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RESEARCH GROUP

Orphan Diseases, Bringing the Trial to the Patient

A True Focus on Patient Centricity

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Individuals living with orphan diseases

An orphan disease may be a rare disease presenting within a small population or can also include conditions that are not receiving adequate attention from the pharmaceutical industry, perhaps due to the geographical spread, such as in developing nations. Orphan diseases have a strict legal definition in many countries in order to encourage research in these areas. The US Food and Drug Administration (FDA) defines orphan drugs as those intended to treat rare diseases/disorders that affect fewer than 200,000 people in the U.S., or that affect more than 200,000 persons but are not expected to recover the costs of developing and marketing a treatment drug[1].

The struggle people go through with orphan illnesses to find the right consultant, to undergo the correct assessments, to be given an accurate diagnosis and crucially receive effective treatment is well documented[2]. Living with an orphan disease is often tortuous with many likely to suffer from depression, anxiety, worry about lack of information and future outlook of their disease, as well as reporting feelings of isolation[3].

Many of the people living with rare diseases are 'desperate to do something to influence their illness.'[4] Their eagerness to influence their illness can potentially lead them to take greater risks surrounding their treatment. This may also include a lack of proper consideration as to whether participation in a particular clinical trial is really suitable

Could more be done to improve the lives of orphan disease patients?

Clinical trials could be made more patient-centric. In simple terms, patient-centricity in clinical research can be defined as putting the patient at the centre of the trial. Mobile research nursing is one way to ensure that the patient is kept at the heart of clinical research by bringing the trial to the patient. Mobile research nursing involves qualified research nurses conducting clinical trial visits at a safe location chosen by the patient, bringing mobile equipment, investigational medicinal product (IMP) and data collection tools with them reducing the impact on the patient's life while still being able to participate in clinical research.

To gain an understanding of how the industry feels about mobile research nursing in orphan disease studies and patient centricity in general, Illingworth Research Group collected data from contract research organisations (CROs), patient groups, sponsor organisations, charities, laboratories and other pharmaceutical research service providers.

It isn't surprising that when asked if patient-centricity has been truly embraced by sponsors working in orphan drug trials, sponsors indicated that greater progress has been made, whereas respondents working within contract research organisations (CROs) were less convinced.

With patient-centricity currently receiving more publicity than ever before, one would believe that all is well in the eyes of the patient. When asked if patient centricity has been truly embraced by sponsors working in orphan drug trials, there was a visible difference between groups. Where sponsors have indicated that progress is being made, CROs disagreed, believing there is more that can be done, especially in the world of orphan drugs.

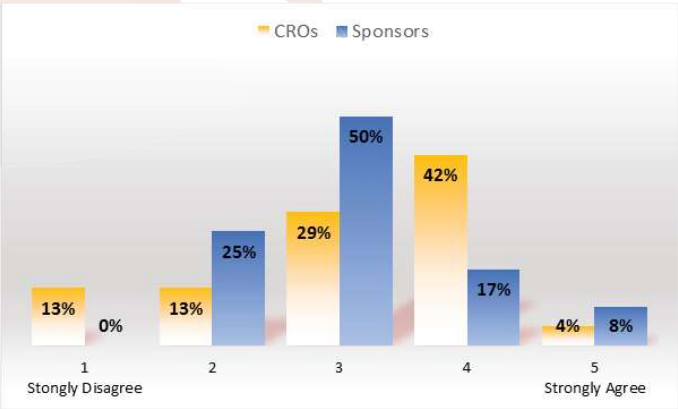


Figure 1: CROs vs sponsors 'patient-centricity has truly been embraced by sponsors working in orphan drug clinical trials'

"I think it's a changing paradigm. Some companies have been doing this for longer than others... and are starting to understand the value of the patient voice in drug development"
Representative of a Sponsor Organisation.

Case study: Duchenne Muscular Dystrophy

Figure 2: Why the biopharmaceutical industry believes patients choose to drop out of clinical trials

Peter is 6 years old, goes to school and lives on the Isle of Man. He has Duchenne Muscular Dystrophy (DMD), a condition that gradually causes his muscles to weaken, leading to an increasing level of disability. His parents are his carers and he has a brother and a sister. Peter has been enrolled into a clinical trial and the closest centre is Great Ormond Street in London, over 250 miles away. This involves him flying to London for his study visits. One of his parents must accompany him while the other parent ensures Peter's brother and sister continue with their routine, while still going to work. Every time Peter has a clinical trial appointment, he misses two days of school and his parent, two days of work. The study requires Peter and his parent to fly to London for a trial visit on a weekly basis.

