Report on DEBRA International Industry Partnering Panel (IPP) Breakfast meeting 07:15 – 08:45 25TH September 2017, Salzburg, Austria

Meeting aim

DEBRA International Industry Partnering Panel (IPP) has been established to expedite translation of posssible EB therapies into the clinic through collaboration among stakeholders to address key pre-competitive challenges.

The aim of the inital 2017 meeting was to bring together representatives of 10 companies that have an interest in EB (engaged in or considering clinical trials in EB) with researcher-clinicians treating people with EB, and delegates from DEBRA, to identify priorities and establish mechanisms for mutual assistance in driving EB research into significant clinical benefit for people with EB.

Brief presentations from the key stakeholder groups established perspectives which enabled discussion of common priorities and unmet needs, and ways in which barriers might be overcome by working together.

Key outcomes and Next steps:

The idea of pre-competitive collaboration was well received despite initial differences in stakeholder priorities – there is a common ultimate goal. Today's meeting provided a neutral ground for open dialogue and information exchange, including previously unappreciated stakeholder perspectives, and country differences in approaches to market access, regulation and reimbursement.

A further meeting should work out more detail about these priorities, and mechanisms for working together. Priorities include: optimizing clinical-trial design for patient participation; patient-centred and disease relevant metrics and validation of clinical endpoints; standardisation-harmonisation in clinical trials, optimizing approaches to regulators and payors; engaging new industry partners.

Summary

The patient - clinician perspectives

- EB is hugely intrusive on everyday life and this must be considered when planning clinical trials. Study sponsors and CROs need to appreciate the magnitude and impact of what they are seeking from patients when designing clinical trials.
- Industry partners need to have a sound knowledge of EB types and a real appreciation of what living with EB actually entails, in order to design effective clinical trials
    - Protocols that require patients to make significant adjustments to how they manage their condition for weeks (or even months), are unlikely to be adhered to.
    - EB patients have a life-long and constant condition, and are reluctant to change protocols they have developed over time for themselves and their own life circumstances as bearable.
    - EB patients with the same mutation and disease progression may have very different assessments of risk:benefit and desirability of participating in a clinical trial: we're all individuals!
- Even if the real-life situation for people with EB can be successfully considered in clinical trial design, there is a risk this will be wasted if conducting the trial is handed over to a CRO (Clinical Research Organisation) that lacks the depth of knowledge and

understanding required to conduct the trial: CROs often do not have experience in rare diseases.

- EB is not a single disease – the different types have a wide spectrum of clinical presentation, impact on lifestyle and prognosis.
    - Producing drugs or other products for 'all EB patients' does not recognize disease diversity and is therefore not realistic, and such proposals are unlikely to result in a significant contribution to EB treatments.
    - Clinical trials open to diverse EB subtypes are, for the same reason, less likely to yield significant results.
- There is a need for collection of comprehensive sequencing data to further define the mutations underlying the different EB types.
- In general, clinicians are very willing to share information about the biology of EB and living with EB and want to help industry understand the disease, but…
    - being contacted on numerous occasions by people from the same company (seeking largely the same information) is not sustainable. Clinicians have significant pressures on their time and repetition of the same interviews, usually starting right from the beginning again, is frustrating, time consuming and counter-productive.
    - Industry must improve its internal communications and limit the points of contact, including with any sub-contracted CROs.
- Some surveys collecting patient information vary in data quality, often as a result of poor or rushed design: qualitative vs quantitative data and with limitations in interpretability. Patient perspectives and socioeconomic impact data are important, but data-collection initiatives that are patient-reported may lack clinical / molecular confirmation of diagnosis.

