after oral glucose tolerance test ≥0.4 µg/L; (2) elevated IGF-I; and (3) clinically active. A definition of the term “clinically active” is not provided. GH and IGF-I are key biochemical parameters to assess disease activity in acromegaly, but the variability in assay performance and broad normal ranges may limit their predictive value of disease control. For patients on pegvisomant (PEGV) treatment, normalization of IGF-I is the only reliable marker of disease control, as PEGV blocks the GH receptor and results in elevated rather than reduced GH levels [11].

Even when biochemical control is achieved, patients may still experience disease-specific symptoms such as fatigue, arthralgia, and a generally reduced health status and QoL [6, 12, 13]. The patients’ own perspectives of their health status may therefore be an important additional measure to assess the level of disease activity and for clinical decision-making.

In patients with significantly elevated IGF-I levels, the treatment goal of achieving biochemical control seems an obvious decision [9, 10]. Despite this, acromegaly registries have reported failure to fully control IGF-I in more than 30% of patients over time [14, 15]. Whether a mild elevation in IGF-I level in a patient without symptoms

requires treatment may be more controversial. The same applies for patients with normalized IGF-I levels who have impaired QoL and/or clinical signs of disease activity.

Our first objective was to convene a panel of acromegaly experts to identify the most relevant and meaningful set of clinical parameters and their severity level in order to define disease activity status of patients with acromegaly. Second, we conducted a discrete choice experiment to observe the level of agreement between these parameters, including defined severity levels, and the treatment goals utilized in routine clinical practice by endocrinologists specialized in acromegaly. The results are being used to build the Acromegaly Disease Activity Tool (ACRODAT) that will support objective as well as patient-reported indicators of management.

Materials and Methods

Identification of key parameters

A panel of 10 experts in the field of endocrinology, neurosurgery, and acromegaly management was convened to determine the appropriate health status parameters and scoring algorithm for ACRODAT development. During five full-day panel meetings over a 2.5-year period, members were asked to map all disease parameters associated with acromegaly. The combined list was refined based on criteria related to their importance in enabling clinical monitoring of disease activity, which data would be readily available as part of routine clinical practice, the relevance to health status focusing on the clinical as well as patient perspective, and the responsiveness of these chosen parameters to appropriate clinical action. The panel members were then asked to define clinical descriptions for the three levels of severity of each individual parameter: level 1: the patient is adequately controlled; level 2: the patient shows mild disease activity, further evaluation of the patient's condition is needed; level 3: the patient shows significant disease activity, requiring clinical action.

Validation study

The next step in the development of ACRODAT was to evaluate the predictive validity of the five selected key parameters and their severity levels by a separate cohort of endocrinologists who routinely managed patients with acromegaly in clinical practice. The validation study had two main objectives: (1) to assess the inter-rater agreement of disease activity status among practicing endocrinologists and (2) develop and assess a model that predicts renowned endocrinologists' judgment of disease activity status in

patients with acromegaly, based on a set of hypothetical patient scenarios. ICON plc (Dublin, Ireland), an independent contract research organization, was contracted (project number 0002-1088) to perform the validation study.

For each scenario, the physicians were asked whether the patient (i.e., adults with confirmed diagnosis of acromegaly) described by the hypothetical profile was “stable” (S: the patient is adequately controlled), had “mild disease activity” (M-DA: the patient shows mild disease activity, further evaluation of the patient’s condition is needed), or had “significant disease activity” (S-DA: the patient shows significant disease activity requiring clinical action). The three disease activity categories were color-coded as green (S), yellow (M-DA), or red (S-DA). The five parameters, and three levels within each parameter, produced a total of 243 (35) possible patient profiles or scenarios. Though some scenarios may have reflected a patient profile that would unlikely be seen in clinical practice, the expert panel recommended retaining all possible scenarios for completeness and to avoid making any assumptions about the feasibility of the scenarios.

It was estimated that it would take each physician approximately 1 hour to rate a total of 52 scenarios; therefore, the number of possible scenarios to be rated per individual endocrinologist was set at 52. The study was designed to ensure sufficient variation and coverage of health parameters in the scenarios by using a random selection approach. In addition, a subset of scenarios specifically selected to reflect a range of health status severity was presented to all participants to allow for examination of inter-rater agreement. The 10 “common” scenarios were selected by the expert panel and included clinically plausible scenarios representing a wide range of overall health status, from fairly good health (all parameters at level 1) to very poor health (all parameters at level 3). In the survey, each parameter was color coded according to the level of severity as an easy reminder for the rater as to the defined differences in level and to reduce random error. A summary page was included at the end of the survey to allow physicians to review all of their response and go back if they wanted to change an answer.

Selection of participants

In all, 42 endocrinologists (at least five per country) were identified by the expert panel to be invited to participate. Initial solicitation e-mails were sent by the expert panel member who had recommended the physician. Those who agreed to participate were contacted by ICON via telephone or email and screened for eligibility. Endocrinologists had to meet

the following criteria: (1) worked in a hospital, hospital outpatient clinic, or private outpatient clinic; (2) saw at least five acromegaly patients annually or, if fewer, supervised others who treat acromegaly patients; (3) not familiar with ACRODAT or was not involved in extensive development activities for ACRODAT prior to this study; (4) able to read and understand English; (5) willing and able to participate in the study, which involved completing an online survey lasting approximately 60 min.

After providing agreement to participate in the study, physicians were emailed a link to complete the online survey. Participants were compensated for their time in completing the survey.

Sample size

Due to the exploratory nature of this study, formal sample size calculations were not considered appropriate. Nevertheless, in studies where multivariable modeling is expected to be performed, the study should have at least 10 events for each variable included in the model. In this study, predictor variables comprised the five health status parameters, each of which had a three-level ordinal variable. For each health status parameter, indicator variables were created for all but one of the levels (the referent level S was not coded because it is a linear combination of the other levels). Therefore, the multivariable model would have 10 variables.

