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# Rare and Orphan Diseases Reimbursement Strategies Roundtable

## Part 2: Obtaining Evidence

## Obtaining Evidence

ICON recently convened experts from its Commercialisation and Outcomes practices to discuss the current state of affairs, challenges, and trends in the rare and orphan disease development space in relation to reimbursement. The practice leaders' discussion was transcribed and divided into three instalments. The first instalment addressed strategies for identifying the evidence important for payers.

In this second instalment, we discuss ways to efficiently obtain evidence for reimbursement, particularly in face of small or difficult-to-access patient populations and related quality challenges. The final instalment of the round table will address communicating reimbursement evidence.

## ICON Roundtable Participants

David Pruce
**Pricing & Market Access**

Luis Bettinelli
**Peri-Approval & Observational Research**

Aura Mackenzie
**Pricing & Market Access**

Juliette Thompson
**Health Economics & Epidemiology**

Katy Benjamin
**Clinical Outcomes Assessment/ Patient Reported Outcomes**

## How do you address the challenge of identifying a valid comparator within small patient populations?

PRUCE: The fact that populations are so small complicates trials and the generation of convincing evidence. Having a comparator can be quite difficult because, often, there is not a natural standard of care. The current standard of care in these patients frequently is simple, palliative care. So it is the dual challenge of finding sufficient people to take part in clinical trials as well as finding an appropriate comparator that creates difficulty in these small populations. With some indications, there is further burden of having the correct diagnosis, as many conditions are not easily diagnosed.

## "Less than half (48%) of orphan drugs utilise placebo-controlled RCTs."

Dupont AG & Van Wilder PB. Access to orphan drugs despite poor quality of clinical evidence. BJCP. 2011, 71(4):488-496.

MACKENZIE: The choice of a comparator seems to be the most simple, but it is often the most frequent problem that we see. While that may not sink an orphan drug's approval, it certainly detracts considerably from the value element and results in unnecessary work down the road, such as chart reviews, to build that value story back up. If the study can be done right at the start, a lot of that evidence collection is already done for you.

BETTINELLI: The standard of care must be carefully understood and characterised. The selection of a comparator may be very difficult or impossible in some cases. Therefore, alternative designs should be considered like epidemiology data on the natural disease progression or comparison against Standard of Care in pragmatic study designs.

BENJAMIN: Another issue is that no single country will likely be able to generate a sufficient sample size, which adds a dimension to defining the standard of care. The example I always use is haemophilia, a relatively common rare disease. There are two ways to treat. One is prophylactically, in other words by providing people with the factor before they have a bleed. Or, patients may receive the factor on-demand when the patient has a bleed. Most western countries at this point with a relatively healthy economy will pay for prophylaxis treatment for adults as well as children. The standard of care for children is clearer worldwide; they get prophylaxis. This is not so for adults. After the age of 18, patients receive prophylaxis if in Canada, but not in Romania. There is not always one standard of care all the time that can be used for the comparator.

MACKENZIE: One could prioritise by those countries that take the comparator arm most seriously, which tend to be France and Germany, who have rigorous assessments. Other countries are more understanding on this front. What payers are looking to see, at least from a European perspective, is the inclusion of at least some European patients. Sometimes that does not happen. This is to ensure that the clinical trial takes place in markets where the healthcare systems are markedly robust. This mitigates the potential that the patients are normally undertreated.

BENJAMIN: For more ultra-rare conditions, the differences between countries can be even more variable.

PRUCE: Yes, I think we need to differentiate between orphan and ultra-orphan drugs. Ultra-orphan indications are often ones for which there are so few people that one must resort to real-world evidence. With most orphan drugs, you can generate the desired evidence. It is the simple stuff that may be omitted: having an appropriate comparator and having measures that are meaningful to payers as well as regulators. For ultra-orphan drugs, more imaginative approaches may be needed. But for orphan drugs, one has to get the simple things right.

MACKENZIE: A lot of these decisions come down to financial realities on the part of the manufacturer and what is reasonable to ask of a company that is designing a drug for potentially as few as 500 people around the world. Is it reasonable to have all the bells and whistles when the trial will include one-tenth of the patients who are going to be treated? If a trial will deliver evidence that will not be a driver for revenue, capital expenditures can be difficult to justify.

## With a limited patient population, what existing data sources could be explored to compensate for the inevitable gaps in available evidence?

BENJAMIN: I just had this discussion recently at a DIA meeting. For the FDA and regulatory agencies around the world, the gold standard is natural history. However, natural history will not exist for most rare conditions. First of all, it takes about eight years on average for a person to receive an appropriate diagnosis. Little may be certain about what occurred in the time period before the patient is finally diagnosed. During that time, the patient may have received inappropriate treatments that actually did harm. There may be a layer of depression because of the inability to achieve a diagnosis or successful treatment. A patient's disease stage will not always be known, either. All of this has to be accounted for.

Having said that, there are registry studies. Most of these rare conditions are not treated locally. There are specialty clinics to which patients, if they are lucky, will travel for treatment. Those clinics will be a significant source of patient and patient data, not to mention that patient advocacy groups hold other keys. Finding these patients in a large administrative database is fairly hopeless because many of these conditions to do not have diagnostic codes. In ICD-9, for example, Duchenne muscular dystrophy and Emery-Dreifuss muscular dystrophy shared the same code, even though they are different diseases. You have to go to more proximal sources to find patients.

