Incorporating the Patient Voice in Hydrocephalus Research

Hydrocephalus Association

Translation to Transform Project

WHITE PAPER

INCORPORATING THE PATIENT VOICE IN HYDROCEPHALUS RESEARCH

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ABSTRACT

Object: In recent years, efforts to incorporate the patient perspective into clinical trial design have increased, however, there has been little effort to involve patients with hydrocephalus and their families in this process. This report starts the process by sharing the key outcomes of the Translation to Transform (T2T) Project.

Methods: The T2T Project consisted of an online webinar and in-person workshop. The webinar was designed to educate patient representatives about the clinical trial process, research ethics, and introduce them to key terms and definitions. The workshop brought together medical professionals, researchers, and patient representatives to discuss clinical trial ethics, barriers to clinical trial participation, and patient-centered outcomes. All workshop participants were asked to fill out a post-workshop survey to self-identify key discussion points.

Results: The webinar and workshop were well received by patient representatives, medical professionals, and researchers. Major themes that became apparent during the workshop were age-related differences in patient priorities, the importance of cognitive outcomes and activities of daily living, and age-related differences in barriers to clinical trial participation.

Conclusion: The T2T Project was designed to start a dialogue between hydrocephalus patient representatives, medical professionals, and researchers. Incorporating the patient perspective into clinical trial design can help researchers bypass some of the common challenges to patient enrollment and clinical trial completion, as well as ensure that the outcomes are meaningful to patients. This report relates the key outcomes of those discussions and should serve to help guide clinical trial development for hydrocephalus and other chronic conditions as well as encourage future dialogue.

INTRODUCTION

In recent years, patient advocacy groups and other organizations have sought to increase patient and caregiver participation in the development of clinical trials.[1,2] It is believed that early engagement will help clinical researchers overcome common challenges, such as low patient recruitment and retention, and that clinical trials will, in turn, provide the patient community with more meaningful results. For hydrocephalus research, effective engagement requires understanding the diversity of the hydrocephalus patient population, which includes infants with congenital hydrocephalus, children and adults who develop hydrocephalus due to injury or infection, and adults who develop idiopathic Normal Pressure Hydrocephalus (iNPH).

Hydrocephalus occurs when there is an imbalance between cerebrospinal fluid (CSF) production and absorption within the brain. It is a complex, chronic condition that can affect anyone at any age. It is estimated that congenital hydrocephalus occurs at a rate of 0.6 to 1.0 per 1,000 live births[3-5] and iNPH affects as many as 770,000 elderly adults in the United States.[6]

Currently, the only effective method to treat hydrocephalus is neurological surgery to place a ventricular or lumbar shunt or perform an endoscopic third ventriculostomy (ETV). Even with treatment, hydrocephalus is often associated with significant cognitive and developmental sequelae. Children with hydrocephalus often have intellectual, learning and motor disabilities,[7-12] chronic headaches,[13-15] and mood disorders.[16-18] In addition, both treatments have extremely high failure rates.

In children, approximately 30-50% of shunts and 30% of ETVs fail within the first two years,[19-22] and 80% of shunts fail within 4 years.[20] Shunt failure has a 1-2% risk of death,[23,24] and, for some patients, the number of neurosurgeries (i.e. shunt revisions) can exceed 100 over a lifetime. Emergency room visits are common for children with hydrocephalus, accounting for 0.6% of all pediatric hospital stays and 1.8% of all pediatric hospital days in 2003.[25] Given the paucity of available treatment options and their inherent limitations and high failure rates, the development and testing of novel non-surgical therapies and better devices for the management of hydrocephalus is essential.

Promising clinical and pre-clinical research on new technologies for intracranial pressure (ICP) monitoring as well as pharmaceutical therapies to manage or prevent some forms of hydrocephalus are underway. Considering the unique vulnerabilities of the hydrocephalus patient population and the dire consequences of not receiving timely intervention, investigators may face considerable barriers in recruiting and retaining patients for clinical trials. Increasingly, patient advocates and others have called for clinical trial design that accounts for and considers the risk tolerance of patients and families and incorporates outcomes that are important to them, i.e. patient-centered

outcomes.[2] Obtaining patient and caregiver input before clinical trials are designed and undertaken will help mitigate potential enrollment and retention barriers.

As a first step, the Hydrocephalus Association (HA), with funding from the Patient Centered Outcomes Research Institute (PCORI), developed the Translation to Transform (T2T) Project. The T2T Project brought together medical professionals, researchers, and patient representatives to discuss clinical trial ethics, barriers to clinical trial participation, and patient-centered outcomes. This report details major themes identified during the T2T Project and the results of two T2T surveys.

METHODS

TRANSLATION TO TRANSFORM PROJECT

The T2T Project was designed to start an active dialogue between patient representatives and hydrocephalus researchers while providing patient-centered feedback for clinical trial design and implementation. The project consisted of a webinar for patients and caregivers followed by an in-person workshop attended by patients, caregivers, medical professionals, and researchers. Participating patients and caregivers were part of the HA Patient Partner Committee (PPC) and represented a broad range of hydrocephalus patients in terms of etiology, age, and treatment. Participants included parents of children who were diagnosed as infants (e.g. congenital and posthemorrhagic), adults with hydrocephalus who were diagnosed and treated as children, adults diagnosed in young or middle age, and older adults with iNPH and their caregivers.