An “event” can be defined as the physician categorization of a hypothetical patient as S (or having M-DA or S-DA). An assumption was made that an “event” would occur in roughly one third of the patients (i.e., roughly one third of the hypothetical patients would be categorized into each of the three possible outcomes), which meant that the study would require 300 responses (10 events / 10 variables / [1/3]). Since the same physician was expected to evaluate many different scenarios, observations in the dataset were not independent, causing some statistical power to be lost. As an attempt to adjust for this potential loss in statistical power, the number of observations was doubled, resulting in a dataset with a minimum of 600 observations. Given that 21 physicians were available to evaluate the scenarios, the study required each physician to evaluate a minimum of 29 scenarios (600 / 21).

Statistical analyses

Survey results were analyzed using SAS® 9.3 (SAS Institute Inc, Cary, NC, USA). The Fleiss’ kappa was calculated to provide a summary statistical measure for assessing the

reliability of agreement between endocrinologists in rating the common scenarios. For algorithm development to predict disease activity categorization based on values of the five health status parameters, a combination of the Classification And Regression Tree (CART) method and multivariable logistic regression was implemented.

Because the purpose of this analysis was not to test any specific hypothesis, no p-values were presented, no significance testing was performed, and no adjustments for multiple comparisons were made.

Results

Key parameters and levels of severity

Five parameters were selected by the panel of acromegaly experts as key aspects of the patient's condition: IGF-I level, tumor status, comorbidities, signs and symptoms, and health-related QoL (HRQoL). A funnel approach was used to crystallize these key parameters from a large set of disease parameters (Table 1).

Table 3: Selection of key parameters associated with disease activity in acromegaly using the funnel approach

Parameters Associated with Acromegaly	Disease Parameters (Routinely) Measured in Clinic	Key Measure of Disease Activity[a]	Selection of Key Parameters by Exclusion Criteria[b]
Biochemical	IGF-I, GH, prolactin, IGFBP3	IGF-I, GH, prolactin	IGF-I
Pituitary tumor	Pituitary tumor size increase / reduction, tumor invasiveness, visual field defects, headache, apoplexy	Tumor size increase / reduction, tumor invasiveness (measured by MRI), loss of vision	Tumor size increase, tumor invasiveness (measured by MRI), loss of vision
Comorbidities	Hypertension, hyperlipidemia, left ventricular hypertrophy, cardiomyopathy, congestive heart failure, arrhythmias, valvular heart disease, cardiac disease, carpal tunnel syndrome, arthritis, osteoporosis, acral changes, glucose intolerance / diabetes, hypopituitarism, colonic polyps, colonic cancer, other malignancies, sleep disturbances, OSA, menstrual abnormalities, infertility,	Hypertension Cardiac disease Glucose intolerance / diabetes OSA Hypopituitarism	Cardiac disease (including hypertension, hyperlipidemia, or other cardiac abnormalities) Diabetes OSA

Parameters Associated with Acromegaly	Disease Parameters (Routinely) Measured in Clinic	Key Measure of Disease Activity[a]	Selection of Key Parameters by Exclusion Criteria[b]
	galactorrhea, family history		
Symptoms	Headache, excessive sweating, joint pain, fatigue, soft tissue swelling, numbness or tingling of extremities, prognathism, frontal bossing, skin tags, oily skin texture, gigantism	Headache, excessive sweating, joint pain, fatigue, soft tissue swelling (measured by SSS)	Headache, excessive sweating, joint pain, fatigue, soft tissue swelling (measured by SSS)
HRQoL	Depression, pain, low energy, decreased libido, impotence, low self-esteem, social isolation	Physical and psychological (appearance and personal relations), domains covered by AcroQoL	Physical and psychological (appearance and personal relations), domains covered by AcroQoL

IGF-I insulin-like growth factor-I, *GH* growth hormone, *IGFBP3* insulin-like growth factor-binding protein 3, *MRI* magnetic resonance imaging, OSA obstructive sleep apnea, SSS Signs and Symptoms Score, AcroQoL Acromegaly Quality of Life Questionnaire

[a]That could also be modified by existing treatment options (both for acromegaly and for concomitant diseases).

[b]Criteria include: (i) minimal data entry requirement, (ii) exclude if not fully confirmatory of disease activity, and (iii) difficult to collect in routine practice

Each parameter was defined and agreed upon by the panel at three levels of severity (Table 2).

Table 4: Five selected parameters and their level of severity

Health Status Parameter	Parameter Levels
IGF-I	1. = IGF-I is within normal limits 2. = IGF-I exceeds the ULN but not >1.2× ULN, or is below LLN 3. = IGF-I is significantly elevated, >1.2× ULN
Tumor Status	Based on the most current MRI: 1. = Tumor is not visible or has not changed since prior MRI 2. = A slight increase in tumor size (≤20 %) is observed 3. = A clinically significant increase in tumor size (>20 %) and/or invasiveness is observed since prior MRI and/or a worsening in vision is observed
Comorbidities	1. = No diabetes diagnosis, complaints of sleep apnea are absent, and cardiac disease, if present, is well controlled 2. = Diabetes controlled by therapy, with no concomitant complaints of sleep apnea, and cardiac disease, if present, is controlled with therapy *or* no diabetes diagnosis but complaints of sleep apnea and/or cardiac disease that is not well controlled with therapy 3. = Diabetes is not well controlled by therapy *or* diabetes is well controlled, with complaints of moderate to severe sleep apnea and/or uncontrolled cardiac disease
Symptoms	1. = Mild: Patient reports no or only mild symptoms on SSS (all symptoms rated ≤2) 2. = Moderate: Patient reports presence of some symptoms on SSS but no single symptom exceeds a score of 6 (mild to moderate) and mean score is ≤4 overall 3. = Severe: Patient reports significant symptoms on SSS, with mean score >4 *or* one or more symptoms rated >6
Health-related QoL Impairment[a]	1. = Patient reports no or minimal impairment in QoL (score ≥60) 2. = Patient reports mild to moderate impairment in QoL (40 ≤ score <60) 3. = Patient reports significant impairment in QoL (score <40)

IGF-I insulin-like growth factor I, *ULN* upper limit of normal, *LLN* lower limit of normal, *MRI* magnetic resonance imaging, *SSS* Signs and Symptoms Score, *QoL* quality of life, *AcroQoL* Acromegaly Quality of Life Questionnaire.