The industry perspective

- An ongoing issue with clinical trials, and likely to get more pronounced with an increasing number of treatments entering trials, is patient recruitment. EB clinical trials experience challenges recruiting patients, which leads to delays, higher costs, early closure and, consequently, a lack of evidence.
- Clinical trials need robust endpoints and these are difficult to define in EB.
    - Regulators demand solid endpoints which may not be achievable in conditions such as EB. For example, a reduction in the number of skin blisters or the size of skin lesions would be valued by patients, but possibly rejected by regulators who would consider them dynamic changes and insufficiently robust as an endpoint.
    - The regulatory considerations need to be taken into account at the outset of clinical trial design; the required data cannot be obtained at the last minute or retrospectively.
- There are also issues in the bodies awarding marketing authorisation or drug licences may have different requirements from those of the payors who are involved in pricing and reimbursement (P&R).
    - One issue is the comparator drug in a study. Drugs must be compared with placebo to obtain a licence but P&R bodies may demand the 'standard of care' as a comparator.
    - Companies need assistance from DEBRA and clinicians in defining what is a realistic comparator that will be suitable to gain reimbursement.
- The issue was raised of how feasible it is to define a standard of care, since patients will change their behaviour from day to day and may not be carrying out recommended procedures
- Obtaining drug approval can be problematic, since the drugs that are acceptable to regulators are not necessarily those that fulfil unmet needs for patients.

- Patients need to appreciate that by taking part in certain social media discussions about trials they have been involved with can compromise the data and maybe even affect progress of that drug through approval and other regulatory processes.
- The requirement for effective industry/charity/clinical partnering are clear goals, resources, and free sharing of expertise and funds. It is important to have both the patient and the commercial viewpoint from the outset.

What can a patient organization – industry partnership achieve together?

- A PO is able to provide disease information, and patient perspectives, and thereby relieve the pressure on clinicians, but currently also experiences the same issues of repeat requests from companies personnel and subcontracted CROs.
- PEBLES: To create a reference dataset for researchers and industry, DEBRA partnered with UK London hospitals to undertake PEBLES (Prospective Epidermolysis Bullosa Longitudinal Evaluation Study).
    - The aim is to collect comprehensive longitudinal data from over 400 patients with Recessive Dystrophic Epidermolysis Bullosa (RDEB). It will be extended to other EB types.
- ERN: On a wider scale, European Reference Networks (ERNs) have been established to co-ordinate patient registries and to harmonise diagnostic measures.
    - Clinical diagnosis can often be inaccurate, so an aim of ERNs is to harmonise diagnostic criteria, to provide training, include registries and look at clinical outcomes.
- Clinical Practice Guidelines are a series of guidelines on various aspects of EB management. They have been developed (via DEBRA International), using an established methodology, by an international group of experts and patients and are freely available to both clinicians and patients.
- A genuine 'natural history' is difficult to derive as most patients receive some symptomatic treatment: in Chile, dermatologists see patients who have not received medical care; this has provided an opportunity to document the natural history of EB seen when no interventions have been made.
- It was suggested that perhaps a minimal standard of care could be defined that may not be appropriate for every patient, but could be suitable for regulatory purposes.
- A patient organization – industry partnership could develop some key performance indicators, for example, defining metrics that are of key benefit to the patient. This could be valuable for patients, companies and regulators.
- A patient organization cannot provide direct access either to patient registers, nor individual patient data.
- A PO-industry partnership can however, provide a route to rapid access to disease information, patient perspectives, and to reach out to networks of clinicians or patients.
- POs, clinicians and industry are all interested in the development of diagnostic markers, and new therapeutic approaches to address unmet medical needs: a partnership can contribute to defining unmet needs, potential markets, and areas of research that need to be undertaken.
- Clinical trials occasionally give disappointing results. Patients may need support to cope with their involvement in clinical trials that are not successful – although primarily the responsibility of the trial's sponsors, a PO-industry partnership could create disease-appropriate standards for such support.

CLINICIAN PERSPECTIVES:

Clinician perspective 1:

Operationalising clinical studies: patient-centric information and developer access; resources, capacity and study co-ordination

The EB centre at Freiburg is one of the largest EB centres in Europe, with about 1200 patients in the registry. It is involved in three preclinical studies with companies and six clinical trials, where it is involved in consultation, planning and participation.

A lot of commercial companies contact the centre to gain information, understand what EB is and to seek access to patients. From a clinical point of view, the data collected on patients must be of a very high quality with well documented precise, accurate diagnosis.

The industry partner must have a good background knowledge of EB, understand the causes, the different types, the heterogeneity and know about the basic biology and clinical features of EB.