T2T PARTICIPANTS

PPC MEMBERS

The T2T PPC participants were composed of eight patients and seven caregivers (Table 1). All participating PPC members were themselves patients or caregivers of patients who had been treated with surgery, including shunts (n=13), ETV (n=1), and shunt and ETV with choroid plexus cauterization (ETV/CPC) (n=1). In three cases, the patient and caregiver(s) were from the same family.

Characteristics of the Patient Partner Committee (PPC)

PPC Member	**Hydrocephalus Patient**		
Relationship	Year of Birth	Age at Diagnosis	Treatment
Parent	2008	Prenatal	Shunt
Self	1985	0-1 months	Shunt
Parent	2000	0-1 months	Shunt
Other Relative	1983	1-11 months	Shunt
Self	1983	1-11 months	Shunt
Parent	1983	1-11 months	Shunt
Self	1987	1-11 months	Shunt
Parent	2004	1-12 years	Shunt, ETV/CPC
Self	1980	19-59 years	ETV
Self	1953	19-59 years	Shunt
Spouse	1955	19-59 years	Shunt
Self	1955	19-59 years	Shunt
Self	1937	60+ years	Shunt
Self	1942	60+ years	Shunt
Spouse	1942	60+ years	Shunt

Table 1: PPC member association with hydrocephalus and demographic information.

RESEARCHERS

The T2T Project engaged basic and translational hydrocephalus researchers as well as medical professionals who conduct clinical research (see addendum for full list).

T2T WEBINAR

The webinar was held one month prior to the workshop. The webinar focused on educating patients and caregivers about clinical trial design and research ethics while introducing some of the key topics that would be discussed during the workshop. A full agenda can be found at http://www.hydroassoc.org/conferences-and-workshops/.

Following the webinar, PPC members were asked to complete a post-webinar survey which included basic demographic information and ratings on the structure and content of the webinar. In addition, recollection of key concepts was assessed, and PPC members were asked to identify topics that should be revisited or expanded upon during the workshop.

T2T WORKSHOP

The workshop was held on June 16, 2016, in Minneapolis, MN, and brought together patients and caregivers affected by hydrocephalus with translational science and clinical researchers. The workshop contained a research ethics component followed by presentations and discussion centered on three topics:

1) Intracranial pressure (ICP) monitoring

   Clinical example: Study validating non-invasive ICP monitoring against the 'gold standard' invasive ICP monitoring in patients already undergoing invasive ICP monitoring.

2) Non-invasive treatments:

   Clinical example: Study testing the effectiveness of the drug acetazolamide in iNPH patients who had not been surgically treated.

3) Preventative therapies

   Clinical example: Safety study involving the administration of autologous cord blood to children with brain injuries.

These topics were selected because translational and clinical research was being conducted in all three areas. In addition, advancements in each area would have a significant impact on the hydrocephalus community. Finally, each area presents different research challenges that could potentially benefit from early patient engagement. Following each presentation, the group engaged in moderated discussions focused on barriers to research participation, patient-centered outcome measures, risk trade-offs, and ethical considerations for the clinical trial topic presented. A full agenda can be found at http://www.hydroassoc.org/conferences-and-workshops/.

All workshop participants were asked to complete a post-workshop survey to self-identify key discussion points. Researchers were specifically asked if the workshop would lead to changes in their work.

ANALYSIS

This report brings together the key topics discussed during the T2T Project and provides suggestions for next steps. The key themes discussed were identified through the post-workshop survey and a review of the workshop notes by the planning committee. The opinions and recommendations presented reflect the core ideas brought forth during the facilitated discussions.

RESULTS

PATIENT PRIORITIES

Neurosurgical outcomes have dominated the hydrocephalus research literature for many years and remain a top priority for families living with this condition. However, families and patients affected by hydrocephalus also have concerns that fall outside the realm of most neurosurgery departments. At the T2T workshop, PPC members voiced research goals and identified topics that should be prioritized for future study. It is important to note, however, that PPC members had a difficult time prioritizing one topic or outcome over another.

RESEARCH GOALS

PRENATAL OR INFANTILE DIAGNOSIS

Children diagnosed prenatally or in early childhood often suffer from significant impairments, even after treatment. PPC members representing these families viewed good outcomes as a blessing, but they were also acutely aware that treatment complications could occur at any time and that additional decline is possible.

The research goals for these families were that new treatments and therapies would improve cognitive and long-term functional outcomes. There was also an emphasis on creating treatments with a lower risk of complications as well as creating devices that monitor intracranial pressure – either non-invasively or by chronic implantation of a device. The therapeutic goals and expectations voiced by this group were centered on decreasing treatment failure and complication rates, improving cognitive and long-term outcomes, and, in doing so, reducing stress and anxiety on the family.

ADULT DIAGNOSIS

The expectations of patients diagnosed later in life, especially those with iNPH, contrasted markedly with people diagnosed in early childhood. PPC members representing patients diagnosed as adults expected that shunt placement or ETV surgery would result in a complete reversal of symptoms and a return to normalcy, including

normal cognitive function. Many were disheartened when initial improvements were not sustained long-term, and, in some cases, the PPC caregivers and patients attributed not achieving a full return to baseline to the treatment (i.e. shunt placement or ETV) itself. For PPC members representing patients diagnosed as adults, their priorities were focused on attaining full and sustained recovery of physical and cognitive function and on the development of non-surgical therapies.