[a]The endocrinology experts selected AcroQoL as the most suitable currently available tool to address disease-specific QoL assessment. In order to avoid response bias, the term “health-related quality of life” was used in the validation study.

The IGF-I levels were assigned using deviations from normal levels. The tumor status parameter was based on results of magnetic resonance imaging and levels were assigned based on a significant mass effect resulting in a worsening of vision or a change in tumor size and invasiveness over time. The comorbidities parameter was assigned based on the presence or absence and severity of several acromegaly associated conditions (i.e., diabetes, sleep apnea, and cardiac disease). The symptoms parameter was the Signs and Symptoms Score (SSS), based on an abbreviated version of the original Patient Assessed Symptom Questionnaire (PASQ); it is a disease-specific five items questionnaire, scored 0–8, that considers headache, perspiration, joint pain, fatigue, and soft tissue swelling. The maximum score of 40 is indicative of severe signs and symptoms [3]. The HRQoL impairment parameter was based on the standardized total score from a validated measure of the Acromegaly Quality of Life Questionnaire (AcroQoL). The AcroQoL is a disease-specific questionnaire covering physical and psychological aspects of acromegaly. It comprises 22 questions, each having five possible responses, scored 1–5; the maximum score of 110 reflects best possible QoL and is quoted as a percentage [16]. The parameter of HRQoL was described in general terms and the interpretation of scores was based on three levels of impairment: none or minimal, moderate, and severe. The specific measure was not identified in the validation study to avoid response bias based on the clinician’s familiarity with and perceptions of the utility of any single instrument.

Validation study

A total of 21 physicians from Canada, France, Germany, Italy, Spain, and the United Kingdom completed the internet-based survey in 2015. The overall characteristics of the participants are summarized in Table 3. Fourteen of the 21 endocrinologists worked in a hospital outpatient clinic. On average, they reported having more than 20 years of experience in treating acromegaly and had treated an average number of 48 patients with acromegaly annually.

Inter-rater agreement

Inter-rater agreement was assessed for the subset of scenarios (common scenarios) that all participating physicians were asked to rate. The extent to which physicians agreed on each scenario (how many rater–rater pairs were in agreement relative to the number of all possible rater–rater pairs, and represented by Pr in Table 4) varied by scenario. The most extreme scenarios — all parameters at the lowest level of severity (level 1) or all parameters at the highest level of severity (level 3) — had complete agreement among physicians (Pr = 1), with all physicians rating level 1 and level 3 as S and S-DA, respectively. The Fleiss' kappa value was 0.526, which indicated a moderate amount of inter-rater agreement. Because a single physician rated one scenario as S whereas all other physicians rated this scenario as S-DA, a sensitivity analysis on inter-rater agreement was performed, excluding this physician. With the outlier removed, a Fleiss' kappa value of 0.549 was observed.

Algorithm development

Of the 21 physicians, 20 evaluated the maximum number of scenarios each (52 scenarios), whereas one physician evaluated 51 scenarios, yielding a total of 1,091 observations. The outcome variable was an ordinal three-level physician assessment of hypothetical patient condition (disease activity categorization).

Generally, an IGF-I >1.2x upper limit of normal or the worst tumor status (both indicated as level 3) tended to have high scores for S-DA and very low scores for S. Similar patterns for the highest levels of severity were observed for comorbidities, symptoms, and HRQoL impairment; however, the distributions were less extreme. Medium levels of severity (level 2) of each health status parameter tended to have higher scores for M-DA and S-DA compared with S. No apparent trend was observed for the lowest level of severity (level 1) of the health status parameters.

In the CART decision-tree model, only two of the health status parameters had an immediate influence in the ultimate disease activity rating: IGF-I and tumor status (see Fig. 1). If IGF-I was indicated as level 3, then disease activity was immediately rated as S-DA. Otherwise, tumor status was evaluated and if it was indicated as level 3, then disease activity was similarly rated as S-DA. These straight-away terminal nodes in the decision tree based on a level 3 indication of either IGF-I or tumor status suggested a non-compensatory decision-making process. Regardless of the level of the other three clinical parameters, there was no opportunity for them to compensate for high levels of

IGF-I or tumor status. Hence, it was decided that the overall disease activity status would be classified as S-DA if either IGF-I or tumor status was indicated as level 3. However, if neither of these two health status parameters were indicated as level 3, then the other three health status parameters (comorbidities, symptoms, and HRQoL), along with the remaining levels of IGF-I and tumor status, appeared to operate in a compensatory manner.