Importantly, there must be a limited number of defined contact people in industry involved in the project. It is not unusual to have several people making contact from a company to discuss the same issues - starting from square one, many times. This is a strain on already extremely busy, pressured clinical departments.

There are numerous centres willing to partner with industry, but there must be caution. Some centres have small and heterogeneous patient populations in whom there is a lack of accurate diagnosis.

Projects may be initiated between an industry partner and the clinical unit and then the project is delegated to a CRO (Clinical Research Organisation) which too often has a lack of background information, ignorance of the condition and unrealistic expectations of what can be achieved in rare diseases. The CRO personnel may be dealing with common less severe skin conditions, such as atopic dermatitis, and do not appreciate the problems with EB. This leads to misunderstandings and confounds efficient and reliable data collection.

The International Consensus Classification of EB has identified 19 causative genes which produce a lot of mutated proteins that give rise to the specific types of EB. Different EB types are not the same, each having their own unique clinical features. The key to a successful clinical trial is a proper understanding of EB.

An ‘onion skin’ approach to understanding EB has been suggested. Diagnosis should start with clinical diagnosis based on phenotype, this should be followed by biopsy and molecular diagnosis (e.g. using immunofluorescence mapping and electron microscopy) and finally mutation analysis. Mutation analysis is the gold standard; however, this may not be possible in some centres if there is no access to gene sequencing technology.

European Reference Networks (ERN) have been established to co-ordinate patient registries and to harmonise diagnostic measures. ERNs are being established with EU support that have the same registry architecture for all rare diseases, including all rare skin diseases. Within rare skin conditions EB is one of the largest groups. Clinical diagnosis can often be inaccurate, so an aim of ERNs is to harmonise diagnostic criteria, provide training, include registries and look at clinical outcome.

ERNs will hold a minimal anonymised dataset for each patient, including age, sex, country of residence, country of origin, diagnosis (which will state whether genetic, molecular or clinical) the mutations, protein levels and clinical subtype and severity.

There are many small registries that have yet to be harmonised and the registry has to have restricted access to comply with European Data Protection regulations. How these will work is still under consideration.

Industry needs to appreciate that clinical trials on 'all forms of EB' is not a valid approach and will not produce robust results. Different types of EB are very different conditions. DEBRA can provide invaluable information to companies in this context.

Clinician perspective 2:

Understanding the natural history of EB: selecting appropriate clinical measures for regulatory validation and meaningful patient outcomes

Clinical trials need endpoints and these are difficult to define in EB. There are a lot of different types of EB, each presenting different challenges. It is a life-long condition, but there are variations with age and other confounding factors. So, defining valid endpoints needs a real understanding of the disease, how it affects the patient, how it changes over time and how interventions affect the disease trajectory. The cost of current care also needs to be understood and how any new innovations will impact on those costs.

EB has been investigated in a study called PEBLES: Prospective Epidermolysis Bullosa Longitudinal Evaluation Study. This study focused on Recessive Dystrophic Epidermolysis Bullosa (RDEB) and recruited patients from the pool of over 400 patients seen at Great Ormond Street, Guy's and St Thomas' hospitals. Detailed clinical aspects of the disease were documented along with laboratory data, details of investigations (e.g. Dexa scans, echocardiograms) disease severity scores, subjective scores (e.g. QoL, pain and itch), photographs of the skin and a record of economic costs (e.g. dressings, carer costs).

This generates a huge amount of data – over 2,000 items for a patient at each review. It is longitudinal data collected every 6-12 months. Analysis is ongoing. This will provide a significant dataset for reference or to provide a benchmark against which any intervention can be judged. In future, this initiative will be expanded to other centres and be a web-based data collection system. It will also be expanded to other EB subtypes.

INDUSTRY PERSPECTIVES:

Industry perspective 1:

Challenges in EB drug development.

There is a problem in terms of drug regulation in that the drugs that are acceptable to regulators and gain approval are not necessarily those that are clinical meaningful and address unmet needs for patients. Regulatory agencies approve drugs based on how patients feel, function or survive. Requirements are based on clinical or surrogate evidence of substantial benefits that outweigh risks of therapy. Treatments must be clinically meaningful and here it can be difficult to reach expert consensus.