RESEARCH PRIORITIES AND PATIENT-CENTERED OUTCOMES

NEUROSURGICAL AND TREATMENT COMPLICATIONS

The only current treatments for hydrocephalus are neurosurgical. While commonly used clinical outcome measures, such as shunt and ETV revision rates and shunt infection rates are very important to families, they fail to capture the full impact of the condition. Patient-centered outcomes in the area of neurosurgical and treatment complications include factors such as time off work and school, out-of-pocket expenses, and caregiver and patient stress and anxiety.

DISEASE MONITORING

Chronically implanted ICP monitors, non-invasive ICP monitors, and other technologies designed to identify shunt obstructions are currently being developed, tested, and used in some hospitals. Families are very excited about these devices as they should help reduce the uncertainty around treatment failure and allow proactive decision-making.

PPC members identified multiple patient-centered outcome measures related to these devices. For example, the new technologies should reduce the time it takes to diagnose treatment failure and reduce the need for computed tomography (CT) and other types of radiological imaging. For devices that are designed for continuous or in-home use, caregiver and patient anxiety and stress should be measured to ensure that the device is decreasing rather than increasing these feelings. A related patient-centered measure is whether these devices alter the number of emergency room or doctor visits for suspected treatment failure.

NEUROPSYCHOLOGICAL OUTCOMES

Neuropsychological outcomes are a significant concern for all families affected by hydrocephalus. When discussing cognitive outcomes, including intelligence, memory, and executive function, PPC members focused on school and job performance. For school-aged children, the use of an individualized education plan (IEP) may be a surrogate outcome measure as an indication of cognitive challenges in the academic environment, in addition to grade point average. For adults, the ability to maintain full or part-time employment was a high priority as well as the ability to stay focused in a work environment. PPC members also described quality of life measures such as the degree of independent living, the ability to establish and maintain relationships, and the capacity to drive a car safely.

Many patients affected by hydrocephalus and their families experience stress, anxiety, and depression. Understanding how these neuropsychological issues affect overall quality of life and determining whether new therapies or devices improve quality of life by measuring social and family function is also extremely important.

PAIN MANAGEMENT

Debilitating headaches and chronic pain are commonly reported complaints by patients with hydrocephalus.[13,14,26] Despite the significant impact pain can have on a patient's quality of life, there has been little research in this area. PPC members viewed pain research as a high priority. As new hydrocephalus treatments are developed, the incidence of headaches or presence of chronic pain could be used as a patient-centered outcome measure. However, PPC members also stressed that research on pain management strategies for patients with hydrocephalus needs to be conducted as well.

VISUAL ACUITY

PPC members also viewed visual acuity as an important, but understudied, area in hydrocephalus research. Similar to pain, visual impairment may be used as a patient-centered outcome measure as new hydrocephalus treatments and management strategies are developed. However, research on early identification of visual impairments and therapies that repair damage to key structures, such as the optic nerve, is needed.

CLINICAL TRIAL PARTICIPATION

Low patient recruitment and retention can lead to clinical trial failure.[27] The T2T workshop identified barriers to patient recruitment in hydrocephalus clinical trials. PPC members voiced many commonly described barriers to clinical trial participation. In addition, they also identified barriers more specific to the unique nature of hydrocephalus and the current treatment modalities (Table 2).

Barriers to Clinical Trial Participation

Barriers to Participation		Recommendations
Common	Time Commitment	• Incorporate study visits and testing into standard of care model • Use alternative data collection methods (i.e. online surveys) • Provide study participants with periodic feedback on trial progress
	Logistical Concerns	
Hydrocephalus Specific	Additional Surgical Procedures	• Enroll patients already scheduled to undergo the standard surgical treatment
	Infection Risk	• Avoid repeated invasive procedures • Use minimally invasive procedures and those with the lowest risk of infection
	Delaying Standard Treatment	• Use an additive study design in which the study intervention is paired with standard treatment

Table 2: Barriers to clinical trial participation and recommendations

COMMON BARRIERS

TIME COMMITMENT AND LOGISTICS

PPC members voiced many commonly described barriers that would prevent them from participating in a clinical trial. The primary barriers identified were time requirements and logistical concerns. This included the need for additional doctor's visits and diagnostic testing outside of the standard of care (i.e., blood work, CT scans, MRIs). During the workshop,

discussions also revealed an apparent misconception among patients and caregivers who believed that significant changes in cognitive function could be adequately assessed over a relatively short-time frame (i.e., months) and that long-term assessment was not necessary.

To address these concerns, PPC members made several suggestions to assist clinical trial participation and retention. First, they recommended incorporating trial outcome measures into a standard of care model, since hydrocephalus patients, especially children, often have routine clinic visits. They believed careful coordination between the study teams and clinical care providers would decrease the need for additional visits and promote participation. Second, PPC members recommended using alternative data collection methods, such as online surveys, to improve participation. Finally, it was suggested that study teams periodically provide patients with feedback on the progress of the trial to help maintain participant enthusiasm and improve retention.

HYDROCEPHALUS-SPECIFIC BARRIERS

ADDITIONAL SURGICAL PROCEDURES

Throughout their lifetime, most patients with hydrocephalus require multiple surgical procedures. During the workshop, PPC members were wary of participating in studies that require patients to undergo additional surgical procedures. Specific examples included testing a non-invasive ICP monitor against the 'gold standard' invasive ICP monitoring or testing drugs that require intraventricular administration. PPC members indicated that they would only be willing to participate in studies requiring surgical intervention if it was incorporated into a planned procedure, independent of the study.