To further elucidate the contribution of all parameters, logistic regression models were constructed. Multivariable logistic regression was performed only on the parts of the CART decision tree that were deemed to behave in a compensatory manner. Specifically, the independent variables were the three-level categorical variables related to comorbidities, symptoms, and health-related quality of life impairment (outlined in Table 2). The outcome variable was modeled as two separate binary choices, which may more closely resemble what occurs in clinical practice. The first choice (Model 1) was whether the patient was considered to be S or M-DA/S-DA; that is, whether the patient was stable or not. If the physician failed to rate the scenario as S, then the second choice (Model 2) was whether the patient was considered to be S-DA versus M-DA. To create a single scale from both models, the predicted probabilities from Model 1 and Model 2 were combined. For each scenario, the probability of it being rated as S was defined as the predicted probability from Model 1, and the probability of it being rated as S-DA was defined as the predicted probability from Model 2. The probability of each scenario being rated as M-DA was then computed as 1 minus the sum of the other two probabilities. Hence, for each scenario, the probabilities (P) of it being rated as S (P_S), M-DA ($P_{M\text{-}DA}$), or S-DA ($P_{S\text{-}DA}$) summed to 1.

A single continuous ACRODAT score for each scenario was calculated as a weighted average of these single scale probabilities (P_S, $P_{M\text{-}DA}$, and $P_{S\text{-}DA}$), then transformed onto a 0 to 1 scale as follows:

$$\text{ACRODAT Score} = \{[(1^* P_S) + (2^* P_{M\text{-}DA}) + (3^* P_{S\text{-}DA})] - 1\} / 2$$

Worked examples for the calculation of the single continuous ACRODAT score are provided in the Appendix. It was further decided to classify the overall disease activity status for scenarios with an IGF-I and/or tumor status level below 3 as M-DA if PM-DA was higher than P_S, and as S if P_S was higher than $P_{M\text{-}DA}$.

Discussion

The present study shows the development of the ACRODAT tool intended to help clinicians in measuring disease activity among patients with acromegaly. The funnel approach to extract key parameters of disease activity for acromegaly from an evidence-based review and consensus to enable individualized treatment goals for patients and endocrinologists was found to be feasible. In addition, the adoption of such translation of clinical targets, which also includes the patient's perspective through patient-reported outcomes such as SSS and AcroQoL, provides a holistic approach to disease management. Consideration in selection of these key parameters included their ease of availability in routine clinical practice as well as their likelihood of responsiveness to available treatments.

The validation study outcome was a confirmation of the current status of acromegaly management, which demonstrated a main focus on tumor status and IGF-I value. Whether inclusion of patient-reported outcomes as well as comorbidity status would improve the quality of clinical decision-making remains to be demonstrated, but the tool devised from our study facilitates a holistic approach and may alert the treating endocrinologist to the patient's needs and comorbidity status.

In the validation study, IGF-I and tumor status definitions for the highest level of severity (level 3) were generally accepted and validated as representing significant disease activity requiring clinical action. If neither of these two health status parameters were indicated as level 3, then the other three health status parameters (comorbidities, symptoms, and HRQoL) along with the remaining levels of IGF-I and tumor status appeared to operate in a compensatory manner.

When the pituitary tumor mass effect is clinically insignificant and the lesion is considered to be stable, remission in acromegaly is often defined exclusively in biochemical terms. Although biochemical control is considered key to achieve remission / cure, it does not guarantee symptom relief and the general well-being of the patient. Symptoms of acromegaly and reduced QoL may persist despite normal post-treatment serum IGF-I levels [6, 12, 13]. The benefits to patients and their QoL are therefore a relevant consideration in the medical management of acromegaly, as also proposed in recent guidelines [10]. It is also recommended to closely monitor and rigorously manage patients with acromegaly for associated comorbidities [9].

When considering both GH and IGF-I, elevated IGF-I levels were regarded by the panel to be the preferred biochemical predictor for disease activity in acromegaly, and reliable, age-related normative data have recently become available for IGF-I assays [17]. For patients receiving PEGV treatment, normalization of IGF-I is the only available biochemical marker of disease control [11]. Over the years, consensus statements have recommended varying levels of GH to represent control whereas IGF-I guidance has remained the same, stating that the age-adjusted levels should be in the normalized range [9].

Diabetes, cardiovascular disease, and sleep apnea were selected as the key comorbidities, as these can be managed and improved upon by appropriate modification of treatments used for acromegaly and for comorbidity-specific treatments. Other comorbidities characteristic to acromegaly, such as arthritis, osteoporosis, and colonic polyps, were not selected. Although prevalent, these comorbidities are less modifiable by treatments used for acromegaly, especially in advanced disease state. Cardiovascular disease is considered a key factor because of the heightened risk for cardiovascular complications and consequent need for early identification and treatment. Diabetes, even if it was adequately controlled with anti-diabetic medication, was considered by the expert panel as an independent risk factor requiring further evaluation. Obstructive sleep apnea is a comorbidity that may occur in 25 to 60% of patients, and may contribute to hypertension and cardiovascular disease. The apnea-hypopnea index may improve during effective treatment of acromegaly [18, 19]. To which degree disease control and treatment approach are related to QoL is still a matter of debate. Rowles et al [3] found no correlation between biochemical control and any measure of QoL. QoL is a multifactorial issue that needs an individualized approach for detection and management [20].

Despite the availability of different treatment options, patients do not always achieve disease control as defined by the treatment guidelines. Success of surgery is very much dependent on the type of tumor (microadenoma vs. macroadenoma, invasion of cavernous sinus) and the experience of the pituitary surgeon [21, 22]. Medical therapy with dopamine agonists or somatostatin analogs results in biochemical control in only 20–40% of drug-naïve patients [23-26]. Second line medical treatment with PEGV has been shown to normalize IGF-I levels in 75–97% of patients [27–29], but is often considered a last-resort treatment. Radiotherapy is considered a viable therapy in only a subset of patients due to its long-term side effects [9]. Other factors may contribute to the

lack of disease control in some patients: the patient's reluctance to escalate therapy, non-compliance, discordant levels of IGF-I and GH in the individual patient, and modifications in pharmacotherapy [15]. This underlines the importance of continuous monitoring of the patient's condition.