THOMPSON: Often, one needs to move away from the idea of a clinical trial and look more at an observational study design. That is a key way to generate larger quantities of evidence. In a retrospective review of charts or databases, identification of these patients from a single entity can be quite difficult. One useful database is EURORDIS, which is a Europe-wide database that is quickly expanding with rare disease data. If you are reviewing charts, especially within ultra-orphan diseases, the database often has excellent data.

Specialists, as you mentioned, can be another robust source for data, as few specialised practitioners may exist and patients may travel a great distance to be treated by them. As patients arrive and their charts are sent over, this one site may accumulate a surprisingly large number of charts for this one ultra-orphan disease. In a project underway right now for an ultra-orphan disease that affects infants, we are working with one physician in Germany who has more than 200 charts for the condition — a great number of records that would not otherwise be accessible. If specialist access is not feasible, setting up a registry and working through charts can be another option, although not ideal. A question will still remain: who will be the specialist who would actually be entering these patients into the registry?

"Creativity and innovative thinking is required not only to reduce inefficiencies, but also to achieve synergies."

BETTINELLI: From the business perspective, we should differentiate between pharmaceutical companies that have an extensive record of research, vast experience, and powerful networks in the therapeutic area from those companies that have developed a novel drug that may introduce a significant change in the disease management and outcomes, but are relatively new in the area. A service provider has to offer a customised approach to complement and enhance the sponsor situation. It is important to promote a dialog to become true partners and trust each other.

BENJAMIN: Also, there may be less willingness on the part of the patients to participate in an RCT, especially one that is placebo-controlled. Children will often be very hesitant; they just want the drug, whether or not it has been proven to help them. To prevent gaps in evidence, there may be a need to do an open-label trial or a crossover design to get these people into studies.

BETTINELLI: You have mentioned exactly the type of considerations that a multidisciplinary team should take into account. You mentioned, for example, design considerations such as the value of a crossover versus a comparative analysis. Doctors may need to answer whether such designs are even technically possible.

BENJAMIN: Or a historical drug control.

BETTINELLI: Yes, this is absolutely right. The development of drugs for orphan diseases required close cooperation of multidisciplinary teams. Creativity and innovative thinking is required not only to reduce inefficiencies, but also to achieve synergies. Earlier and coordinated efforts can better leverage limited resources and sources of information.

"Increasing the study complexity may impact both the data quality and doctors' burden and motivation with the study. The simpler a study, the more successful it will be."

## How can quality be ensured in these studies, which by nature are highly complex and difficult to control fully?

BETTINELLI: In traditional explanatory trials, you have the possibility to control your study framework, which allows a high level of internal validity. Patient data is normally cleaned to almost 100%; every inconsistency is addressed via a query and the doctor responds with complete and consistent data. Additionally, it is always possible to increase the sample size as an instrument to increase the precision of the analysis. However, in the orphan disease arena, these instruments may not be completely available; thus, a pragmatic approach during the planning phase has to be developed and implemented. Firstly, one must have alternative methods to maximise sample size as much as one can. That is when, coming back to the prior discussion, accessing a patient, research or claim database may help to identify trends and indicators that then can be further evaluated in an exploratory analysis.

Secondly, achieving data of quality in the orphan disease arena is also a combination of traditional data cleaning with a thoughtful study design that ensures that bias and confounders are anticipated and well managed. Patient data may have inconsistencies and some information may be vague or ambiguous; therefore, the alignment between the research question and the methodology for data collection, analysis, and evaluation is crucial. The quality of the data is defined by the quality of the design and not by any single point. Here is, again, where multidisciplinary teams are important to put in place early the methodological instruments to control bias and confounders.

BENJAMIN: I recently participated, at a DIA meeting on endpoint development, in an afternoon session on endpoints for rare diseases. Lori McLeod, a biostatistician at RTI, raised an interesting strategy in the context of there never being a large enough sample size in programs targeting these very small populations. Instead of using the typical strategy of measuring a few endpoints using large populations, one can measure a larger number of endpoints and then evaluate them to see whether or not the information merges. She called it the Portfolio Assessment Strategy.

BETTINELLI: We see more and more of this approach in the rare disease space. A frequent challenge during the strategic planning phase is how to combine the viewpoints and priorities of the internal stakeholders into a single and simple strategy for the study. A pragmatic approach is required in order to avoid, for example, that too much data will be requested, which may

distract from the main research question.  It is understandable the desire to document a much data as possible as it is difficult to access to a larger patient population. However, increasing the study complexity may impact both the data quality and doctors' burden and motivation with the study.  The simpler a study, the more successful it will be.

Identifying key data is crucial step in the project planning. If the proposed data points will characterise the same outcome, but these would not add additional information to the research, then it should be discussed whether the research question can be addressed with a leaner data collection. These kinds of assessments frequently require contributions from more than one internal stakeholder; views may be needed from a statistician, a doctor, and an epidemiologist to find the right balance.

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**Part 1: Identifying Evidence –**
Recognising differences in payer priorities and the value of early planning.

**Part 2: Obtaining Evidence –**
Look beyond a traditional clinical trial for gathering appropriate evidence.

**Part 3: Communicating Evidence –**
The importance of setting early expectations and strategies for successful evidence communications.

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