It was not clear if this unwillingness to participate in a clinical trial was irrespective of the potential benefits. For example, if a new treatment had the potential to abolish or greatly reduce the risk of future surgeries, some patients may be willing to participate. Although a rare occurrence, this has been evident in the hydrocephalus community when a shunted hydrocephalus patient undergoes an elective ETV procedure with the hope of becoming shunt-independent.

INFECTION RISK

Shunt infection is a major area of concern for the neurosurgery community,[28,29] for patients, and for families. The majority of PPC members at the workshop represented shunted hydrocephalus patients and all shared this concern. Each shunt revision increases the risk of shunt infection and can result in a grueling cycle of shunt revisions, shunt infections, and subsequent shunt revisions.[28-31] In turn, these cycles can result in new medical complications for the hydrocephalus patient.

It was therefore not surprising that PPC members were resistant to enrolling in studies that involved repeated invasive procedures. Their concern, however, did not carryover to studies involving minimally invasive procedures with an exceedingly low risk of infection, such as shunt taps to collect CSF.

DELAYS IN STANDARD SURGICAL TREATMENTS

Hydrocephalus patients and caregivers understood that, although not ideal, shunt placement and ETV procedures save lives. They also understood that delaying these treatments could negatively impact the patient. During the workshop, PPC members and the participating researchers and medical professionals discussed the risks and benefits of delaying standard surgical treatments to test a new therapy. PPC members were concerned that delaying standard treatment would subject the patient to additional neurological injury and associated sequelae. However, the researchers countered that it may be necessary to delay the standard treatment during clinical studies in order to determine the efficacy of a novel therapy. Despite this, some PPC members stated that they would be unwilling to take this risk. However, views differed between patient populations (see below, Age-Specific Considerations for Clinical Trial Design). Overall, PPC members were more amenable to participating in studies with an additive design, i.e. the new intervention was paired with a standard treatment.

PATIENT-DERIVED THERAPIES

Despite the barriers discussed above, it is worth noting that PPC members viewed patient-derived therapies, such as treatment with autologous stem cells, with much more optimism and much less concern than other types of treatments. At the workshop, participants discussed a recent safety trial involving the administration of autologous cord blood to patients with hydrocephalus. Many PPC members felt that studies testing patient-derived therapies, even in the early stages of research, had the potential to improve neurological outcomes by promoting neuroprotection or neuroregeneration. PPC members also felt that these therapies could be administered without changing or delaying standard treatments. The overall perception was that therapies using patient-derived tissue had a lower risk of adverse side effects than drug treatments and were more likely to produce positive results.

AGE-SPECIFIC CONSIDERATIONS FOR CLINICAL TRIAL DESIGN

In addition to the barriers to clinical trial participation mentioned above, some age-specific considerations also arose during the workshop. These concerns may affect the willingness or ability of specific patient populations (i.e., infants and children, adolescents, adults) to participate in clinical research studies. Researchers should be cognizant of these issues when designing clinical trials for patients with hydrocephalus. This section details these issues and provides specific recommendations (Table 3).

CLINICAL TRIAL DESIGN: INFANTS AND CHILDREN

Within the pediatric hydrocephalus population, neurosurgical intervention usually occurs within the first year of life, and often, within the first weeks of life. For families, the primary goal is to achieve the best treatment possible. At

the workshop, PPC members representing pediatric hydrocephalus patients and families identified barriers to clinical trial participation involving infants and children including: parental anxiety and stress, fear of delaying standard treatments, and uncertainty about long-term outcomes.

PARENTAL ANXIETY AND STRESS

During the workshop, participants identified a number of reasons why clinical trials may increase parental stress and anxiety, leading to low enrollment rates in this patient population. First, at the time of diagnosis parents must process much information and make critical decisions regarding their child's care. Deciding whether to enroll their infant in a clinical trial adds to this already heavy burden. Second, parents want clarity about the 'best' path forward, but clinical trials are designed to test different paths. Being approached to enroll in a clinical trial can therefore increase uncertainty about what the 'right' clinical care decision is for the child. Third, parents want to have confidence in the care team. Random assignment to a treatment or agreeing to

Age-Specific Considerations in Clinical Trial Design

Age-Specific Concerns		**Recommendations**
Infants and Children	Parental Anxiety and Stress	• Give parents as much time as possible to process information and ask questions • Connect "new" parents with "experienced" parents who have had mentorship training
	Delaying Standard Treatment	• Use an additive study design in which the study intervention is paired with standard treatment
	Long-term Outcomes	• Perform studies to better identify the long-term cognitive effects of hydrocephalus and existing treatment modalities
Adolescents	Decision-making Capacity	• Design assent process to accommodate individuals with cognitive impairment and to be waived if necessary • Evaluate and take into account the adolescent's familiarity with the health care system during the assent process
	Parental Role	• Assess the parent(s) influence on adolescent's decision-making and consult ethics and/or research oversight boards if needed
Young and Middle Age Adults	Loss of productivity	• Design trials to limit time off work, cost to the patient and impact on patient's lifestyle and day-to-day functioning
	Risk of cognitive decline	• Pair study intervention with standard treatment whenever feasible • Characterize long-term cognitive effects associated with existing treatment modalities
Elderly Adults	Risks of surgery and anesthesia	• Provide detailed counsel to patients and caregivers on the risks and benefits of surgery • Design trials to test novel non-surgical, pharmaceutical interventions for this patient population • Connect newly diagnosed patients with other patients in their age group who have undergone the proposed treatment who had mentorship training

Table 3: Age-specific considerations for clinical trial design and recommendations.

follow a set study protocol for treatment decisions can make parents feel that the doctors are not free to act in the best interest of the child.