One important limitation of the validation study is that other factors not considered in ACRODAT may influence the overall disease activity status of the patient. It goes without saying that physicians should always utilize their own knowledge and judgment when assessing the disease activity of their patients and making adjustments to their plan of treatment.

The next step in the ACRODAT development project will be to prospectively evaluate whether patients monitored by ACRODAT, with appropriate clinical decisions based on disease activity status, benefit from improved treatment outcomes both in the short- and long-term. The resulting algorithm that yielded an overall continuous score (ACRODAT score) to rate overall disease activity on a 0 to 1 scale may be a beneficial tool for physicians to use in evaluating patients with acromegaly. The tool's design will not be to provide any treatment recommendations; however, it will provide guidance as to whether clinical action is deemed necessary for one or more of the key parameters.

In summary, we were able to develop a disease activity tool specific for acromegaly based on five easily measurable key outcome disease parameters. Monitoring changes at regular intervals may facilitate better treatment decisions and support a holistic approach to acromegaly disease management. SAGIT®, another clinician-reported outcome instrument currently in development, reaffirms the need for such instruments to support acromegaly management [30]. The unique methodology applied to the development of ACRODAT may also be useful in other rare disease settings.

COMPLIANCE WITH ETHICAL STANDARDS

Disclosure of Potential Interests

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Research Involving Human Participants and/or Animals

This survey does not contain studies with human participants or animals performed by any of the authors.

Informed Consent

For this type of study, formal consent was not required.

Appendix

Worked examples for the calculation of the single continuous ACRODAT score based on two of the 10 common scenarios. Scenario 92: IGF-I: level 2; Tumor size: level 1; Comorbidities: level 2; Symptoms: level 1; QoL: level 2. Physicians (n=21) rated this hypothetical patient case as follows: stable (n=4), mild disease activity (n=16), significant disease activity (n=1). Based on multivariable logistic regression, the predicted probability of the scenario being rated as S versus M-DA/S-DA was 0.133. The predicted probability of the scenario being rated as S-DA vs. M-DA (among non-S) was 0.06. Therefore, the predicted probability of the scenario being rated as M-DA was 1–(0.06+0.133) = 0.807 and

the ACRODAT Score = {[(1* 0.133) + (2* 0.807) + (3*0.06)] – 1} / 2 = 0.463. As $_{PM-DA}$ is higher than P_S, the overall disease activity is classified as M-DA.

Scenario 243: IGF-I: level 3; Tumor size: level 3; Comorbidities: level 3; Symptoms: level 3; QoL: level 3. All physicians rated this hypothetical patient case as having significant disease activity. The P_{S-DA} is 1, P_S and P_{M-DA} are both 0 and the resulting ACRODAT Score = {[(1* 0) + (2* 0) + (3* 1)] – 1} / 2 = 1. As IGF-I and Tumor size are both indicated as 3, the overall disease activity is classified as S-DA.

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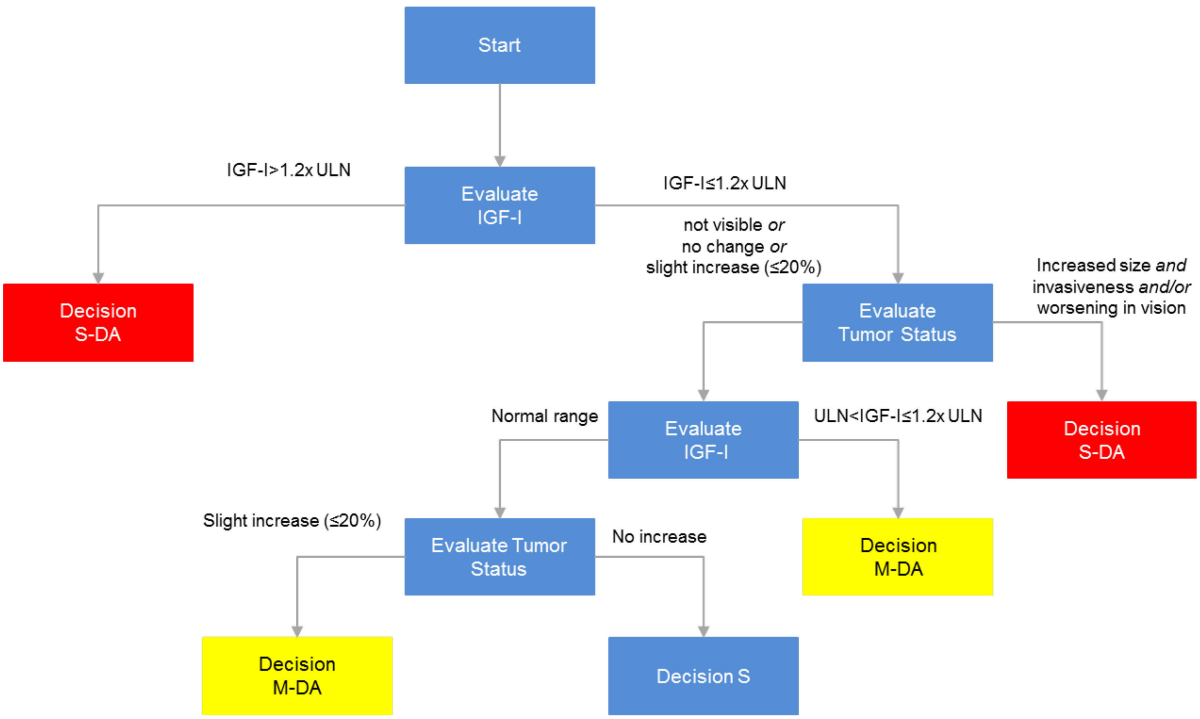
Figure Legend



IGF-I insulin-like growth factor-I, *M-DA* mild disease activity, S stable, *S-DA* significant disease activity, *ULN* upper limit of normal