This study schedule puts enormous pressure on the family. Having to take time off work becomes increasingly difficult for the parents and the stress of the journey for someone with an orphan disease like Peter is considerable. The sponsor of the trial was concerned with patient retention on the study as the pressure described above had already led to a number of boys dropping out.

We asked respondents to our questionnaire to select the main reasons for patient drop-out in clinical trials and the results are listed in Figure 2.

After Illingworth Research Group mobile research nurse visits were adopted into the DMD case described above, not a single patient withdrew for the remaining 2 years of the study. With the inclusion of mobile research nurse visits, three-quarters of Peter's visits could take place at home and, as a result, trips to Great Ormond Street only needed to occur monthly rather than weekly.

Furthermore the home visits were performed early in the morning, allowing Peter's parents to continue working and allowing him to go to school as normal.

Enabling the subject and his family the choice over the location of the majority of the visits and the resulting reduction in the logistics, time and effort involved, had a very tangible and measurable effect on the study i.e. the cessation of subject withdrawals and importantly reduced the stress and burden on the patient and their whole family.

Lighten the Load

Illingworth Research Group have almost 20 years of experience working with sponsors, CROs and investigator sites providing trained, qualified and experienced research nurses to conduct clinical procedures at a location of the patient's choice; home, work, school or alternative location.

This is often at home, as is the case with patients who live in remote areas, are distant from the study site or those who are less mobile due to their condition or age.

Using portable equipment, a wide spectrum of clinical procedures may be conducted at off-site visits and these may include vital signs, physical assessments, blood sampling (including processing and centrifugation), administration of study drug (topical, intravenous, via a central line, sub cutaneous/intramuscular, oral, inhaled etc.) and applying wound dressings and collection of adverse advents.

If required, approved couriers, ensuring global GxP compliance, work directly with the research nurse to deliver IMP using validated shipping under controlled conditions. Following the visit, blood samples can be transported under the same conditions.

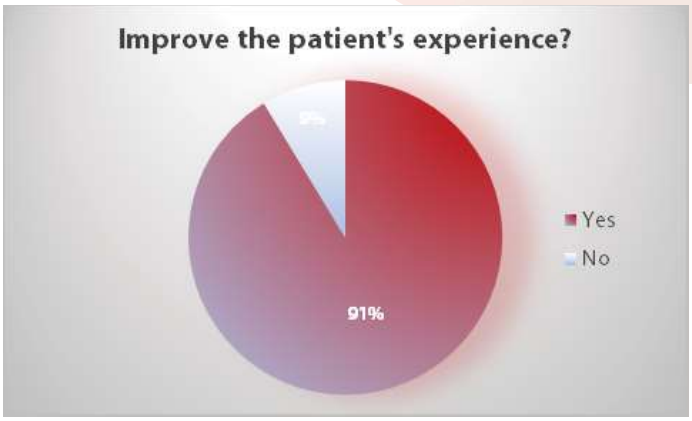
A recent study required daily IMP dosing by a research nurse. This would be logistically difficult for many patients due to the location of the site, however the introduction of off-site visits opens the trial up to a much larger population benefitting both the patients and the trial. Most importantly pressure on the patient is released.

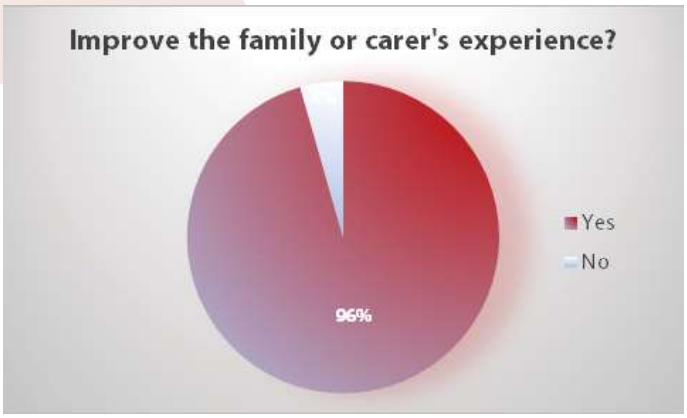
Visits are conducted around the patient's schedule, in surroundings that make them feel comfortable. A relationship is developed between the research nurse and the patient, the patient then no longer feels isolated or forgotten, but are now at the centre of the clinical trial; patient centricity in action! Rather than undergo difficult time consuming journeys, visits to site are reduced to when they are absolutely necessary.