These barriers are not easily overcome. Providing ample time for parents to process and ask questions about the trial could improve enrollment rates. PPC members also suggested connecting parents of newly diagnosed infants and children with 'experienced' parents. Establishing this connection could ease anxiety and help new parents make an informed decision about enrolling their child in a clinical trial. Appropriate training for the mentoring parents would be necessary. Mentoring may result in a significant increase in patient enrollment.

DELAYS IN STANDARD SURGICAL TREATMENTS

As previously discussed, many PPC members identified delaying standard surgical treatments as a major barrier to clinical trial participation. This sentiment was expressed most strongly by PPC members representing patients diagnosed at birth. To address this concern, PPC members recommended incorporating standard treatments into the trial design whenever possible. Studies designed with shunt placement or ETV procedure as an outcome measure, may be viewed by parents as a delay in standard treatment, and in turn deter them from enrolling their child.

LONG-TERM OUTCOMES

PPC members representing parents of children with hydrocephalus were also hesitant to enroll their children in intervention studies when the long-term cognitive effects were unknown. For example, parents wanted information on whether a treatment would affect their child's risk of having a learning disorder, attention deficit disorder, or psychiatric disorder. In most cases, however, this data does not exist. This finding underscores the need for multidisciplinary hydrocephalus treatment studies to assess both the surgical and neuropsychological outcomes of various treatments.

CLINICAL TRIAL DESIGN: ADOLESCENTS

More research is needed on adolescents with hydrocephalus, but special considerations need to be in place when conducting this research. The workshop discussion on adolescents in clinical trials focused on the evolving ability of the adolescent to provide meaningful assent and the roles of the parents and adolescent in the parental permission/ assent process to clinical trial enrollment.

DECISION-MAKING CAPACITY

Adolescents have limited, but evolving, decision-making capacity (i.e., the ability to make reasonable decisions) and individual experiences play a key role in this evolution. Knowledge, health status, anxiety, experience with decision-making, and each child's unique cultural, familial and religious background as well as their values all play a role in a child's understanding of their situation and impact their ability to make decisions. For adolescents with

hydrocephalus, a number of additional considerations should be addressed including the cognitive impact of the condition and the unique life-experiences of adolescents with hydrocephalus.

The cognitive impact of hydrocephalus varies between individuals, but, in many cases, may impair the decision-making capacity of adolescents with the condition. One option discussed at the workshop was to exclude patients with severe cognitive impairment. However, workshop participants felt that excluding these patients would skew study results, limit the generalizability of the research, and in many ways, be a disservice to the hydrocephalus community. The PPC members suggested designing the assent process to accommodate people with impaired decision-making capacity and that, in some cases, assent could be waived by the Institutional Review Board.

Paradoxically, living with hydrocephalus may actually improve an adolescent's decision-making capacity. Adolescents with hydrocephalus frequently must determine whether a symptom, such as pain or fatigue, is related to their hydrocephalus and decide when they should tell their parents. In addition, adolescents diagnosed in infancy are likely to have greater familiarity with medicine and the healthcare system in general, which may make them better able to understand the potential risks and benefits involved. However, this familiarity may also make them less risk averse.

For some adolescents, however, the intimate involvement of their parents in healthcare decisions may limit the adolescent's ability to independently participate in the assent process.

PARENTAL ROLE

During the workshop, PPC members who were parents of adolescents indicated that they maintained full responsibility for their child's healthcare at this stage, including the decision to participate, or not, in a clinical trial. This sentiment is consistent with information the Hydrocephalus Association has received from other families and poses a problem for ensuring appropriate assent for clinical trial participation in adolescent patients.

The participating medical professionals and researchers were concerned that, given the level of parental involvement in healthcare decisions, even if the adolescent was involved in the conversation, the adolescent would be greatly influenced by the perspective of the parent. This raises important considerations related to the adolescent's voluntariness and ability to meaningfully participate in decision-making, including their willingness to do so. Ultimately, clinician-investigators must consider the individual clinical trial, especially the risk/benefit profile, while accounting for the views of both parents and adolescent participants. When appropriate, additional consultation with local ethics and research oversight boards may be helpful.

CLINICAL TRIAL DESIGN: ADULTS

Adult PPC patients were more willing than younger age groups to participate in clinical trials. However, even within in the adult population, there were clear divides between young to middle aged patients (19-59 years old) and those who were elderly (≥60 years old).

CLINICAL TRIALS INVOLVING YOUNG AND MIDDLE AGED ADULTS

The primary concern for young and middle aged adults, whether diagnosed as a child or as an adult, was how trial participation might impact their productivity. PPC members indicated that their willingness to enroll in a clinical trial would take into consideration factors such as time off work, cost, and alterations to lifestyle. These concerns highlight the distinct characteristics of this patient population. Many of these patients had careers, families, and other responsibilities that would affect their decision about participating in clinical research.