Table 1: Selection of key parameters associated with disease activity in acromegaly using the funnel approach

Parameters Associated with Acromegaly	Disease Parameters (Routinely) Measured in Clinic	Key Measure of Disease Activity[a]	Selection of Key Parameters by Exclusion Criteria[b]
Biochemical	IGF-I, GH, prolactin, IGFBP3	IGF-I, GH, prolactin	IGF-I
Pituitary tumor	Pituitary tumor size increase / reduction, tumor invasiveness, visual field defects, headache, apoplexy	Tumor size increase / reduction, tumor invasiveness (measured by MRI), loss of vision	Tumor size increase, tumor invasiveness (measured by MRI), loss of vision
Comorbidities	Hypertension, hyperlipidemia, left ventricular hypertrophy, cardiomyopathy, congestive heart failure, arrhythmias, valvular heart disease, cardiac disease, carpal tunnel syndrome, arthritis, osteoporosis, acral changes, glucose intolerance / diabetes, hypopituitarism, colonic polyps, colonic cancer, other malignancies, sleep disturbances, OSA, menstrual abnormalities, infertility, galactorrhea, family history	Hypertension Cardiac disease Glucose intolerance / diabetes OSA Hypopituitarism	Cardiac disease (including hypertension, hyperlipidemia, or other cardiac abnormalities) Diabetes OSA
Symptoms	Headache, excessive sweating, joint pain, fatigue, soft tissue swelling, numbness or tingling of extremities, prognathism, frontal bossing, skin tags, oily skin texture, gigantism	Headache, excessive sweating, joint pain, fatigue, soft tissue swelling (measured by SSS)	Headache, excessive sweating, joint pain, fatigue, soft tissue swelling (measured by SSS)
HRQoL	Depression, pain, low energy, decreased libido, impotence, low self-esteem, social isolation	Physical and psychological (appearance and personal relations), domains covered by AcroQoL	Physical and psychological (appearance and personal relations), domains covered by AcroQoL

IGF-I insulin-like growth factor-I, *GH* growth hormone, *IGFBP3* insulin-like growth factor-binding protein 3, *MRI* magnetic resonance imaging,

OSA obstructive sleep apnea, SSS Signs and Symptoms Score, AcroQoL Acromegaly Quality of Life Questionnaire

[a]That could also be modified by existing treatment options (both for acromegaly and for concomitant diseases).

[b]Criteria include: (i) minimal data entry requirement, (ii) exclude if not fully confirmatory of disease activity, and (iii) difficult to collect in routine practice.

Table 2: Five selected parameters and their level of severity

Health Status Parameter	Parameter Levels
IGF-I	1. = IGF-I is within normal limits 2. = IGF-I exceeds the ULN but not >1.2× ULN, or is below LLN 3. = IGF-I is significantly elevated, >1.2× ULN
Tumor Status	Based on the most current MRI: 1. = Tumor is not visible or has not changed since prior MRI 2. = A slight increase in tumor size (≤20 %) is observed 3. = A clinically significant increase in tumor size (>20 %) and/or invasiveness is observed since prior MRI and/or a worsening in vision is observed
Comorbidities	1. = No diabetes diagnosis, complaints of sleep apnea are absent, and cardiac disease, if present, is well controlled 2. = Diabetes controlled by therapy, with no concomitant complaints of sleep apnea, and cardiac disease, if present, is controlled with therapy *or* no diabetes diagnosis but complaints of sleep apnea and/or cardiac disease that is not well controlled with therapy 3. = Diabetes is not well controlled by therapy *or* diabetes is well controlled, with complaints of moderate to severe sleep apnea and/or uncontrolled cardiac disease
Symptoms	1. = Mild: Patient reports no or only mild symptoms on SSS (all symptoms rated ≤2) 2. = Moderate: Patient reports presence of some symptoms on SSS but no single symptom exceeds a score of 6 (mild to moderate) and mean score is ≤4 overall 3. = Severe: Patient reports significant symptoms on SSS, with mean score >4 *or* one or more symptoms rated >6
Health-Related QoL Impairment[a]	1. = Patient reports no or minimal impairment in QoL (score ≥60) 2. = Patient reports mild to moderate impairment in QoL (40 ≤ score <60) 3. = Patient reports significant impairment in QoL (score <40)

IGF-I insulin-like growth factor I, *ULN* upper limit of normal, *LLN* lower limit of normal, *MRI* magnetic resonance imaging, SSS Signs and Symptoms Score, *QoL* quality of life, *AcroQoL* Acromegaly Quality of Life Questionnaire

[a]The endocrinology experts selected AcroQoL as the most suitable currently available tool to address disease-specific QoL assessment. In order to avoid response bias, the term “health-related quality of life” was used in the validation study.

Table 3: Characteristics of the participants in the validation study

Physician Characteristic	
Males, n (%)	14 (66.6)
Females, n (%)	7 (33.3)
Age, y	
Median (range)	51 (40–67)
Mean (SD)	51.8 (7.4)
Country of origin, n (%)	
Spain	7 (33.3)
Canada	6 (28.6)
United Kingdom	2 (9.5)
Italy	2 (9.5)
Germany	2 (9.5)
France	2 (9.5)
Unique acromegaly patients seen annually, n	
Median (range)	40 (5–140)
Mean (SD)	48.3 (34.3)
Location of treatment, n (%)	
Hospital outpatient clinic	14 (66.6)
Hospital	5 (23.8)
Private outpatient clinic	2 (9.5)
No. of years treating acromegaly patients	
Median (range)	20 (10–35)
Mean (SD)	21.2 (8.8)

SD standard deviation

Table 4: Inter-rater agreement of common scenarios

Scenario[a]	S	M-DA	S-DA	Pr
Scenario 1 [11111]	21	0	0	1.000
Scenario 5 [11122]	17	4	0	0.676
Scenario 11 [11212]	14	7	0	0.533
Scenario 59 [13122]	1	9	11	0.433
Scenario 92 [21212]	4	16	1	0.600
Scenario 122 [22222]	1	17	3	0.662
Scenario 166 [31121]	2	8	11	0.400
Scenario 203 [32222]	1	3	17	0.662
Scenario 230 [33222]	1	0	20	0.905
Scenario 243 [33333]	0	0	21	1.000
Pc	**0.295**	**0.305**	**0.400**	**κ = 0.526**

S stable, *M-DA* mild disease activity, *S-DA* significant disease activity.