A crucial consideration is: what is the clinical endpoint? In EB therapy adequate or relevant endpoints have not been widely adopted by regulatory agencies. Regulatory standards seek direct outcome measures of symptoms, functional status on survival for example: PFS (progression free survival), PGA (physician global assessment), PRO (patient reported outcomes), QoL, or complete wound closure.

However, in EB logical clinical endpoints may differ. For example, if the body surface area that is covered in blisters can be reduced in size that is of benefit to the patient, but the FDA would

not accept a dynamic endpoint such as a change over time; they require static endpoints. So even demonstration of improvement in the patients' condition is not sufficient; the FDA would demand totally, or nearly, clear skin.

It is not easy to define what is clinically meaningful, since the FDA demand overwhelming evidence of clinical meaningfulness and a clear objective endpoint to measure. In trying to address such demands, it might be possible to define laboratory parameters or biomarkers which can be regarded as predictive of clinical outcome. If the natural history of the patient is known in detail, and it can be correlated with laboratory data, the biomarker may be regarded as appropriate and sufficient.

Drug approval agencies can also, in some cases, be responsive to patient needs. About a year ago a drug was approved for muscular dystrophy. The drug has demonstrated only a 13% benefit to patients, which was not statistically meaningful. However, the patient groups and parents of sick children lobbied the FDA explaining what was meaningful to a patient. On that basis the drug was granted a licence.

Industry perspective 2:

Finding patients for clinical trials

This company had a drug granted Orphan status and the company is approaching their first clinical trial, so have interest in locating and identifying patients with this rare mutation.

In seeking suitable patients, there are open source databases, such as the International Registry for DEB patients and associated COL7A1 mutations. These databases give an indication of the number of appropriate patients there are available worldwide, but beyond that their usefulness is limited. This is because some databases are not up to date and the quality of the data may not always be reliable.

Similarly, publications can provide data on patient numbers, but the information in papers is frequently out of date and verification of information with the paper's authors is cumbersome, time consuming and sometimes just not possible.

There are also closed sources of information. The DEBRA organisations are useful but often they do not collect the type of information being sought. There is now a European initiative, but this is in its early stages and the information will not be available soon enough.

Talking to physicians takes a lot of time and effort. Physicians are not always responsive and many of their patients have not had their genetic mutation sequenced. So, the EB community needs more reliable data on mutations and sequencing and there is a need to make these data available to industry partners.

Industry perspective 3:

Demonstrating value to payors; how to address different payor models, and uncertainties related to pricing and reimbursement procedures.

Europe has very different systems from the US for evaluating and licensing drugs and regulating pricing and reimbursement. Systems also vary in different countries within Europe. There are discussions over unifying the systems, but if that does happen, it is a long way off.

Health Technology Assessment (HTA) is a systematic evaluation of the properties and effects of a health technology, addressing the direct and intended effects of this technology as well as its indirect and unintended consequences, and aimed mainly at informing decision-making

regarding health technologies. The goals of an HTA are to examine the consequences of the adoption of a particular technology and ensure that these represent good value for money.

However, the way HTAs are employed varies. Considering the top five European countries:

France has the Autorité de Santé (HAS) that makes decisions based on clinical and economic factors.

The UK has NICE (National Institute for Health and Care Excellence) which considers cost-effectiveness as key to granting reimbursement.

Germany' Gemeinsame Bundesausschus (BA) and Institu für Qalität Wirtshaflichkeit im Gesundheitswesen (IQWiG) are not concerned with economic factors; only clinical factors are taken into consideration. Some drugs are even reimbursed on a case-by-case basis.

Italy has the Agenzia Italaian dei Farmaco (AIFA) and Spain the Subdirecciòn General de Calidad de Medicamentos y Productos Sanitarios (SGCMPS). However, these countries have different systems because the countries are highly regionalised. So, while the decisions are made on clinical and economic factors at a national level the use of the drug and its reimbursement are decided at regional levels, meaning that drug may be available in one part of the country but not another.