The majority of the respondents to the questionnaire (84%) indicated that mobile research nursing providing visits within homes, schools or the workplace would be helpful to clinical trials, particularly those involving paediatrics, elderly patients, terminally ill, mentally frail, physically disabled or those with embarrassing conditions.

In addition, the results presented below (Figure 3) show that the overwhelming majority of respondents felt that the use of mobile research nursing services will lead to an improvement in both the patient's and their family's clinical trial experience.

Figure 3: Would you agree that the use of mobile research nurses would…





Site visits are still a necessity

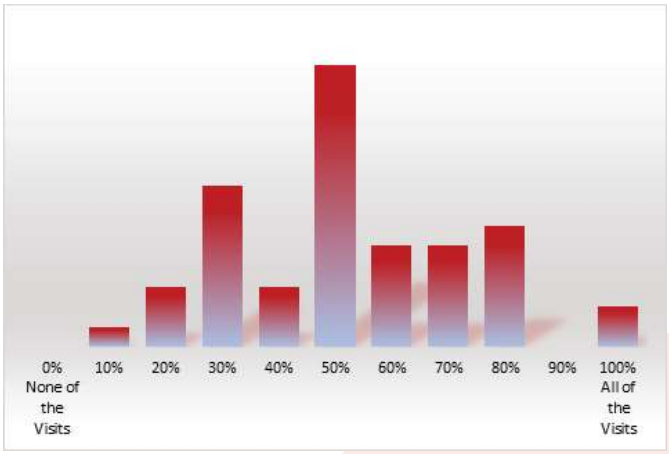


Figure 4: Percentage of study visits respondents believed could be performed outside of the hospital site

When asked what percentage of study visits could potentially be performed off site, the results displayed In Figure 4 were offered.

The results indicate that many respondents believe around half of the study visits could be performed off-site.

Many study protocols have routine follow-up visits and providing these visits do not require specialist equipment that can only be held at site or specific medical input, there is no reason why a mobile research nurse cannot be engaged.

Why isn't Mobile Research Nursing more common?

Mobile research nurse visits away from the study site are still a new concept to some despite the recent focus on patient centricity. When asked for the reasons why mobile research nursing would not be utilised, the responses below (Figure 5) were offered:

At 32%, the most common reason for not using mobile research services was the perception that the protocol potentially did not lend itself to off-site visits. In some studies this may be true, however when reviewing schedules of events, routine visits involving standard assessments and IMP dosing (as mentioned previously) occur regularly and often fit the off-site visit model.

19% of the respondents believed there may be a lack of mobile research oversight and 18% believed the safety of the volunteer may be at risk. At Illingworth Research Group, we differ from many other providers as we only provide qualified, experienced research nurses who are good clinical practice (GCP) trained, have current clinical research experience and hold current licenses. When referring to homecare nursing, there is a distinct difference between home care nurses and qualified, experienced research nurses.