During the workshop, PPC members who were diagnosed as adults were asked to describe barriers that would keep them from participating in a clinical trial either after they were diagnosed, but before receiving surgical treatment, or after the diagnosis was made and initial surgical treatment was performed.

After diagnosis, but before surgical treatment, the major barriers identified were the inclusion of a placebo arm, delay of shunt placement or ETV surgery of more than three months, and the risk of cognitive decline or loss of productivity as a result of delaying standard treatment. Similar to trials involving infants, PPC members were more open to participating in a clinical trial if the trial did not alter standard of care. Once the diagnosis was made and initial surgical treatment was performed, the major barriers identified were whether the trial would interfere with current treatment (i.e. shutting off the shunt valve), if there was a risk for cognitive decline, or if the experimental treatment would impact day-to-day functioning (i.e., ability to continue work, school, etc.). In both scenarios, loss of productivity and cognitive decline were common underlying concerns for this patient population.

CLINICAL TRIALS INVOLVING THE ELDERLY

During the workshop, elderly PPC patients and their caregivers expressed that the surgical treatment for hydrocephalus posed a greater concern for them compared to the younger adults present. Some PPC members with iNPH told the group that they were resistant to having the initial shunt surgery. This view is in-line with the sentiments of many iNPH patients and caregivers who have contacted the Hydrocephalus Association for support. In some of these cases, the patients did elect to forego shunt surgery. Other PPC iNPH patients and caregivers indicated, however, that they viewed shunt surgery as an opportunity to take back their lives.

For iNPH patients and caregivers, concerns surrounding surgery included the use of anesthesia and possible interactions with current medications. There was also concern that the trauma of the surgery itself would significantly impact elderly patients, resulting in delayed or incomplete recovery. The participating medical professionals also described the risk of post-surgical depression or apathy, especially if the treatment did not result

in the full reversal of symptoms. As a consequence, the majority of PPC iNPH patients indicated much more willingness to delay surgery and try experimental pharmaceutical interventions than the other age groups.

DISCUSSION

The T2T Project brought together hydrocephalus patient representatives, medical professionals, and researchers to discuss patient priorities, patient-centered outcome measures, the barriers to clinical trial participation, and age-specific considerations for clinical trial design. The T2T Project gave PPC members an opportunity to share their thoughts, feelings, and concerns about the clinical trial process in a meaningful way while providing valuable insight for translational and clinical researchers. The limitations of the T2T Project include the small sample size of the PPC and the limited number of participating medical professionals and researchers.

INCORPORATING PATIENT PRIORITIES AND PATIENT-CENTERED OUTCOMES

The patient priorities and patient-centered outcome measures identified by PPC members included some that are commonly addressed in current hydrocephalus clinical trials, such as treatment failure and shunt infection, and fall within the purview of neurological surgery. While other priorities and outcomes, such as long-term cognitive and behavioral outcomes, familial anxiety, vision, and pain, are not commonly measured and do not fit within the research focus of all neurosurgeons. It was difficult, however, for patients and caregivers to prioritize one topic over another. A systematic trade-off analysis incorporating both clinical and patient-centered outcomes would help researchers set research priorities and perhaps influence clinical trial design.

To address priorities outside of the neurosurgical field, future clinical trials should include medical professionals from other disciplines including neurology, neuropsychology, ophthalmology, and pain management. In addition, the long-term cognitive, social, and behavioral outcomes identified by the PPC will require longitudinal study designs, significant financial support, and high patient retention rates. Patient education is essential to move these studies forward. Explaining the timing of outcome measures, educating patients and families regarding the importance of continued engagement, and a concerted effort to engage patients in creative ways throughout the trial may help in these efforts.

Another topic that highlighted the need for patient education, as well as ethics consultation, was research involving patient-derived therapies. PPC members were excited about and seemed more willing to participate in studies of this type, as well as in studies targeting neuroregeneration and neurorepair, in general. Improving neuropsychological outcomes is a priority in the hydrocephalus community, and these types of studies represent an opportunity that may change the risk aversion profile of hydrocephalus patients. It will be important, however, for investigators to understand what is driving this optimism and determine if these views are based on therapeutic

misconception. If therapeutic misconception is involved, researchers must be especially careful not to oversell the potential benefits of study participation to patients and caregivers.

ADDRESSING BARRIERS TO CLINICAL TRIAL PARTICIPATION

PPC members involved in the T2T Project represented different populations within the hydrocephalus community, but they had some shared apprehensions about enrolling in certain types of clinical trials. The shared barriers to clinical trial participation included the need for additional invasive procedures, infection risk, and delays in standard treatment. This is not unexpected from a patient population that typically must undergo multiple neurosurgical procedures throughout their lives and is regularly warned of the long-lasting complications associated with shunt infections and delays in treatment. As new drugs and devices are developed, minimizing the real and perceived risks of participation will be important for patient recruitment.

Along with the barriers that emerged around clinical trial participation, there were also clear age-specific considerations that should be addressed during clinical trial design (Table 3). Addressing these concerns in the initial design of clinical trials will allow investigators to maximize patient enrollment and retention. For example, elderly patients diagnosed with iNPH were more willing to participate in trials that would delay standard surgical treatment. This is in comparison to other groups, such as parents of infants and children, who are more averse to delays in standard surgical intervention. Therefore, iNPH patients may be suited for early-stage studies evaluating non-invasive therapies meant to prevent the need for surgical intervention.