Pr denotes the extent to which physicians agree on each scenario (physician pairs in agreement relative to the number of all possible pairs), ranging from 0 to 1 and with 1 representing complete agreement.

Pc denotes the proportion of all physician assessments that were assigned to each category. For instance, for the outcome “stable,” it equals the total number of physician assessments rated as stable (n = 62), divided by the total number of possible physician assessments (10 x 21 = 210).

Fleiss' kappa statistic (κ) provides a summary statistical measure for assessing the reliability of agreement between physicians in rating common scenarios.

[a]Bracketed numbers refer to the level of severity for each of the health status parameters. As an example, scenario 166 [31121] as shown in Table 4 describes a hypothetical patient case with IGF-I at level 3, Tumor status at level 1, Comorbidities at level 1, Symptoms at level 2 and QoL at level 1. For a description of the levels, see Table 2.

Appendix K: List of Tables

Table 1: Selection of key parameters associated with disease activity in acromegaly using the funnel approach

Parameters associated with acromegaly	Disease parameters (routinely) measured in clinic	Key measure of disease activity which could also be modified by existing treatment options (both for acromegaly and for concomitant diseases)	Selection of key parameters by exclusion criteria of a) Minimal data entry requirement b) Exclude if not fully confirmatory of disease activity c) Difficult to collect in routine practice
Biochemical	IGF-I, GH, Prolactin, IGFBP3	IGF-I, GH, Prolactin	IGF-I
Pituitary Tumor	Pituitary tumor size increase / reduction; tumor invasiveness, Visual field defects, Headache, Apoplexia	Tumor size increase / reduction; tumor invasiveness (measured by MRI), loss of vision	Tumor size increase, tumor invasiveness (measured by MRI), loss of vision
Co-morbidities	Hypertension, Hyperlipidaemia, Left Ventricular Hypertrophy, Cardiomyopathy, Congestive Heart Failure, Arrhythmias, Valvular Heart Disease, Cardiac Disease, Carpal Tunnel Syndrome, Arthritis, Osteoporosis, Acral changes, Glucose intolerance / Diabetes, Hypopituitarism, Colonic Polyps, Colonic Cancer, other malignancies, Sleep Disturbances, OSA, Menstrual Abnormalities, Infertility, Galactorrhea, Family History	Hypertension Cardiac Disease Glucose intolerance / Diabetes OSA Hypopituitarism	Cardiac Disease (including hypertension, hyperlipidaemia or other cardiac abnormalities) Diabetes OSA
Symptoms	Headache, Excessive Sweating, Joint Pain, Fatigue, Soft Tissue Swelling, Numbness or Tingling of Extremities, Prognathism, Frontal Bossing, Skin Tags, Oily Skin Texture, Gigantism	Headache, Excessive Sweating, Joint Pain, Fatigue, Soft Tissue Swelling (measured by SSS)	Headache, Excessive sweating, Joint Pain, Fatigue, Soft Tissue Swelling (measured by SSS)

Parameters associated with acromegaly	Disease parameters (routinely) measured in clinic	Key measure of disease activity which could also be modified by existing treatment options (both for acromegaly and for concomitant diseases)	Selection of key parameters by exclusion criteria of a) Minimal data entry requirement b) Exclude if not fully confirmatory of disease activity c) Difficult to collect in routine practice
Health related QoL	Depression, Pain, Low Energy, Decreased Libido, Impotence, Low Self-Esteem, Social Isolation	Physical, Psychological, Social domains covered by ACROQoL	Physical, Psychological, Social domains covered by ACROQoL

Table 2: Five selected parameters and their level of severity

Health Status Parameter	Parameter Levels
IGF-I	1. = The patient's IGF-I is within normal limits 2. = The patient's IGF-I exceeds the upper limit of normal but not more than 1.2X the upper limit of normal, or is below the lower limit of normal 3. = The patient's IGF-I is significantly elevated, more than 1.2X the upper limit of normal
Tumor status	1. = Based on the most current MRI, the tumor is not visible or has not changed since the prior MRI 2. = Based on the most current MRI, a slight increase in tumor size (≤ 20%) has been observed 3. = Based on the most current MRI, a clinically significant increase in tumor size (>20%) and/or invasiveness has been observed over the prior MRI and/or a worsening in vision is observed
Comorbidities	1. = The patient does not have a diagnosis of diabetes, complaints of sleep apnea are absent and cardiac disease -if present- is well controlled 2. = The patient has diabetes which is controlled by therapy with no concomitant complaints of sleep apnea, and cardiac disease (if present) is controlled with therapy OR, the patient does not have diabetes but has complaints of sleep apnea and/or cardiac disease that is not well controlled with therapy 3. = The patient has diabetes that is not well controlled by therapy OR the patient has diabetes which is well controlled, with complaints of moderate to severe sleep apnea and/or uncontrolled cardiac disease