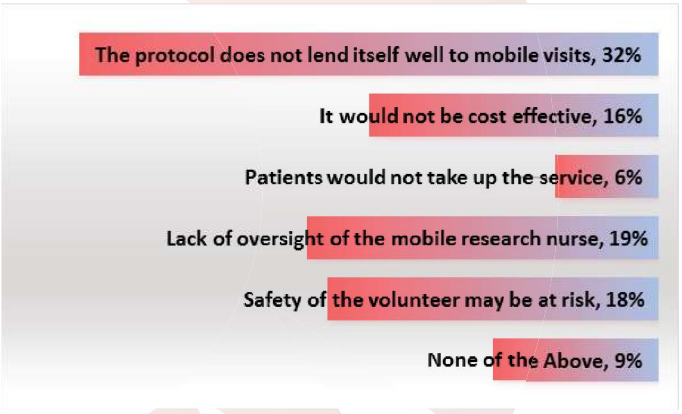


Figure 5: Reasons given for not using mobile research nurse services

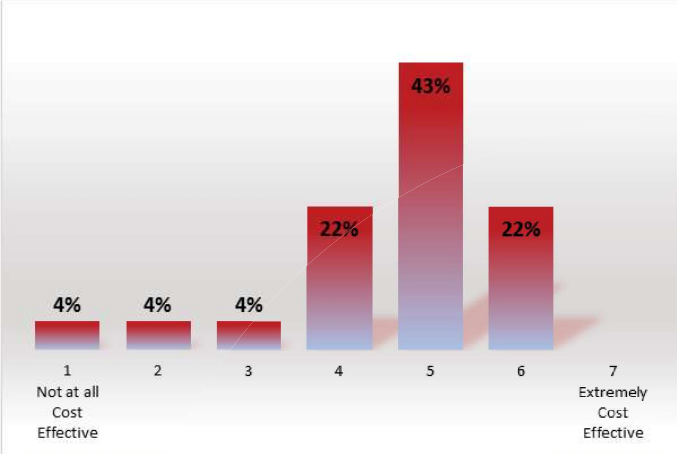
Additionally, Illingworth Research Group mobile research nurses must be approved by the hospital, are involved in study specific training and are assigned duties on the delegation log. They are an integral part of the study team and communication with site and the investigator is crucial.

The mobile research nurses work under the supervision of the investigator and their team. Adverse event identification and reporting is a priority during off-site visits and our nurses stay with the patient for a monitoring period following all IMP dosing. The safety of the subject is paramount and therefore the ethics committees must also approve the inclusion of a mobile research nursing service prior to any off-site visits taking place.

Of course, patient choice is key. Where patients prefer to be seen at site, especially in chronic illnesses and in orphan diseases, additional assistance could be offered to transport the patient comfortably without the pressure of booking flights, finding taxis, parking and expense claims. With dedicated service providers, such as Patient Primary from mdgroup[5], transport arrangements (air/rail/road) can be prearranged and expense reimbursements streamlined with the use of mobile phone app technology, minimising site administration time and reducing the financial burden on the patient and family.

As budgetary considerations are an important factor in study design, we researched the issue of cost and perceived cost-effectiveness of this service:

Figure 6: How cost-effective do you believe inclusion of mobile research nursing in orphan drug trials is?



The majority of CROs surveyed agreed that inclusion of mobile research nursing into orphan drug trials is cost effective.

There will be an increased cost associated with sending a research nurse to a patient, although the investigator site costs will be lower since the work associated with the off-site visits will be directed to the mobile research nurse provider.

Whilst the bottom line may increase, consideration must be given to the positive impact on recruitment, the financial impact of patients withdrawing from a trial and the impact on the integrity of the data, if statistical powering targets are not met.

In our experience ethics committees have welcomed off-site visits, with the well-being of the patient at the forefront of their assessment. Gaining access to a wider group of patients helps to fully recruit and retain subjects, preventing underpowered studies[6].

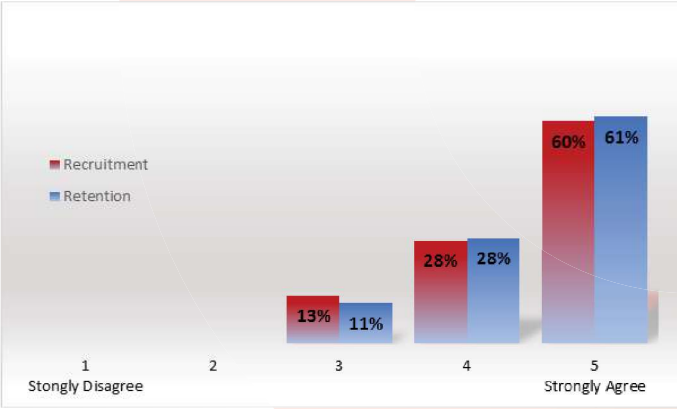


Figure 7: Allowing visits at convenient locations will improve recruitment and retention.

Some investigators appear less willing to 'share' the patient with an external vendor. This is somewhat of a short-sighted view.

Although it is correct that some of the visits will be performed within the home, school or workplace, therefore reducing the tasks performed by the site and, as a result, reducing the per-patient fee that the site receives, it is highly likely that the resource which is freed up at the site will allow them time to potentially enrol more patients than they ordinarily would have, or free up clinic time for non-trial patients.

Additionally, the increased level of attractiveness to participate in the trial will result in increased patient recruitment, retention and overall patient satisfaction.

Indeed, 84% of respondents agreed that mobile research nursing would actually free up study site resources, enabling staff to see other patients and help trials to complete on time and with the required population.