For research involving infants and children, investigators need to be cognizant of how familial anxiety and stress can affect the decision to enroll a child in a clinical trial. This is particularly critical when an intervention must be implemented within a narrow timeframe after diagnosis. In these cases, it may be helpful to identify ‘at risk’ patients early to start a dialog about hydrocephalus, current treatment options, and participation in a clinical trial prior to a definitive diagnosis. Providing access to educational and support resources from organizations, such as the Hydrocephalus Association, early in this process may help ease anxiety and stress.

Other barriers, such as the parent or caregiver desire for long-term cognitive outcome data before enrolling an infant or child in a clinical trial, may not be possible to overcome, but also underscores the importance of long-term follow up if new interventions are to be adopted. In addition, it highlights the need to better educate the public about the clinical trial process and limitations of pre-clinical research.

Enrolling adolescent patients poses unique challenges. Clinical researchers must evaluate the unique characteristics of each adolescent patient living with a chronic medical condition. This evaluation must take into account thecognitive and psychological influences of the condition itself, the effects of growing up with a chronic medical

condition, as well as how parents and caregivers' influence the adolescent's decision-making process. Involving adolescents, such as the Hydrocephalus Association's Teens Take Charge group, early in the development of new clinical trials may help address the ethical concerns surrounding parental permission and the assent process and provide insight into how to overcome other challenges of involving teens in clinical research.

For adult patients, the impact of clinical trial participation on their daily lives, including time away from their jobs and loss of productivity, was a major concern. These concerns may be specific to high functioning hydrocephalus patients who are living independently, have children of their own, and have careers. Individuals who are more significantly affected, newly diagnosed, experiencing severe symptoms, or who are in treatment failure may not share these concerns. More work needs to be done to further understand the diversity of this group of patients.

Elderly patients diagnosed with iNPH should be viewed as a separate patient population with distinct priorities and concerns. The primary concern for some patients in this population was the surgical treatment itself. As discussed previously, some iNPH patients and families believed that the shunt placement surgery caused additional damage and prevented the patient from making a full recovery. This sentiment highlights the need for medical professionals to provide realistic expectations for this patient population, including education concerning comorbidities, the normal aging process, and delays in treatment affect outcomes.

CONCLUSIONS

To best serve the hydrocephalus community, researchers need to understand and incorporate patient priorities and patient-centered outcomes in both pre-clinical and clinical research. The T2T project serves as a starting point, but more work needs to be done to further understand the needs of the diverse hydrocephalus patient population. Early dialogues with groups, such as the Hydrocephalus Association Patient Partner Committee, can help researchers improve patient enrollment and retention in clinical trials and make meaningful improvements in the lives of those affected by hydrocephalus.

DISCLOSURES

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LITERATURE CITED

1 Carman, K. L. *et al.* Patient and family engagement: a framework for understanding the elements and developing interventions and policies. *Health Aff (Millwood)* **32**, 223-231, doi:10.1377/hlthaff.2012.1133 (2013).

2 Furlong, P. *et al.* How a patient advocacy group developed the first proposed draft guidance document for industry for submission to the U.S. Food and Drug Administration. *Orphanet J Rare Dis* **10**, 82, doi:10.1186/s13023-015-0281-2 (2015).

3 Forrester, M. B. & Merz, R. D. Rates of selected birth defects in relation to folic acid fortification, Hawaii, 1986-2002. *Hawaii medical journal* **64**, 300, 302-305 (2005).

4 Jeng, S., Gupta, N., Wrensch, M., Zhao, S. & Wu, Y. W. Prevalence of congenital hydrocephalus in California, 1991-2000. *Pediatric neurology* **45**, 67-71, doi:10.1016/j.pediatrneurol.2011.03.009 (2011).

5 Blackburn, B. L. & Fineman, R. M. Epidemiology of congenital hydrocephalus in Utah, 1940-1979: report of an iatrogenically related "epidemic". *American journal of medical genetics* **52**, 123-129, doi:10.1002/ajmg.1320520202 (1994).

6 Jaraj, D. *et al.* Prevalence of idiopathic normal-pressure hydrocephalus. *Neurology* **82**, 1449-1454, doi:10.1212/WNL.0000000000000342 (2014).

7 Del Bigio, M. R., Wilson, M. J. & Enno, T. Chronic hydrocephalus in rats and humans: white matter loss and behavior changes. *Annals of neurology* **53**, 337-346, doi:10.1002/ana.10453 (2003).

8 Ravdin, L. D. *et al.* Features of gait most responsive to tap test in normal pressure hydrocephalus. *Clinical neurology and neurosurgery* **110**, 455-461, doi:10.1016/j.clineuro.2008.02.003 (2008).

9 Houliston, M. J., Taguri, A. H., Dutton, G. N., Hajivassiliou, C. & Young, D. G. Evidence of cognitive visual problems in children with hydrocephalus: a structured clinical history-taking strategy. *Developmental medicine and child neurology* **41**, 298-306 (1999).

10 Bakar, E. E. & Bakar, B. Memory difficulties of adult patients with shunted hydrocephalus: a clinical study. *Turkish neurosurgery* **21**, 325-329, doi:10.5137/1019-5149.JTN.4133-11.0 (2011).