Achieving pricing and reimbursement in Europe involves fulfilling specific country-based requirements. So, therapeutic benefit is required in all of the five countries mentioned, but cost-effective modelling is not required in Italy and Germany. The budget impact will be considered in all five countries, as will head-head comparisons with Standard of Care, but innovation is not a consideration in the UK, Germany or Spain.

A global patient organization – industry consortium for EB?

LifeArc

Life Arc is a medical research charity foundation, created initially to exploit commercial development of discoveries made in MRC units.

LifeArc is now an independent self-funding charity and among its activities it has a drug discovery facility: an area of interest in this section was humanising monoclonal antibodies for immunotherapy, the latest of which is Keytruda® (pembrolizumab). This drug has been very successful, so that as well as providing resources, LifeArc now has a source of income that it can bring to the table.

LifeArc's new strategy is creating '*Communities for Impact*' to drive medical innovation. Its aim is to share resources to help others translate discoveries; to broaden their skills, capabilities and technologies to create more value for the charities. Two new funds have been launched to this end. One is a philanthropy fund in the area of rare disease and the second is a sink fund which is the next stage along the way.

More than 65 charity clients have engaged with LifeArc since 2012 from the UK, USA and Europe. Advisory services were provided to >35 of these.

In April 2016, LifeArc signed an agreement with DEBRA Austria. It has been a fruitful collaboration. Initially they looked at DEBRA Austria's research portfolio as a whole and LifeArc have helped DEBRA Austria identify the most promising results which could be suitable for translation into better treatments, and will also advise on strategies to progress these projects to benefit patients.

PO- industry consortia:

LifeArc has previously brokered successful consortia of patient organizations and industry in other disease areas to translate fundamental discoveries into therapeutically useful agents. Features of such consortia include:

- Identifying unmet medical-need priorities
- Match funding by patient organizations and one or two (or more) companies so that the cost of translation is shared and disease and target insights are shared.
- Initiatives have also been developed with LifeArc to manage intellectual property exploitation and obtain licensing agreements.
- Companies that initially would not talk to each other are now working in collaboration.
- 'Working together to do things they would not do alone'.
- Exploring de-prioritised assets from industry because many projects leave data unused due to the project being shelved

Can such a consortium be replicated for EB?. A strength of working in a rare disease context is that there is a focus and urgency that is not seen in other disease areas.

To facilitate the process, clear goals, resources, sharing of expertise and funds are required, with recognition of both the patient and commercial viewpoints from the outset to identify realistic goals that are important in the real world setting.

IPP meeting discussion summary

Considering the role of the European Medicines Agency (EMA), it was explained that EMA approves drugs based on scientific evidence, but does not become involved in pricing and reimbursement which is conducted individually by each EU country. So, an EMA approved drug may be available in all European countries, but its use will not be funded by healthcare systems; in that sense it is not 'freely available' to be prescribed. In some countries the health budget is not managed by the state but is managed at a regional level. Also, while most European countries have a National health service, this is not always the case and some systems are organised at a regional level.

There are parallels with the US, where insurance companies differ in the drugs they will pay for. So, a drug may be available in the sense of being FDA approved but not funded. The US is moving towards a more European-style of reimbursement.

Spain has recently rejected reimbursement of a number of drugs for rare diseases on purely economic grounds. Healthcare is not a moral right; it is more of a service. Each country makes its own decisions.

The heterogeneity in European funding systems and the different quality and types of data required by different regulatory authorities presents opportunities but also challenges for a Pharma company in designing a strategy.

There is a challenge in that at least two different perspectives must be considered when planning a clinical trial. The first is that of the clinicians and then the regulators and the payors. This makes planning a clinical trial even more complex and the regulatory considerations need to be taken into account at the outset; the required data cannot be obtained at the last minute or retrospectively.

An example was given of a drug for a rare lipid disorder which was approved by the EMA in 2013, but he company is still fighting for reimbursement four years later. One question raised by the regulatory authorities was: what is the drug comparator? The drug had to be compared with placebo to gain a license but payors want a 'standard of care' comparator. So, an important issue in EB is defining the standard of care. Companies need assistance from DEBRA and the clinicians in defining what is a realistic comparator that will be suitable to gain reimbursement.