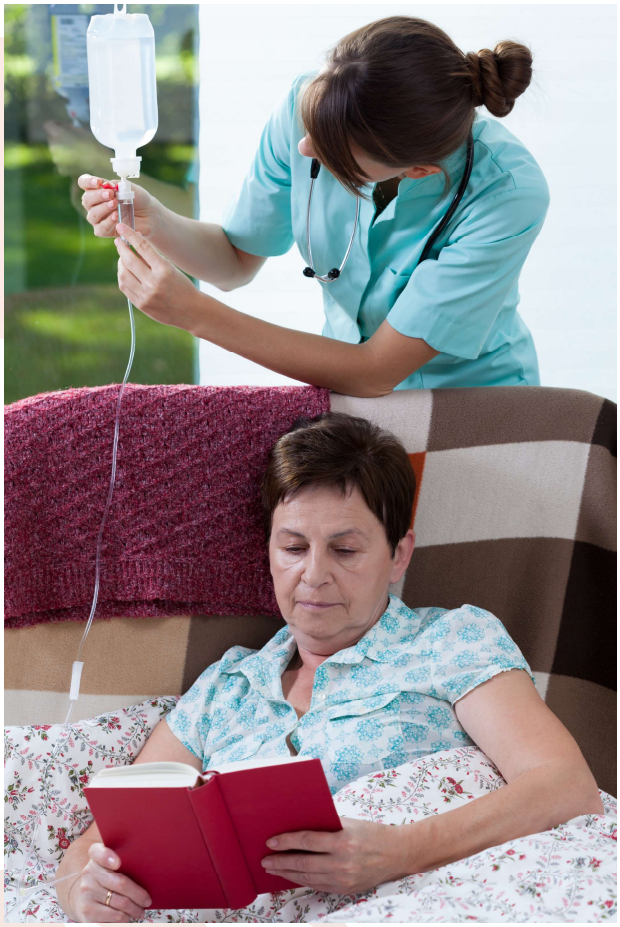
Mullins *et al* (2014)[7] suggest that 'Using an approach that allows the inclusion of a broad participant population can provide decision makers with the regulatory approval and evidence necessary to make effective decisions regarding the use of a treatment in subpopulations, such as the elderly, who may be underrepresented in traditional clinical trials'.

Customer Testimonials

The facts and figures speak for themselves but our best ambassadors are the patients that our nurses have visited and cared for and our satisfied clients. The testimonials below show how the patient-centric view can improve clinical trials.

The availability of home visits was one of the deciding factors in my agreeing to take part in the current clinical trial. The trial involves a good number of "attendances" or contacts with the medical professionals – if I had to go to hospital for every one, which is a round trip of almost two-hours of travelling along busy urban motorways, I wouldn't have volunteered for it. Even the expenses paid wouldn't have compensated for the aggravation involved.

Mobile research nursing patient, August 2016



Rather than patients having to attend hospital visits daily, Illingworth's research nurses went into the patient's homes Tuesday-Friday every week and the patient would attend the hospital clinic every Monday.

If a home research nursing solution is not used, patients, who are terminally ill, have had to travel to the hospital every day until disease progression or death. This is a huge commitment, especially in this patient population. The nurses are incredibly flexible, allowing patients to choose the time of the visit to fit around their daily activities, family and home life.

All logistics are handled by Illingworth. For example, the drug needs to be transported temperature controlled and is picked up from the hospital pharmacy daily by the research nurse and taken to the patient's home via temperature monitoring. Involving home research nursing has improved the quality of life for all these patients. At the end of life, enrolling into a trial is a stressful experience. With patient centric care, it becomes less stressful and helps to enrol and retain research patients when they know this resource is available to them.

UK-based Biotech, September 2016.

Enrolment in the UK far exceeded expectations while maintaining high quality…It reduced the burden on the patients and this certainly helped enrolment overall as many visits could be performed within the patient's home or place of work.

US-based Biotech, July 2016

Conclusion

While orphan diseases are receiving more publicity and patient-centricity is the industry buzz phrase, there is still much more work to do to improve conditions for isolated and immobile patients.

When an orphan drug trial is available it is in the interests of all parties to gain access to as wide a patient population as possible. It is inevitable that orphan disease patients will be spread thin over an extensive geographical area and access to potentially life changing treatment should not just be decided based on location.

When there are now workable options giving patients and their carers the choice of where many of their visits can take place, why is the industry not embracing this flexibility to be built into protocols across different therapeutic areas? Indeed, patient centricity is a buzzword but is this really being addressed or is the Biopharmaceutical Industry simply paying it lip service?

Introduction of mobile research nursing with off-site clinical trial visits, really can **bring the trial to the patient.**

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