11 Mataro, M. *et al.* Cognitive changes after cerebrospinal fluid shunting in young adults with spina bifida and assumed arrested hydrocephalus. *Journal of neurology, neurosurgery, and psychiatry* **68**, 615-621 (2000).

12 Dalen, K., Bruaroy, S., Wentzel-Larsen, T., Nygaard, M. & Laegreid, L. M. Non-verbal learning disabilities in children with infantile hydrocephalus, aged 4-7 years: a population-based, controlled study. *Neuropediatrics* **37**, 1-5, doi:10.1055/s-2006-923839 (2006).

13 Rekate, H. L. Shunt-related headaches: the slit ventricle syndromes. *Child's nervous system : ChNS : official journal of the International Society for Pediatric Neurosurgery* **24**, 423-430, doi:10.1007/s00381-008-0579-7 (2008).

14 Abbott, R., Epstein, F. J. & Wisoff, J. H. Chronic headache associated with a functioning shunt: usefulness of pressure monitoring. *Neurosurgery* **28**, 72-76; discussion 76-77 (1991).

15 Edwards, R. J., Britz, G. W. & Marsh, H. Chronic headaches due to occult hydrocephalus. *Journal of the Royal Society of Medicine* **96**, 77-78 (2003).

16 Urban, M. & Rabe-Jablonska, J. Undiagnosed normal pressure hydrocephalus as a cause of diagnostic difficulties in a patient with depression. *Journal of psychiatric practice* **19**, 501-504, doi:10.1097/01.pra.0000438191.04786.5f (2013).

17 Kito, Y. *et al.* Neuropsychiatric symptoms in patients with idiopathic normal pressure hydrocephalus. *Behavioural neurology* **21**, 165-174, doi:10.3233/BEN-2009-0233 (2009).

18 Iddon, J. L., Morgan, D. J., Loveday, C., Sahakian, B. J. & Pickard, J. D. Neuropsychological profile of young adults with spina bifida with or without hydrocephalus. *Journal of neurology, neurosurgery, and psychiatry* **75**, 1112-1118, doi:10.1136/jnnp.2003.029058 (2004).

19 Drake, J. M. *et al.* Randomized trial of cerebrospinal fluid shunt valve design in pediatric hydrocephalus. *Neurosurgery* **43**, 294-303; discussion 303-295 (1998).

20 Kestle, J. R. *et al.* Lack of benefit of endoscopic ventriculoperitoneal shunt insertion: a multicenter randomized trial. *Journal of neurosurgery* **98**, 284-290, doi:10.3171/jns.2003.98.2.0284 (2003).

21 Lam, S., Harris, D., Rocque, B. G. & Ham, S. A. Pediatric endoscopic third ventriculostomy: a population-based study. *Journal of neurosurgery. Pediatrics* **14**, 455-464, doi:10.3171/2014.8.PEDS13680 (2014).

22 Shannon, C. N., Carr, K. R., Tomycz, L., Wellons, J. C. & Tulipan, N. Time to First Shunt Failure in Pediatric Patients over 1 Year Old: A 10-Year Retrospective Study. *Pediatric neurosurgery* **49**, 353-359, doi:10.1159/000369031 (2013).

23 Sainte-Rose, C. *et al.* Mechanical complications in shunts. *Pediatric neurosurgery* **17**, 2-9 (1991).

24 Smith, E. R., Butler, W. E. & Barker, F. G., 2nd. In-hospital mortality rates after ventriculoperitoneal shunt procedures in the United States, 1998 to 2000: relation to hospital and surgeon volume of care. *Journal of neurosurgery* **100**, 90-97, doi:10.3171/ped.2004.100.2.0090 (2004).

25 Simon, T. D. *et al.* Hospital care for children with hydrocephalus in the United States: utilization, charges, comorbidities, and deaths. *Journal of neurosurgery. Pediatrics* **1**, 131-137, doi:10.3171/PED/2008/1/2/131 (2008).

26 Rekate, H. L. & Kranz, D. Headaches in patients with shunts. *Seminars in pediatric neurology* **16**, 27-30, doi:10.1016/j.spen.2009.01.001 (2009).

27 Gardner, H. R., Fraser, C., MacLennan, G. & Treweek, S. A protocol for a systematic review of non-randomised evaluations of strategies to improve participant recruitment to randomised controlled trials. *Syst Rev* **5**, 131, doi:10.1186/s13643-016-0308-3 (2016).

28 Simon, T. D. *et al.* Risk factors for first cerebrospinal fluid shunt infection: findings from a multi-center prospective cohort study. *The Journal of pediatrics* **164**, 1462-1468 e1462, doi:10.1016/j.jpeds.2014.02.013 (2014).

29 Simon, T. D. *et al.* Infection rates following initial cerebrospinal fluid shunt placement across pediatric hospitals in the United States. Clinical article. *Journal of neurosurgery. Pediatrics* **4**, 156-165, doi:10.3171/2009.3.PEDS08215 (2009).

30 Kulkarni, A. V., Rabin, D., Lamberti-Pasculli, M. & Drake, J. M. Repeat cerebrospinal fluid shunt infection in children. *Pediatric neurosurgery* **35**, 66-71, doi:50393 (2001).

31 Kestle, J. R. *et al.* Management of shunt infections: a multicenter pilot study. *Journal of neurosurgery* **105**, 177-181, doi:10.3171/ped.2006.105.3.177 (2006).

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