A local initiative by DEBRA Austria has been to investigate what is the burden of the costs of EB to patients. This is not a medical study, but is gaining practical information from families about costs of bandages etc. and costs of care. The idea behind the study was to have a body of evidence that could be used to demonstrate cost savings to payors if more effective treatments were proposed. This approach may well not be successful in some countries because the payors are different: those who pay for drugs do not pay for consumable items such as bandages. It is also difficult to define a regular pattern of bandage usage. Blisters and wounds vary over time and some weeks bandage consumption will be very high, while other weeks it will be more modest as lesions heal.

The issue was raised of how feasible it is to define a standard of care, since patients will change their behaviour from day to day and may not be carrying out recommended procedures. It was suggested that perhaps a minimal standard of care could be defined that may not be appropriate for every patient, but could be suitable for regulatory purposes.

There is also the issue that being part of a clinical trial may mean that a patient has to alter the way they self-care for their condition for quite a significant period of time. This presents difficulties because patients, and especially EB patients, will not be dictated to and probably will deviate from a standard protocol. Patients also have their own preferences for items such as bandages and will tend to use what they prefer.

The role of a patient organization as an interface between companies and patients was considered. Several companies have approached DEBRA seeking information about EB, about prevalence, but more often, what it is actually like to live with the condition. The same problem with the companies, as mentioned by the clinicians, was that different people from the same company contacted DEBRA for the same information. So, DEBRA was repeatedly being asked the same thing and having to start at the beginning with a new person each time. DEBRA is happy to provide information, but when companies do not pass this information on to the relevant people within the organisation, it becomes frustrating and time consuming.

Companies often want to get a clinician on-board immediately to help developing drugs or trials but sometimes the involvement they want so quickly is just asking too much of the clinicians; a patient organization cannot provide information when it comes to patient registers, nor give access to patient data.

It was suggested that maybe a platform could be developed as a tool for providing information to companies, but it was felt that usually every company is different and their requirements are also different. A face-to face meeting is usually necessary to understand the way in which patient organizations can best work with the company.

For a company being able to go through an umbrella patient organisation to reach clinicians or patients is a good starting point and can give the company a lot of information quickly. It also gives credibility and reassurance to the patients that if they are requested to take part in a clinical trial, the trial has been developed in conjunction with a respected patient group. Patients find it challenging to make time for engagement in information giving and in trials so having it co-ordinated could be helpful. Medical and clinical advisors could contribute as well so that the patient group has a reliable body of information it can share with companies.

In Chile, South America there are many specialist dermatologists who see EB patients who have not been receiving medical care. This has allowed a body of information on the ‘real’ natural history of the disease and the standards of care to be collected that would not be accessible in the UK or USA.

Another issue is that ethical committees vary throughout the world. It is important we work together since most ethical committees ask the same questions and need the same information They take variable amounts of time to approve protocols and what is acceptable in some countries may not be allowed in others.

DEBRA is interested in other issues as well, for example development of diagnostic markers. So, as well as giving information to companies they can also contribute to defining areas of research that needs to be undertaken.

Patients may need help and psychological support to cope with involvement in clinical trials that are not successful. The patient community is small and talking about failed trials may have a very negative impact on fellow patients. The lack of success in a trial must be put in context and explained properly. Companies must be open about why trials fail.

Part of informed patient consent could include an explanation that by taking part in certain social media discussions about trials they have been involved with can compromise the data and maybe even affect progress of that drug through approval and other regulatory processes. Patients also need to understand that while a clinical trial may not show benefit for one particular individual, it is the long-term picture that is important.

Patient organisations also have an important role in explaining what clinical trials are and what the data mean in lay terms.

While an individual patient organization can address some issues, others may present too big a challenge and the question was raised of whether it would be feasible for companies to join into a consortium to lobby regulators to change the variation and inconsistencies in EB reimbursement. In this context it was suggested that DEBRA might help in developing some key performance indicators. For example, defining metrics that are of key benefit to the patient could benefit patients, companies and regulators.