



Living with a Rare Disease: The Transition from Pediatric to Adult Care During a Clinical Trial

Highlights:

- With advances in treatments, many rare disease patients are now living into adulthood.
- The transition from pediatric care to adult care comes with a set of challenges that can impact clinical trials.
- Investigators and CROs can improve compliance to study protocols and retain subjects for longer term trials if we improve our own understanding and attention to these transitions.

Introduction

As the paradigm for treating rare diseases shifts, we are seeing new challenges. Thanks to medical advances and access to new treatments, many rare disease patients are living into adulthood with diseases that were once lethal in childhood. When it comes to treating these diseases, pediatricians currently are the experts. But as the next generation of patients grows older, they will need to transition from a specialty children's hospital setting to adult care.

As drug developers, we need to support this transition of care. Looking forward, there will be more adult physicians becoming principal investigators on trials that were once run solely by pediatricians. We will also see mixed models, where pediatricians and adult physicians both support the trial, especially in longer-term trials that might last for 7-10 years. The patients will often age out of the children's hospitals as the trial continues. The transition of care needs to be supported within the clinical trial framework in order to keep the patients enrolled in the trial or else they may drop out or be lost to follow-up.

1 What are the biggest challenges on the horizon in the shift from pediatric care to adult care for adolescents with rare diseases?

80% of rare diseases impact kids. Most of these patients were probably diagnosed in childhood and have had treatments at children's hospitals, with their parents as the caretakers and managers of their care. It is even possible that adult physicians may not have seen these diseases before. Rare diseases often involve multiple systems within the body and therefore require multi-disciplinary care. For example, the disease could be a neuromuscular indication that causes respiratory decline or a metabolic disorder that leads to blindness.

As these children become young adults they now have to (and usually want to) coordinate their own care, which can be a hard transition for both the person with the illness and for their family. In children's hospitals, the principal investigator was a pediatrician; now it may be someone who works only with adults. In the children's hospital setting, the care was often multidisciplinary and was coordinated by a care team – either parents or the physician's office – but in the adult setting, their care becomes fragmented, they must see multiple different specialists. Navigating this space can present challenges for young adults suffering from rare diseases as well as for their extended care teams.

New issues they didn't have to address when children's hospitals coordinated their care may become overwhelming for them, especially on top of additional changes in life, such as going to college or starting to work.

2 What can we learn from children's hospitals as children with rare diseases live longer into adulthood?

Children's hospitals have access to multidisciplinary care centers that are not as common in adult care settings. The collaborative and comprehensive care offered to rare disease patients suffering from a multitude of symptoms requires careful coordination across various departments at a site, possibly including neurologist, geneticist, respiratory therapist, physical therapist, dietician and/or others.

Anticipating challenges for our subjects requires thought be given to the transition of care plan to aid the children in the transition while also addressing, with investigators, these expected challenges. The best practice is to start that conversation with the child at around age 13 or 14, helping to establish goals for them and a plan on how to meet those goals, so they will eventually be capable of managing their own care within the context of adulthood.

This plan helps them to not deteriorate while going through this transition (which is often a big problem – the disease can worsen while the young adult is going through periods of stress.) The plan usually starts with things as simple as taking their medications on their own, at the right time, and being aware of their symptoms on a conscious level, since it is not unusual for them to stop taking their meds without telling anyone.

In addition, the sponsor and CRO must work together to find principal investigators and appropriate sites with relevant expertise, access to patients, required equipment, and an understanding of the transitions subjects are going through.

3 What are the most important things for adult-focused physicians to know in the transition from pediatricians as principal investigators on these types of trials?

Coordination of care with other specialists and with the previous pediatrician is critical, especially during the subject's transition to adulthood. For the patient, the disease may worsen during this critical transition period. Investigators must be conscious of this.

Researchers must look at ways to make the trials work for the patients, and not overburden them. A child who started in a trial at age 10 or 11 may now be a college student; they might be living elsewhere, want to have a social life, and continuing to participate in the trial may seem onerous. So we often use telemedicine so they

don't miss school, use apps on their phones for questionnaires, identify what their motivations are and subsequently customize pre-emptive solutions to keep them in the trial. It is important because of the small sample size; sponsors need them to not drop out. Look at the size of the trial; is it small enough that it can be customized per individual? If so, it may be worth the cost to do that.

Principal investigators must realize that this transition impacts the entire family unit. Parents who have been caretakers may find it challenging to give up control as the children take over their own care. Their concern for their children doesn't end just because the children have become adults. Helping the previous caretakers to adjust to the young adult's growing independence provides advantages that cannot be measured easily but that probably contribute to quality of life benefits for everyone involved.