Health Status Parameter	Parameter Levels
Symptoms	1. = Mild: The patient reports no or only mild symptoms on the SSS (all symptoms rated ≤ 2) 2. = Moderate: The patient reports the presence of some symptoms on the SSS but no single symptom exceeds a score of 6 (mild to moderate) and the mean score is ≤ 4 overall 3. = Severe: The patient reports significant symptoms on the SSS with the mean score > 4 OR one or more symptoms rated > 6
HRQL Impairment (as measured by AcroQoL)	1. = The patient reports no or minimal impairment in quality of life (score ≥ 60) 2. = The patient reports mild to moderate impairment in quality of life (40 ≤ score < 60) 3. = The patient reports significant impairment in quality of life (score < 40)

Table 3: Characteristics of the participants in the validation study

Characteristics of Participating Physicians	
Physician Gender	**N(%)**
Male	14 (66.6%)
Female	7 (33.3%)
Physician Age	
Median (range)	**51 (40–67)**
Mean (stdv)	51.8 (7.4)
Physician Country of Origin	N(%)
Spain	7 (33.3%)
Canada	6 (28.6%)
United Kingdom	2 (9.5%)
Italy	2 (9.5%)
Germany	2 (9.5%)
France	2 (9.5%)
Number of Unique Acromegaly Patients Seen Annually	
Median (range)	40 (5–140)
Mean (stdv)	48.3 (34.3)

Characteristics of Participating Physicians	
Location of Acromegaly Patients Seen	**N(%)**
Hospital Outpatient Clinic	14 (66.6%)
Hospital	5 (23.8%)
Private Outpatient Clinic	2 (9.5%)
Number of Years Treating Acromegaly Patients	
Median (range)	20 (10–35)
Mean (stdv)	21.2 (8.8)

Table 4: Inter-rater agreement of common scenarios

Scenarioa	S	M-DA	S-DA	Pr
Scenario 1 - [11111]	21	0	0	1.000
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Scenario 92 - [21212]	4	16	1	0.600
Scenario 122 - [22222]	1	17	3	0.662
Scenario 166 - [31121]	2	8	11	0.400
Scenario 203 - [32222]	1	3	17	0.662
Scenario 230 - [33222]	1	0	20	0.905
Scenario 243 - [33333]	0	0	21	1.000
Pc	**0.295**	**0.305**	**0.400**	**k = 0.526**

S = Stable, M-DA = Mild Disease Activity, S-DA = Significant Disease Activity.

Pr denotes the extent to which physicians agree on each scenario (physician pairs in agreement relative to the number of all possible pairs).

Pc denotes the proportion of all physician assessments that were assigned to each category

k denotes the Fleiss' kappa statistic, which provides a summary statistical measure for assessing the reliability of agreement between physicians in rating common scenarios.

The numbers in brackets refer to the level of severity for each of the health status parameters.

Appendix L: Examples of ACRODAT Physician Research Qualitative Survey quotes

Re: Biochemical control of patients with acromegaly:

"If I can manage to cure them, this is done through surgery. Otherwise I control the disease with the drugs I have available" (Italy)

"Our main aim is the normalisation of these two factors, IGF-1 and GH" (France)

"We can talk about biomarkers if you like, but for me the essential goal is to improve their symptoms: the feeling bloated, the uncomfortable feeling, controlling their diabetes" (Spain)

"It can take a long time and a lot of work with different medications to achieved goals. Patients have medication, surgery, radiotherapy, over several years" (France)

"Complete disease control is only achieved in about 30-40% of patients who were not cured with surgery" (Spain)

"We rarely reach our objectives because patients don't start therapy, because the drugs we have available are not very satisfactory" (Italy)

"We don't always get a response to drug therapy or surgery and it can be hard to control side-effects from drugs" (Italy)

Re: Delay in taking next therapeutic step in uncontrolled acromegaly:

"We have a new treatment option now with pegvisomant, but I still feel that we don't have enough" (Spain)

"Sometimes patients might ask to switch treatments. For example with Somavert, they find it restrictive because they have to have injections every day" (France)

Re: Addressing biological measurements vs. symptoms:

"It's more important to look at biologic measurements than symptoms. Some patients could have a bad IGF-1, but feel well despite this, so it's important not just to look at symptoms" (France)

"We look at the clinical aspects, whether the patients change physically, whether their faces change, the visual aspect of the patient" (Italy)

"We have very little time to spend with each patient and we have to get straight to the point. Of course I ask how they are and the symptoms have been progressing and if they have new ones, but I don't keep quality of life scores" (Spain)

"You get an immediate idea of the stage of the disease so you could make different decisions" (Italy)

"It offers no help with treatment decisions, it offers the chance to keep patient details to hand, but therapy decisions remain the same" (Italy)

"It could help us to react quicker to a problem with a patient's treatment (France)

"This software wouldn't help us achieve goals, it would help us see how successful our work has been, it helps with monitoring patients" (France)

"If we have a patient whose IGF-1 levels are borderline, because this would take all measurements into account, it could help us figure out if they need to change treatment or not" (France)

"The advantage is that it is visual so you can see where you've come from and where you are going!" (Italy)

"It's not always easy to get all information in front of us clearly, and this would do it for us, and it would help us to show it to the patient" (France)

"It would make you focus not only on their blood test results, but also remind you that quality of life is also important and that perhaps something else would need to be done to improve it" (Spain)

Re: Main barriers to ACRODAT adoption

*"**Accessing the internet at my hospital can be rather difficult**. But if there was an easy access at my office, I would use it for all my acromegaly patients" (Spain)*

*"We're **always short of time** so if someone else could do this that would be great" (France)*

*"**I'm not really into very technical things**, so I can't see myself using this much in practice. I don't think I'd be likely to use it during consultation" (France)*

*"I'm **a bit concerned about the extra work** that this might create" (France)*

*"My concern is that it could be an extra job for the physician, which takes up more time, **writing a paper report may be quicker** than finding the right page to enter data on this software" (Italy)*

*"I wouldn't have the time to complete it in actual consults because I only have 15min for each patient. **It's just not feasible to complete it in daily practice**" (Spain)*