4 How can clinical researchers and CROs best impact this transition in the clinical trial setting?

As CROs we may now need to have dual principal investigators for these trials, one in a children's hospital and another outside a pediatric setting, to provide better support for patients across a broad age range. Give thought to mixing up your sites in studies, with some who handle pediatric patients and others who handle adults from the outset, or start the trial with co-principal investigators.

Much of the patient education – to help them take charge of their care in and outside of the trials – falls to the CRO. Educating and empowering the patients helps with maintaining compliance to the protocol itself – including mandated visits, filling out questionnaires – and also increases retention over the long term. Ensure age appropriate materials are ready in advance. For example, graphics for rating scales and QOL (quality of life) questions and health literacy informational text adapted for various age groups. Encourage sponsors to understand that although the content is broad it builds on itself as the person ages. Can some of it be digital apps on smart phones? Use communication devices that are comfortable and common for young children through young adults.

Facilitating physician education to inform principal investigators on timing and how long they will be on the trial is important. Talk with them about considerations for patients at the age they are now, how long the trials will last, and at what age subjects will be by the end of the trial, remembering there could be a big difference in their lives at that point. Encourage the doctors to have an individual transition plan for each person in the study.

Endpoints must be age appropriate, too. For example, what might be clinically relevant or significant for a 15-year old might not be valid for a 20-year-old. Look at the protocol and see if it can stand the test of time – as the person ages does this still work? Quality of life questions are different per age, lifestyle, and cognitive abilities. Validation for a teen might be different from that for an adult.

CROs must also customize their plans, recognizing that if the patient presents to the ICU or emergency room, they may be treated differently depending on their age. Information about the trials should be in their records so that touchpoints know the protocol and do not undermine it. When Mom or Dad are no longer the advocate, the young adult needs to know what study they're on, what to do and how to manage if they have a flare-up.

A multidisciplinary team may also be required at the CRO, and good communication among them to manage expectations is a must-have.

5 Are there any ethical considerations that must be taken into account?

It is important to remember that these kids have dreams just like any teens and young adults. Their disease often gets in the way of being just a “normal” kid – so we must look at ways to support them, in general, and also to keep them involved in trials.

One is a “patient” forever when they have a rare disease, but only a “subject” when in a trial. Have respect for their personhood, making sure we are doing what’s best for subjects. After a certain age (depending on the state/country), it is their right to include parents or not. They must have consent forms once they hit the legal age, a new document, not just an assent form.

Show them how you are partnering with them to address their illnesses. They have anxiety about the unknown, even as young adults, not just to little children. Help them find ways to cope and to overcome stigma, help them with their “story” to keep it brief and matter-of-fact. Also, help them also to develop a brief explanation of the study they are participating in, and why, to increase their confidence and ability to share this information with others they trust. Young adults might like to learn relaxation techniques, diet information, mindfulness, or how to join support groups with others who have the same illness, online or in person.

Help the college student to understand how they can elicit support from friends and roommates and when to call doctors, parents or teachers, despite how they might feel at the moment. For example, some diseases can impact cognition and specifically decision-making. Help them to see that there are times when they may not make the best decisions. It is important to develop easy tracking methods for recording of symptoms to get teens to comply.

Last but not least, help them look for doctors who are compassionate and trustworthy.

6 How do we help caregivers fit into this mix?

Young adulthood can be really hard on parents, even when their children don’t have a rare disease. Delicate discussions on things like birth control, frequency of sexual relations, use of recreational marijuana or alcohol must be kept private. If trust is not established, it will create barriers to enrollment.

By helping the child, you are helping the parent, but educate them on the transition, too, as they may not have thought about it much. Recommend videos or articles to them that can help them to understand how their children are feeling. They can describe, from the teens themselves, how they took over ownership of their treatment, the mistakes they made, and what they learned from it. Videos can help parents to see that their young adult family members want to know how to manage their own lives and that includes their illness.

7 Compliance and financial considerations?

One other area we may consider that takes additional research support is this: financial considerations. How can we help people get funding or additional support they may need in order to participate in the study? For example, health insurance, SSDI, section 8 housing assistance, transportation to clinics/Uber cards, prepaid

debit cards for specific elements, or service animals – can all be helpful. If sponsors cannot support these, or if patients cannot get around well enough to benefit from these supports, look at other options. Visiting nurses, electronic questionnaires, monitoring devices like digital watches or health tracking devices may also be options to consider.

When we anticipate and identify challenges – helping the transitioning teen to see the issues they may face in college or in a job, how to find advocates, possible triggers and levels of severity, adverse events/side effects that they should report to the doctor – then we will be better able to develop compliance mitigation strategies. Ultimately, we will benefit from better compliance to the protocols of the study, and everyone will benefit from the new medicines to treat these illnesses.

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